Optimising the management of diabetic retinopathy in pregnant women with pre-existing diabetes in Australia

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ABSTRACT

Background: Diabetic Retinopathy (DR) is a leading cause of blindness among people of reproductive age and is thought to be worsened by pregnancy. Findings from prior studies have been conflicting, many are outdated, and the majority only studied women with type 1 diabetes (T1DM). It is crucial to identify those within this population who are most at risk of developing DR progression towards sight-threatening disease, so that appropriate management can be planned. Clinical decisions regarding DR management in pregnancy can be fraught, due to the need to give timely sight-saving treatment while also minimising adverse effects to the foetus. Despite these concerns, DR management guidelines have been inconsistent across the globe due to disparate findings.

Purpose: This thesis aimed to 1) report the prevalence of DR, sight-threatening DR (STDR), and its progression rate during pregnancy in Metropolitan Melbourne; 2) assess the use of optical coherence tomography angiography (OCTA) in evaluating retinal changes in diabetic patients during different stages of pregnancy; and 3) determine the adherence rate and the barriers to the recommended eye screening guidelines in pregnant women with pre-existing diabetes.

Research Design and Methods: This doctoral research project was a prospective longitudinal cohort study of women with T1DM or type 2 diabetes who were pregnant or planning to get pregnant from two tertiary maternity hospitals in Melbourne, Australia. Eye examinations were scheduled in each trimester and at 3-months postpartum. DR severity was graded for each eye from 2-field retinal photographs. Progression was defined as worsening by ≥1-step on the Airlie House classification, development of diabetic macular oedema (DMO), or the need for laser treatment during pregnancy. Sight-threatening (ST) progression was defined as development of proliferative DR or DMO. Additionally, 3x3-mm OCTA scans (macula-centred) were taken from participants who attended Melbourne Eyecare Clinic using swept-source OCT (Triton, Topcon Corp). Foveal avascular zone (FAZ) area and vessel density (VD) from the superficial capillary plexus were measured. Barriers to attending eye screening were assessed with the modified Compliance with Annual Diabetic Eye Exams Survey.

Results:

Aim 1: A total of 147 from 191 eligible women (77%) were recruited, with at least one eye exam performed in 130 (88.4%). Sixty-two women (47.7%) had T1DM. DR and STDR prevalence were 20.8 (95% confidence interval [CI] 16.3-26.1) and 6.6 (CI 4.1-10.4) per 100 eyes, respectively. Among the 144 eyes (72 women) with more than one eye exam, 9.7% (CI 5.8 - 15.8) had DR progression and 4.5% (CI 1.9 - 9.6) had ST progression. Elevated systolic blood pressure (risk ratio [RR] 10.36, CI 3.14 - 34.12) and pre-existing DR (RR 5.07, CI 1.90 - 13.49) in early pregnancy significantly increased the risk of progression.

Aim 2: A total of 125 eyes from 64 women were imaged. The majority of women were in the pregnant group (77%) with 38 (59%) having T1DM. The majority of eyes had no DR (81.6%) or DMO (97.6%). The VD in the pericentral region and superior, temporal, and nasal subfields were significantly lower in eyes with DR than eyes without in the non-pregnant and pregnant groups (p-values $\leq$0.039). The nasal VD in eyes with no DR in the pregnant group was significantly higher than that of the postpartum group (p=0.010). Although not reaching statistical significance, a trend towards higher VD in the pregnant group than the non-pregnant group was observed in all subfields, except in the temporal subfield. The temporal VD was lower in the pregnant group than the non-pregnant group and was especially marked in eyes with DR. No significant difference was found in the mean FAZ area between various pregnancy statuses and DR severities.

Aim 3: There were 125 pregnant women who completed the survey. The median age was 34 years (range 19-47). Sixty-four respondents (51.2%) had T1DM. A retinal assessment was performed at least once in the first trimester in 56 (44.8%) and 33 (26.4%) had the ideal number of examinations. Competing priorities (p=0.012) and the belief of having reasonable diabetes control (p=0.007) were the main reasons given for non-attendance. Interestingly, the presence of multiple eye care providers in the neighbourhood was also associated with non-adherence (p=0.003).

Conclusion: This PhD study has provided updated data on the prevalence of DR and its rate of progression in the Australian pregnant population with pre-existing diabetes, illustrated the use of OCTA in this population, and reported the adherence rate and barriers to the recommended eye screening guidelines. The DR prevalence in pregnant

women was similar to the non-pregnant diabetic population in Australia. However, nearly 1 in 10 eyes had DR progression during pregnancy, with almost half of these developing STDR. DR presence could be reflected by a decrease in the VD in the OCTA scan, which is in concordance with the findings from previous studies in non-pregnant populations, suggesting a potential role for OCTA in the evaluation of DR during pregnancy in a non-invasive manner. Worryingly, more than half of our cohort did not adhere to the recommended eye screening schedule in pregnancy, and about 70% did not receive frequent exams as recommended, highlighting the need to address barriers to eye screening attendance given the significant risk of vision loss from DR in this population. This study benefits society by providing findings that may help inform the future development of evidence-based guidelines for DR screening and management in this unique and growing population. Based on this study's findings, it is recommended that pregnant women with pre-existing diabetes should have an eye examination in the first trimester or as soon as pregnancy is recognised. If no DR is found, an additional exam during pregnancy is advised only for women with T1DM. However, if DR is present, an eye exam in each trimester is recommended irrespective of diabetes type.

DECLARATION

This is to certify that

i. the thesis comprises only my original work towards the degree of Doctor of Philosophy except where indicated in the Preface;

ii. due acknowledgement has been made in the text to all other material used;

iii. the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

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PREFACE

In agreement with University of Melbourne policy, I acknowledge that certain aspects of this work were conducted collaboratively with my co-investigators. Overall, I performed the literature review, designed studies and the statistical analysis, interpreted data, authored chapters, and incorporated all feedback from my supervisors in this thesis. Outlined below are the contributions of each individual involved in this PhD work.

Systematic review and meta-analysis of DR in pregnancy

With the guidance of A/Prof. Lyndell Lim, this project was conceived and designed by me and completed with the support of Mr Jim Berryman (a liaison librarian at the Brownless Biomedical Library at the University of Melbourne), Mrs Sophie Rogers, and Dr Rathika Kandasamy.

The prevalence and progression rate study (Aim 1)

This main project was initiated and conceptualised by A/Prof. Lyndell Lim, my primary PhD supervisor. In the development of the research plan, I worked with my supervisors (A/Prof. Lyndell Lim, A/Prof. R.C. Andrew Symons and A/Prof. Alexis Shub), A/Prof. Daryl Guest, A/Prof. Alison Nankervis, and Mrs Sophie Rogers. All of them provided intellectual contributions towards the resultant research outputs (abstracts and presentations).

Aside from the names mentioned earlier, during the conduct of the study, I received assistance and support from A/Prof. Jennifer Conn, Dr. Christine Houlihan, and Dr. Xavier Fagan with the recruitment and examination of study participants, and Dr. M. Bayu Sasongko with the grading of fundus photos. Eye examinations were performed by student optometrists at the Melbourne Eyecare Clinic, under the supervision of optometrist staff (Mr Timothy Martin, Mr Joe Wang, Mr Kent Snibson, Ms Weiling Tsai, Ms Catrina Yap, and Mr Lahiru Kulathunga). For patients who attended the Austin Repatriation Hospital, eye examinations were performed by an orthoptist (Mr Angelo Rando). The development of the study database (the Research Electronic Data Capture

[REDCap]) was assisted by the University of Melbourne's REDCap administrator (Ms Sandra Henley-Smith).

The Optical Coherence Tomography Angiography study (Aim 2)

This investigation was conceived by A/Prof. R.C. Andrew Symons. Under his supervision, I worked with Dr. Mali Okada for the "FAZ pilot study". The automatic FAZ area measurement algorithm was fully developed by Dr. Jeremiah Lim under the guidance of A/Prof. Bang Bui.

The adherence rate and barriers study (Aim 3)

Supported by A/Prof. Lyndell Lim, I initiated and conceptualised this project. For the qualitative analysis, coding and thematic analysis were conducted with the guidance and assistance of Dr. Sandra Staffieri.

Mrs Sophie Rogers contributed to the statistical analysis of each investigation in this thesis. Mr Cameron Patrick (a biostatistician from the Melbourne Statistical Consulting Platform) assisted with the principal component analysis for Aim 3. In the final year of my candidature, Edmund Khong assisted with the patient follow-up and data collection, particularly for visits after delivery.

I am an international student and English is my second language. Aside from my supervisors, I received assistance from Mrs Kelly Mikunda and Edmund Khong in the review of my drafts for grammatical errors.

This study was supported by a grant from the Alfred Felton Bequest. In kind support was received from the Melbourne Eyecare Clinic and the Austin Repatriation Hospital. The Coordinating Investigator, A/Prof. Lyndell Lim, was supported by a NHMRC Early Fellowship (GNT 1109330). I was a recipient of the Indonesia Endowment Fund for Education (LPDP) scholarship which supported me throughout the duration of my candidature. I also received funding from the Australia-Indonesia Institute in the Australian Government's Department of Foreign Affairs and Trade for the conduct of a similar study in Indonesia (not included in this thesis). The Centre for Eye Research Australia receives Operational Infrastructure Support from the Victorian Government.

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A/Prof. R.C. Andrew Symons. Thank you for introducing me to OCTA. Your expert guidance has helped me discover new knowledge and skills that will be useful in the future. I appreciate all the time that you spent to help me understand this new imaging technique.

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My sincere gratitude to my family in Melbourne and Yogyakarta. Thank you to my parents for their encouragement, help, and support. For their willingness to fly back and forth between Yogyakarta and Melbourne to help me nurture my daughter during my studies. Thank you to my siblings who gave me an excuse to take a break from my work during their visits. To my husband, Arius Suwondo, all of this would not be possible without your sincere approval and encouragement to pursue my dream. Thank you for allowing me to be 4,600 km away from you for the last 3 years when I should have been by your side to support you during your studies. Finally, to my beautiful daughter, Alika, thank you for your patience, understanding, and cheerful persona that motivated me to finish my work. It was the hardest thing for me to leave a 9-month-old baby for the first time for two months, but I assure you, your sacrifice was for the greater good and hopefully you will be proud of me someday in the future.

I dedicate this milestone to my daughter, husband, and family whose prayers and support have made this journey come true.

RESEARCH OUTPUTS

CONFERENCE PRESENTATIONS

1. **Poster presentation**: Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Annual scientific meeting, Sydney, Australia, 2019. Widyaputri F, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Adherence to the Recommended Diabetic Retinopathy Screening Guidelines in Pregnant Women with Type 1 and Type 2 Diabetes.

2. **Oral presentation**: Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) Annual scientific meeting, Melbourne, Australia, 2019. Widyaputri F, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Adherence to the Recommended Diabetic Retinopathy Screening Guidelines in Pregnant Women with Pre-existing Diabetes.

3. **Oral presentation**: Invited speaker at the University of Melbourne Doctor of Optometry Student Conference (ODSC), Melbourne, Australia, 2019. Widyaputri F. Diabetic Retinopathy in Pregnant Women with Pre-existing Diabetes.

4. **Oral presentation**: Australasian Diabetes in Pregnancy Society (ADIPS) Annual meeting, Sydney, Australia, 2019. Widyaputri F, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Adherence and Barriers to the Recommended Diabetic Retinopathy Screening Guidelines in Pregnant Women with Type 1 and Type 2 Diabetes.

5. **Oral presentation**: Visit of the Dean of Faculty of Medicine, Dentistry, and Health Sciences at Centre for Eye Research Australia, Melbourne, Australia, 2019. Widyaputri F. Diabetic Retinopathy: More to Diabetes n Pregnancy than Meets the Eye.

6. **Oral presentation**: Melbourne Ophthalmology Alumni Meeting, Melbourne, Australia, 2019. Widyaputri F, Okada M, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Lim LL, Symons RCA. Retinal Vascular Changes during

Different stages of Pregnancy in Type I and II Diabetes Mellitus as Measured Using Optical Coherence Tomography Angiography.

7. **Oral presentation**: The Association for Research in Vision and Ophthalmology (ARVO) Annual meeting, Vancouver, Canada, 2019. Widyaputri F, Okada M, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Diabetic Retinopathy in Pregnant Women with Type I and II Diabetes in Metropolitan Melbourne– Prevalence, Adherence and Barriers to the Recommended Eye Screening Guidelines.

8. **Poster presentation**: The Association for Research in Vision and Ophthalmology (ARVO) Annual meeting, Vancouver, Canada, 2019. Okada M, Widyaputri F, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Lim LL, Symons RCA. Retinal vascular changes during pregnancy in patients with diabetes mellitus as measured using optical coherence tomography angiography.

9. **Oral presentation**: Department of Surgery Research Showcase, University of Melbourne, Melbourne, Australia, 2018. Widyaputri F, Okada M, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Predicting Diabetic Retinopathy Progression in Pregnant Women with Pre-existing Diabetes using Optical Coherence Tomography Angiography (OCTA).

10. **Oral presentation**: Invited speaker at the Royal Australian and New Zealand College of Ophthalmologists (RANZCO) Annual scientific meeting, Adelaide, Australia, 2018. Widyaputri F & Lim LL. Diabetic Retinopathy during Pregnancy.

11. **Oral presentation**: Centre for Eye Research Australia Department Meeting, Melbourne, 2018. Widyaputri F & Lim LL. Diabetic Retinopathy during Pregnancy.

12. **Oral presentation**: Invited speaker at the Diabetic Retinopathy Information Forum by Centre for Eye Research Australia, Melbourne, Australia, 2018. Widyaputri F & Lim LL. Diabetic retinopathy in pregnancy – What we know, what we don't know and why it is so important.

PUBLISHED ABSTRACTS

1. **Widyaputri F**, Okada M, Rogers S, Nankervis A, Conn J, Shub A, et al. Diabetic Retinopathy in Pregnant Women with Type I and II Diabetes in Metropolitan Melbourne – Prevalence, Adherence and Barriers to the Recommended Eye Screening Guidelines. Investigative Ophthalmology & Visual Science. 2019;60(9):4777.

2. Okada M, **Widyaputri F**, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Lim LL, Symons RCA. Retinal vascular changes during pregnancy in patients with diabetes mellitus as measured using optical coherence tomography angiography. Investigative Ophthalmology & Visual Science. 2019;60(9):3024.

3. **Widyaputri F**, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Adherence and Barriers to the Recommended Diabetic Retinopathy Screening Guidelines in Pregnant Women with Type 1 and Type 2 Diabetes. In: Proceedings of the Australasian Diabetes in Pregnancy Society (ADIPS) 2019 Annual scientific meeting; 2019 August 23-25; Sydney, Australia. Sydney: ADIPS; 2019. Available from: http://www.adips.org/documents/ADIPS2019FinalBook.pdf

4. **Widyaputri F**, Rogers SL, Nankervis A, Conn J, Shub A, Fagan X, Guest D, Symons RCA, Lim LL. Adherence to the Recommended Diabetic Retinopathy Screening Guidelines in Pregnant Women with Pre-existing Diabetes. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2019;59(S1):83-116

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AWARDS

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2. University of Melbourne - Student Engagement Grant, 2019.

3. Centre for Eye Research Australia Travel Award, 2019.

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5. The Australia-Indonesia Institute Grant by the Department of Foreign Affairs and Trade, Australian Government.

6. Semi-Finalist of the University of Melbourne 3 Minute Thesis Competition, 2019.

7. Winner of the 3 Minute Thesis Competition, Centre for Eye Research Australia, 2018.

8. Best oral presenter (PhD candidate) - Department of Surgery Research Showcase, Medicine Dentistry and Health Science, University of Melbourne, 2018.

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ABBREVIATIONS

1hBG	1-hour blood glucose
2hBG	2-hour blood glucose
7SF	7-standard field
AAO	American Academy of Ophthalmology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACR	Albumin/creatinine ratio
ADA	American Diabetes Association
ADIPS	Australian Diabetes in Pregnancy Society
AGEs	Advanced glycation end products
AMD	Aged Macular Degeneration
ANOVA	Analysis of variance
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
ARH	Austin Repatriation Hospital
ARVO	Association for Research in Vision and Ophthalmology
ATSI	Aboriginal & Torres Strait Islander People
BCVA	Best corrected visual acuity
BG	Blood glucose
BMI	Body mass index
BOS	Birthing Outcomes System
BP	Blood pressure
C-section	Caesarean section
CADEES	Compliance with Annual Eye Exams Survey
CERA	Centre for Eye Research Australia
CF	Counting finger
CGM	Continuous glucose monitoring
CI	Confidence interval
CLARA	Clinical Lookup and Results Acknowledgement
CMT	Central macular thickness
CSFT	Central sub-field thickness

CSMO	Clinically significant macular oedema
DA	Diameter area
DBP	Diastolic blood pressure
DCCT	Diabetes Control and Complications Trial
DCP	Deep capillary plexus
DESIC	Diabetes Eye Screening and Investigation Clinic
DIP	Diabetes in pregnancy
DKA	Diabetes keto-acidosis
DM	Diabetes mellitus
DMI	Diabetic macular ischaemic
DMO	Diabetic macular oedema
DR	Diabetic retinopathy
DRIL	Disorganisation of retinal inner layers
EDIC	Epidemiology of Diabetes Interventions and Complications
ETDRS	Early Treatment Diabetic Retinopathy Study
EURODIAB	Epidemiology and Prevention of Diabetes study
FAZ	Foveal avascular zone
FBG	Fasting blood glucose
FFA	Fundus fluorescence angiography
GA	Gestational age
GDM	Gestational diabetes
GP	General practitioner
HAPO	Hyperglycaemia and Adverse Pregnancy Outcome study
HbA1c	Glycated haemoglobin A1c
HDiP	Hypertensive disorders in pregnancy
HDL	High-density lipoprotein
HE	Hard exudate
HM	Hand movement
HMA	Haemorrhages/ Microaneurysms
HREC	Human Research Ethics Committee
IADPSG	International Association of Diabetes and Pregnancy Study Groups

IAPB	International Agency for Prevention of Blindness
ICC	Inter-class correlation
ICDSS	International Clinical Disease Severity Scale
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
ICP	Intermediate capillary plexus
IDF	International Diabetes Federation
IGF	Insulin-like Growth Factor
ILM	Inner limiting membrane
INL	Inner nuclear layer
IOP	Intraocular pressure
IPL	Inner plexiform layer
IQR	Interquartile range
IRF	Intra-retinal fluid
IRMAs	Intraretinal microvascular abnormalities
IV	Intravenous
LDL	Low-density lipoprotein
LE	Left eye
LGA	Large for gestational age
LPDP	*Lembaga Pengelola Dana Pendidikan* (Indonesia Endowment Fund for Education)
MA	Microaneurysms
MEyecare	Melbourne Eyecare
M-H	Mantel-Haenszel
MHW	Mercy Hospital for Women
NA	Not applicable
NDSS	National Diabetes Services Scheme
NEHS	National Eye Health Survey
NGSP	National Glycohemoglobin Standardization Program
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit

NPDR	Non-proliferative diabetic retinopathy
NPL	No perception of light
NR	No record
NVA	Neovascularisation of the angle
NVD	Neovascularisation of the disc
NVE	Neovascularisation elsewhere
NVI	Neovascularisation of the iris
OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
OGTT	Oral glucose test tolerance
OR	Odds ratio
ORL	Outer Retinal Layer
PC	Principal component
PCA	Principal Component Analysis
PCR	Protein/creatinine ratio
PDR	Proliferative diabetic retinopathy
PICF	Participant information sheet and consent form
PL	Perception of light
PP	Postpartum
PPL	Predominantly peripheral lesion
PRH	Pre-retinal haemorrhages
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RANZCO	Royal Australian and New Zealand College of Ophthalmologists
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RBF	Retinal blood flow
RBG	Random blood glucose
RC	Retrospective cohort
RCT	Randomised control trial
RE	Right eye
REDCap	Research Electronic Data Capture

RMH	Royal Melbourne Hospital
RPE	Retinal pigment epithelium
RR	Risk ratio
RWH	Royal Women Hospital
SBP	Systolic blood pressure
SCN	Special care nursery
SCP	Superficial capillary plexus
SD	Standard deviation
SE	Side effect
SGA	Small for gestational age
SIGN	Scottish Intercollegiate Guidelines Network
SMS	Short Message Service
SOMANZ	Society of Obstetric Medicine of Australia and New Zealand
SRF	Sub-retinal fluid
ST	Sight threatening
STDR	Sight-threatening diabetic retinopathy
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAFE	technical and further education
TIR	Time in range
UK-NSCG	United Kingdom National Screening Committee guidelines
UKPDS	UK Prospective Diabetes Study
UWF	Ultrawide-field
VA	Visual acuity
VB	Venous beading
VD	Vessel density
VEGF	Vascular endothelial growth factor
VH	Vitreous haemorrhage
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

CHAPTER 1: WHY DIABETIC RETINOPATHY IN PREGNANCY?

1.1. Introduction

The increasing prevalence of diabetes mellitus (DM) is set to reach epidemic proportions in Australia and around the world. Currently, diabetes affects 463 million people globally; with nearly 1.3 million people in Australia alone (13.5% of type 1 diabetes [T1DM], 85% of type 2 diabetes [T2DM]).[1,2] These numbers are expected to rise exponentially with a 51% increase in predicted prevalence by 2045, which will result in a concurrent increase in the incidence of diabetes-associated complications.[2]

Since the discovery of insulin in 1921, the life expectancy of patients with diabetes, particularly T1DM, has increased significantly, with more women reaching reproductive age.[3] As more women with diabetes experience pregnancy, the challenge of achieving satisfactory pregnancy outcomes despite diabetes-related complications has emerged. Although medical advances have made it possible for women with diabetes to give birth to healthy babies, pregnancies in those with diabetes are still associated with poorer outcomes, with a 5-fold higher risk of still birth, 3.5-fold increased risk of neonatal death, and twice the rate of congenital abnormalities compared to the non-diabetic population.[4] Additionally, there is an increased risk of progression of diabetes-associated complications in the mother, such as diabetic retinopathy and nephropathy.[5] **Optimising medical care so that pregnant women with diabetes can achieve similar pregnancy outcomes to pregnant women without diabetes, and preventing the development of diabetes complications during pregnancy are major aims in diabetes care.**[6]

The International Diabetes Federation estimates that pregnant women with diabetes account for 15.8% of global pregnancies with live births.[2] These rates are lower in Australia (9.4% and 1.1% for gestational and pre-existing diabetes, respectively).[1] It is projected that this proportion will increase significantly in the future, with an increasing number of pregnant women with T2DM in particular, due to the ongoing epidemic of obesity, younger age of T2DM onset, and higher maternal age.[7-10] **Because of this, issues of pregnancy and its effect on diabetes and its complications will become a steadily more significant public health problem.**

There are five main complications that can affect people living with diabetes, namely cardiovascular diseases, diabetic eye diseases, diabetic kidney diseases, diabetic foot complications, and acute complications (hypoglycaemia, diabetic ketoacidosis, and hyperglycaemic hyperosmolar state). Diabetic retinopathy (DR) is one of the most frequent diabetes-related complications in the eye. DR is a leading cause of blindness among people of reproductive age and is thought to be worsened by pregnancy.[11-13] As a preventable cause of blindness, it is important to conduct timely screening so that sight saving treatments may be instituted in order to prevent visual loss. Diabetic eye screening programs have been promoted for early detection of DR and examinations are scheduled differently based upon individual clinical conditions, e.g. type of diabetes, degree of DR severity, and HbA1c level.[14] The DCCT/EDIC research group proposed individualising the screening schedule so as to minimize the frequency of eye screening examinations without delaying the diagnosis of significant clinical conditions for diabetic people in general.[15] This approach was not only proven to reduce the frequency of required examinations, hence, increasing attendance rates; but also resulted in considerable cost savings. **Unfortunately, this individualized approach has not been studied well in pregnant women, where the risk of DR progression is thought to be higher than in the non-pregnant population.**

It has been a challenge to make individualized recommendations for diabetic pregnant women because we are still unsure of the risk of DR progression during pregnancy. Findings from previous studies have been contradictory, and few have defined the predictors of progression towards sight-threatening disease during pregnancy. Several biomarkers have been found to have associations with the increased risk of DR progression in the non-pregnant diabetic population. These biomarkers are either from clinical measurements, such as blood pressure and HbA1c, or from retinal imaging, such as observation of retinal vascular lesions and blood flow changes.[16] Changes in the retinal blood flow and vessel diameter have been associated with the worsening of DR during pregnancy.[17,18] However, as standard retinal angiography is relatively contraindicated due to its need for an intravenous dye injection, very limited information is available on the pregnant population. Recently, the advent of a new imaging modality technique, optical coherence tomography angiography (OCTA), has allowed the exploration of angiographic information relating to DR changes in pregnant women's eyes in a non-invasive manner. Understanding the risk factors and markers that predict DR progression

during pregnancy is important, especially so that risk stratification can inform individuals' screening intervals. **It is our challenge as clinicians to design screening programs that can identify every case of sight-threatening DR at a treatable stage and motivate diabetic pregnant women to be involved in these programs, whilst at the same time limiting the number of medical appointments in order to minimize screening burden and maximise patient adherence.**

As an attempt to solve these problems, this PhD study aimed to determine the burden of DR during pregnancy in Australia, to identify risk factors that are associated with DR and STDR progression, to test the use of OCTA in predicting DR progression in the pregnant population, and lastly, to assess the barriers to adhering to current recommended eye screening guidelines in pregnancy. The ultimate aim was to collect and analyse data from a contemporary cohort of pregnant women with pre-gestational diabetes in order to inform the future development of up to date, evidence-based guidelines for DR screening and management in this unique, and growing, population.

1.2. Study Aims

To understand the extent of the problem caused by DR in pregnancy in Australia and discover potential solutions, this PhD study had three main aims:

Aim 1:

To report the prevalence of DR and STDR, and its progression rate during pregnancy and the early postpartum period in metropolitan Melbourne.

Aim 2:

To assess the use of optical coherence tomography angiography (OCTA) in evaluating retinal vascular changes in diabetic patients during different stages of pregnancy.

Aim 3:

To determine the adherence rate and barriers to adherence to the recommended eye screening guidelines during pregnancy in women with pre-existing diabetes.

1.3. Overview of Thesis

This thesis consists of 8 chapters. **Chapter 2** starts with an introduction on diabetes and DR which is then followed by a comprehensive review of DR in pregnancy, including the global and Australian publications related to the aims of this thesis. The management of diabetes and DR in pregnancy is also discussed before lastly exploring the published recommendations on DR screening examinations. This chapter not only describes what is known about DR in pregnancy but also highlights the gaps in the literature. **Chapter 3** presents the systematic review and meta-analysis of the global literature on DR prevalence and progression rate during pregnancy which aimed to provide more accurate estimates. **Chapter 4** describes the overall methodology of this PhD project, including the study set-up, patient recruitment protocol, eye examination and data collection protocol, data entry and storage. **Chapter 5, Chapter 6,** and **Chapter 7** address the first, second, and third aim of this study, respectively. In each chapter, the specific methods, results and discussions for each aim are presented. **Chapter 8** highlights the key findings from the three aims and its clinical implications, the strengths and limitations of this study, and finally the recommendations for future research and guidelines.

CHAPTER 2: LITERATURE REVIEW

2.1. Diabetes Mellitus

Diabetes mellitus (DM) is a chronic and complex health condition. Due to its complications, it has a negative impact on both quality of life and life expectancy. The increasing prevalence of DM is set to reach epidemic proportions in Australia and around the world, with 463 million people (9.3% of the working-age population) affected globally in 2019, and nearly 1.3 million people affected in Australia alone (13.5% with type 1 diabetes, 85% with type 2 diabetes). This number is predicted to rise by 51% by the year 2045.[1,2]

People with diabetes have blood glucose levels that are above than the normal range due to a lack of response to or insufficient production of insulin.[19] Insulin is a hormone produced by pancreatic cells, whose role is to transport glucose from the bloodstream into the body's cells to be converted into energy. Any problem that disrupts this process, such as the lack of insulin production or cell resistance to insulin, can lead to a rise in the level of glucose in the bloodstream (hyperglycaemia) which is the diagnostic criteria for diabetes. Diabetes can be diagnosed by either measuring the fasting blood glucose (FBG), or the 2-hour blood glucose (2hBG) after the ingestion of 75-grams of glucose (oral glucose test tolerance), or the glycosylated haemoglobin level (HbA1c) (**Table 2-1**).[7]

There are three main types of diabetes:

a. Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM) represents nearly 10% of diabetes cases around the world.[2] The pathogenesis involves an auto-immune process that leads to the destruction of pancreatic β cells, the producer of insulin. As a result, pancreatic cells produce very little insulin or even none at all, leading to an absolute insulin deficiency. The onset of this condition usually occurs in childhood or early adulthood but can be observed at any stage of life.

b. Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) contributes to around 90% of all diabetes cases.[2] T2DM

is caused by an inadequate production of insulin and/or an inability of the body to respond to insulin (insulin resistance). This condition mostly happens in older adults, but there is currently a shift towards a much younger age group as a consequence of the increase in people with obesity, poor diets, and sedentary lifestyles.[20] Unfortunately, one in two adults with T2DM are unaware of their condition and consequently, at the time of diagnosis, these people frequently already have some degree of complications from their diabetes.[2]

c. Gestational diabetes mellitus

Diabetes that is first recognised in pregnancy is referred to as gestational diabetes mellitus (GDM). Significant hormonal and metabolic changes during pregnancy affect glucose metabolism and thus can induce hyperglycaemic condition. It has been reported that pregnant women with more severe hyperglycaemia (a blood glucose level fulfilling the criteria for diabetes in non-pregnant adults) have a higher risk of severe pregnancy complications that are less likely to resolve post-delivery compared to pregnant women with a lower degree of hyperglycaemia; thus, these women should be managed differently.[21,22] Therefore, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) has classified diabetes first recognised in pregnancy into two types: Diabetes in Pregnancy (DIP) that covers more severe hyperglycaemia (a blood glucose level within the diabetic criteria) and GDM which covers less severe hyperglycaemia (**Table 2-1**).[23] Moreover, some women with DIP may have T2DM which had not been diagnosed before pregnancy. These women need careful management during pregnancy, including screening for complications of undiagnosed diabetes.[24]

Hyperglycaemia in pregnancy, including GDM and pre-existing diabetes (having either T1DM or T2DM prior to pregnancy), has raised multiple concerns around the world due to its rising prevalence. In 2019, 15.8% of live births worldwide occurred in women with diabetes.[2] In 2015, diabetes was diagnosed in 1 out of every 10 pregnancies in Australia (excluding Victoria),[8] with GDM being diagnosed in 1 in 7 pregnancies in 2017 (with no available data for pre-existing diabetes).[25] Pregnancies complicated by pre-existing diabetes have a higher risk of developing adverse pregnancy outcomes, including congenital malformations, preterm birth, perinatal mortality, preeclampsia and a higher rate of caesarean section.[26] Moreover, these pregnancies may also be complicated by existing vascular damage that can be worsened during pregnancy [27] Although GDM is

associated with a higher risk of adverse events, the complications are less severe and not associated with an increased risk of diabetes-related vascular damage to the mother.[28,29] McElduff and colleagues reported that among 180 pregnancies with pre-existing diabetes in Australia, 45% of cases had T1DM and just over half had T2DM.[30] The latter number is predicted to rise given the increasing number of T2DM cases in general.[31]

Table 2-1. Criteria of diagnosing diabetes[7,31]

	FBG	**1hBG**	**2hBG**	**RBG**
GDM is diagnosed if at least one criterion is found	5.1-6.9 mmol/L	≥10.0 mmol/L	8.5 – 11.0 mmol/L	
DIP is diagnosed if at least one criterion is found	≥7.0 mmol/L	No criteria for diagnosing diabetes using 1hBG	≥11.1 mmol/L during OGTT	≥11.1 mmol/L
	FBG	**2hBG**	**HbA1c**	**RBG**
Diabetes in the non-pregnant population is diagnosed if at least one criterion is found	≥7.0 mmol/L	≥11.1 mmol/L during OGTT	≥6.5% (48 mmol/mol)	≥11.1 mmol/L
	Fasting is defined as no caloric intake for at least 8 hours	OGTT is performed using a glucose load containing the equivalent of 75-g of anhydrous glucose dissolved in water	The test should be performed in a laboratory using a method that is NGSP certified and standardised to the DCCT assay	In a patient with classic symptoms of diabetes* or hyperglycaemic crisis

* Classic diabetes symptoms include frequent urination, excessive thirst, unintentional weight loss.

Abbreviations: 1hBG, 1-hour blood glucose; 2hBG, 2-hour blood glucose; DCCT, Diabetes Control and Complications Trial; DIP, diabetes in pregnancy; FBG, fasting blood glucose; GDM, gestational diabetes mellitus; HbA1c, glycosylated haemoglobin; NGSP, National Glycohemoglobin Standardization Program; OGTT, oral glucose test tolerance; RBG, random blood glucose.

Even though there is currently no cure for diabetes, it is manageable as long as people with diabetes control their blood glucose level through a healthy lifestyle, diet, and medications as required to prevent complications. Uncontrolled diabetes can lead to life-threatening health conditions, including cardiovascular disease, kidney disease, neuropathy, and eye diseases. Diabetic retinopathy is a microvascular complication in the eye associated with diabetes and can lead to blindness.[32]

2.2. Diabetic Retinopathy

Diabetic retinopathy (DR) is a condition where the blood vessels in the retina are damaged due to the chronic elevation of blood glucose levels. The clinical features of DR are divided into non-proliferative and proliferative stages where proliferative DR is characterised by neovascularisation. The non-proliferative stage is graded from mild to severe. DR usually remains asymptomatic until substantial retinopathy is evident on clinical evaluation.

Diabetic retinopathy is projected to develop in approximately one-third of all diabetic people during their lifetime, and it is the leading cause of irreversible blindness in working-age people around the world.[11] Globally, it is estimated that 34.6% of people with diabetes have DR and 10.2% will develop sight-threatening DR (STDR), which is defined as the presence of either proliferative DR (PDR) or diabetic macular oedema (DMO).[33] Extrapolating these numbers with the global diabetes prevalence in 2019, 160.2 million people would have had DR and 47.2 million people would have had STDR.[2] DR in general, and PDR in particular, were more common in people with T1DM than T2DM. However, DMO was equally prevalent across both types of diabetes.[33-35]

With the increasing incidence of diabetes worldwide, the number of people losing vision due to diabetic eye disease will similarly increase. Despite the development of effective treatments to prevent vision loss from DR, several barriers to achieving optimal care through early detection and timely treatment remain.[36]

2.2.1. Pathogenesis and clinical features

Diabetic retinopathy is a condition that affects nerves and blood vessels. Diabetes causes a decrease in neuroglial function in the retina and alters the interaction between these cells and the retinal vasculature.[37] Although it has not been fully understood, several theories have been postulated to explain the pathogenesis of DR, such as elevated advanced glycation end products (AGEs), increased oxidative stress, increased expression of angiogenic factors (e.g., vascular endothelial growth factor, growth hormone, and insulin-like growth factor 1), haemodynamic changes, subclinical inflammation and capillary occlusion.[38] Of these, the role of inflammation, in particular,

has attracted considerable interest in the past few years. This hypothesis proposes that DR occurs as a consequence of chronic inflammation in the eye that leads to damage to retinal capillaries.[39] This inflammation is likely triggered by hyperglycaemia, high cholesterol levels, high blood pressure, elevated AGEs in serum and tissue, and increased oxidative stress.[38] DR causes vision loss by three main mechanisms: capillary occlusion, which in the macular region causes macular ischaemia; ischaemia-induced neovascularisation leading to vitreous haemorrhage and/or tractional retinal detachment; and increased capillary permeability and breakdown of the blood-retina barrier manifesting as diabetic macular oedema.[40]

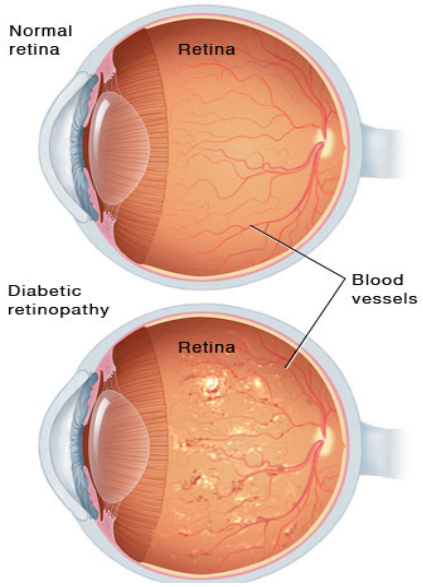


Figure 2-1. Illustration of diabetic retinopathy

Clinically, we can find microaneurysms (initial clinical evidence of DR), intraretinal haemorrhages, cotton wool spots (the swelling of ischaemic axons in the nerve fiber layers), intraretinal microvascular abnormalities (IRMAs), hard exudates (accumulations of lipids in retinal layers), and dilatation or beading of retinal veins in non-proliferative DR (NPDR). In this stage, the abnormalities are limited in the retina. Microaneurysms are seen as small, deep red dots which may vary in diameter (25 to 100 μm) and can leak blood into the retina. As for intraretinal haemorrhages, the appearance depends on the location of the bleed. If bleeding occurs in the nerve fiber layer, a flame-shaped haemorrhage could be seen. However, if it occurs in the deep capillary plexus, it appears as a dot or blot shape. As the disease progresses, abnormal branching of vessels is formed, typically surrounding the non-perfused area, showing as IRMAs.[40,41] The symptoms of NPDR can be none to cloudy or blurred vision, depending on the severity of ischaemia and macula involvement.[40] More complex features found in the retina increase the severity of DR and the risk of progression to vision loss (**Table 2-2**).

When the retina becomes more hypoxic, it induces expression of vascular endothelial growth factor (VEGF) that upregulates angiogenesis, the formation of new blood vessels, to compensate the ischaemic state. These new blood vessels are fragile and bleed easily.

Any evidence of neovascularisation in the optic disc (NVD) or anywhere else in the retina (NVE) marks the progression to PDR. Diabetes may also cause neovascularisation of the iris or anterior chamber angle.[42] If left untreated, the fragile blood vessels can cause a vitreous haemorrhage.[39,43] In severe cases, fibrovascular proliferation could occur causing vitreous traction that leads to retinal detachment (so-called tractional retinal detachment). Any of these lesions can cause severe vision loss and permanent blindness.[40,42]

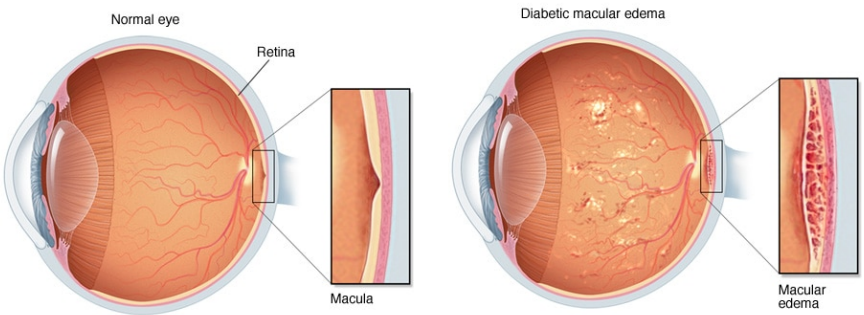


Figure 2-2. Illustration of macular oedema

Image courtesy of Mayo Foundation for Medical Education and Research.

As DR develops, the pathological processes affecting the macular region become a major concern since they directly threaten central vision. Two common features of DR that affect the macula are diabetic macular ischaemia (DMI) and diabetic macular oedema (DMO). Advanced DMI manifests as macular thinning. On the other hand, DMO can be seen as focal or diffuse thickening of retinal layers, the presence of perifoveal hard exudates, or an accumulation of fluid and blood in the macula. These changes are caused by the breakdown of the inner and outer blood-retinal barriers that initiate the increased vascular permeability and development of oedema.[39] Both DMI and DMO can occur during any stage of DR and if any of these abnormalities threaten the fovea (responsible for central vision), vision loss is the most likely outcome.[40] However, several studies reported equivocal findings regarding the association between the central macular thickness (CMT) and visual acuity (VA).[44,45] Recent evidence suggested that foveal disorganisation of retinal inner layers (DRIL) is more useful in predicting vision loss than CMT.[46] DRIL was associated with reduced retinal function and thus poorer vision, even in eyes with early DR.[47] It was postulated that this structural biomarker would be a strong predictor of visual deterioration in DR.[46,47]

Table 2-2. The diabetic retinopathy severity scale based on the Modified Airlie House Classification and the predictive rate of progression (adapted from the NHMRC guidelines[48])

DR severity	DR levels	Description of lesion	Rate of progression (%)			
			To PDR		To high-risk stage	
			1 year	3 years	1 year	5 years
No DR	10	No diabetic retinopathy is visible. No other lesions that could be mistaken for diabetic retinopathy.	Not documented			
	15	Retinal haemorrhage present without any definite MAs.				
Mild NPDR	20	MAs only with no other diabetic lesions present.	5	14	1	15
	35	MAs and one or more of the following: HMA < standard photograph 2A, HE, Venous Loops, Q SE, Q IRMA, Q VB.				
Moderate NPDR	43	(A) MAs and one or more of the following: moderate IRMA > standard photograph 1A in four quadrants or severe IRMA > 2A in one quadrant. (B) MAs and one or more of the following: mild IRMA < standard photograph 8A in 1-3 quadrants	12-26	30-48	8-18	25-35
	47	(A) Showing both characteristics for level 43 (B) MAs and one or more of the following: mild IRMA in four quadrants (C) MAs and one or more of the following: severe IRMA in 2-3 quadrants (D) MAs and one or more of the following: VB in one quadrant				
Severe NPDR	53	(A) Showing > 2 characteristics for level 47 (B) MAs and one or more of the following: severe IRMA in 4 quadrants (C) MAs and one or more of the following: moderate to severe IRMA > standard photograph 8A in >1 quadrant (D) MAs and one or more of the following: VB in > 2 quadrants	52	71	15	56

PDR	61 - 64	Level 20 – 53 (mild to severe NPDR) and scatter treatment scars present			
	65	(A) NVE ≥ ½ DA in ≥ 1 quadrant (B) NVD < standard photograph 10A		46	75
PDR high-risk	71	Showing one of the below characteristics: NVD ≥ standard photograph 10A NVD < standard photograph 10A plus VH and/or PRH NVE > 1/2 DA plus VH and/or PRH VH and/or PRH > 1 DA	Severe visual loss (VA≤5/200) develops in 25-40% within 2 years.		
PDR advanced	85	Showing one of the below characteristics: Macula obscured by VH and/or PRH Retinal detachment at the centre of the macula			
DMO		Retinal thickening within 2-disc diameters of macular centre	Can occur at any stage of DR		
CSMO		Retinal thickening within 500 μm of macular centre or hard exudates within 500μm of macular centre with adjacent thickening	Can occur at any stage of DR		

Abbreviations: CSMO, clinically significant macular oedema; DA, diameter area; DMO, diabetic macular oedema; DR, diabetic retinopathy; HE, hard exudate; HMA, Haemorrhages/ Microaneurysms; IRMA, intraretinal microvascular abnormalities; MA, microaneurysms; NPDR, non-proliferative diabetic retinopathy; NVD, neovascularisation on disc; NVE; neovascularisation elsewhere; PDR, proliferative diabetic retinopathy; PRH, pre-retinal haemorrhages; Q, questionable; SE, soft exudate; VB, venous beading; VH, vitreous haemorrhages.

2.2.2. Management of diabetic retinopathy

Irreversible blindness due to DR can be reduced by appropriate and effective treatment. The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that timely sight-saving treatment could save up to 90% of people with diabetes from developing severe vision loss. In general, there are three main steps to managing DR which are monitoring for sight-threatening progression, providing timely treatment for STDR, and managing DR risk factors.

2.2.2.1 Assessment of diabetic retinopathy

DR severity scales assist clinicians and researchers in assessing and grading the level of DR that may be present in an eye, thus assisting clinicians in their decision making. Up until now, the gold standard for DR classification in a research setting has been the Modified Airlie House Classification, developed by the ETDRS group who graded the retina using dilated fundus photography and categorised DR severity into seven stages, with two more categories for DMO (**Table 2-2**). Initially, 7-standard field (7SF) fundus photography taken using 30º fundus camera was required for grading DR.[49] However using wider field (45º) cameras, 2-field fundus photography showed an agreement rate of 80-85% and a sensitivity of 74-87% compared to 30º, 7SF fundus photography; thus, its use was also accepted for clinical practice.[50]

Other imaging methods which provide a broader view of the retina in a single-field image (termed as "wide-angle"; ranging from 60º to 200º) have been introduced and may improve our knowledge of DR.[51-53] The use of 200º ultrawide-field (UWF) photography, in particular, has garnered significant interest as it can visualise approximately 80% of the retinal area compared to the 30% visualised by 7SF ETDRS photos. Several studies have shown a comparable ability between UWF and 7SF photos in determining DR severity (kappa = 0.77-0.84)[54-56] and diagnosing CSMO (kappa = 0.73-0.77)[56] in the retinal area captured within 7SF images. However, Silva et al. reported that around 30% of the observed DR lesions in their UWF photos were predominantly located outside the standard ETDRS fields, and they labelled these as predominantly peripheral lesions (PPLs).[54] Similar findings were also reported by the DRCR Retina Network (Protocol AA), where 41% of observed eyes had PPLs (mainly haemorrhages and microaneurysms).[55]

The retinal periphery has been recognised for decades as an important region in the assessment of DR. However, visualising and assessing this area, which sits outside the standard ETDRS fields, has only recently become possible due to the advent of UWF imaging.[57] The importance of this region has since been demonstrated by Silva and colleagues who showed that the presence of PPLs in eyes with no PDR at baseline was significantly associated with a 3.2-fold and 4.7-fold increase in risk of progression by 2 or more DR severity levels and progression to PDR, respectively, compared to eyes without PPLs, even after adjusting for duration of diabetes and HbA1c levels.[58] Another study by Talks *et al.* compared standard 2-field 45º photography with UWF retinal imaging for identifying evidence of neovascularisation, and they found that when the area outside standard 2-field imaging was assessed, around 30% more areas of neovascularisation could be identified in patients with referrable DR.[299] These findings may suggest that there is a group of patients with a higher risk of DR progression that cannot be identified using standard retinal imaging; therefore, evaluation of the peripheral retinal can be crucial. Based on these results, an updated DR grading method which includes PPLs as a measure of DR severity may be required. However, further studies are needed to assess the applicability of this in the screening setting.

Fundus fluorescence angiography (FFA), a retinal imaging modality that uses an intravenous dye injection to visualise retinal vasculature and grade any leakage in the retina, provides a means of assessing lesions in the retinal microvasculature, such as macular ischaemia, in much greater detail.[59] In FFA, the size of foveal avascular zone (FAZ) area and capillary nonperfusion have been used to evaluate the degree of DMI. Both parameters were correlated with DMI, as a bigger FAZ area and wider nonperfused area suggested worse DMI.[40] However, FFA is time-consuming, invasive, and is associated with a small, but not insignificant, risk of severe anaphylaxis (1 in 2,000 - 20,000).[48,60] FFA is therefore not used for screening or routine assessment purposes in DR but is used to plan the treatment of sight-threatening disease.

The ETDRS classification system has been simplified by the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) study group in order to save time and reduce the cost associated with grading DR severity.[61] Ultimately, these two classifications have been widely used in the research setting and have made it possible to compare the findings from different studies in different populations.

Despite being recognised as well-standardised grading systems, the Modified Airlie House and WESDR classifications are hard to remember and are impractical for use in clinical settings. It was not until 2003 when Wilkinson *et al.* created a simpler but comparable grading system for use in clinical practice. This grading system, known as the International Clinical Disease Severity Scale (ICDSS) for DR and DMO, consists of 5 levels of DR and 4 levels of DMO (**Table 2-3**).[62] This new classification system has been endorsed by many national health authorities globally and has been used in multiple treatment guidelines.[48,63-66]

With the advent of optical coherence tomography (OCT), a classification system was also introduced for assessing DMO. OCT is a non-invasive imaging modality that utilises light to image tissue and is the current standard of care for diagnosing DMO, as it is able to image all ten layers of the retina in real-time and provide quantitative data, such as retinal thickness, to help define DMO severity and progression/regression.[67] Retinal thickness is measured within the ETDRS grid that is centred on the macula and its value is then compared with the reference database from each OCT machine (**Figure 2-3**). The macula is confirmed as being oedematous if the central retinal thickness exceeds two standard deviations beyond the normal mean value.[68] Other than retinal thickness, data regarding retinal volume can also be beneficial, particularly for assessing non-focal (diffuse) oedema.[69]

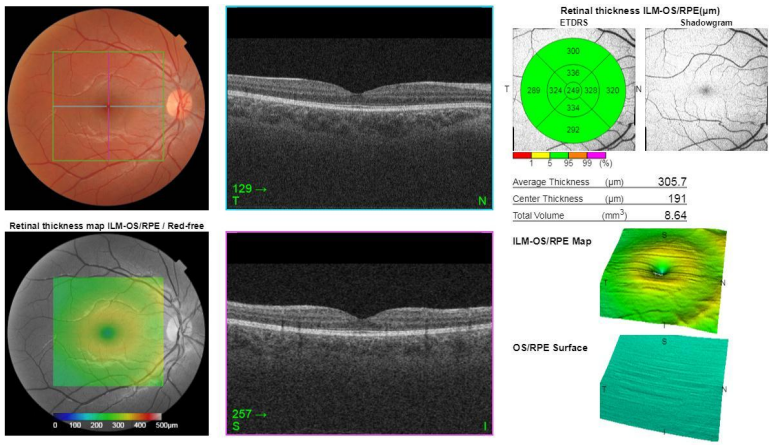


Figure 2-3. Example of the output from the optical coherence tomography machine showing retinal structure and quantitative data of retinal thickness and volume data

Table 2-3. The International Clinical Diabetic Retinopathy and Diabetic Macular Oedema Disease Severity Scales

	Severity Level	**Findings Observable upon Dilated Fundus Examination**
Diabetic Retinopathy	No DR	No abnormalities
	Mild NPDR	Microaneurysms only
	Moderate NPDR	More than just microaneurysms but less than Severe NPDR
	Severe NPDR	Any of the following: - More than 20 intraretinal haemorrhages in each of 4 quadrants - Definite venous beading in 2+ quadrants - Prominent IRMA in 1+ quadrant And no signs of proliferative retinopathy
	PDR	One or more of the following: -Neovascularisation -Vitreous/preretinal haemorrhage
Diabetic Macular Oedema	Absent	No apparent retinal thickening or hard exudates in the posterior pole
	Mild DMO	Some retinal thickening or hard exudates in posterior pole but distant from the centre of the macula
	Moderate DMO	Retinal thickening or hard exudates approaching the centre of the macula but not involving the centre
	Severe DMO	Retinal thickening or hard exudates involving the centre of the macula

Abbreviations: DMO, diabetic macular oedema; DR, diabetic retinopathy; IRMA, intraretinal microvascular abnormalities; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

2.2.2.2 Diabetic retinopathy risk factors

There are several risk factors reported to have an association with the development of DR and its progression. They can be divided into modifiable factors and non-modifiable factors.

Modifiable risk factors

a. Hyperglycaemia

Chronic hyperglycaemia is the main factor responsible for the development of diabetes-related complications, including DR; therefore, maintaining good glycaemic control is important. The Diabetes Control and Complications Trial (DCCT) compared conventional therapy (HbA1c target of <9%) vs intensive therapy (HbA1c target of <7%) in patients with T1DM and found that the reduction in DR incidence risk was significant (by 76% for the development of any DR and by 47% for the development of severe NPDR and PDR).[70] The DCCT/EDIC study, which followed the DCCT's study population over a 28-year period, estimated that the cumulative incidence of progression from no retinopathy to sight-threatening DR was 1.0% over 5 years in patients who had an HbA1c level of 6.0%, compared to 4.3% over a 3-year period in those who had an HbA1c level of 10%.[15] A similar finding was also reported by the United Kingdom Prospective Diabetes Study (UKPDS) which studied DR in T2DM patients, as they suggested that tight blood glucose control could decrease the risk of DR. They reported that a 1% decrease in Hb1Ac was associated with a 35% reduction in DR development in T2DM patients.[71] Moreover, the WESDR study group found that the level of glycaemia was also a significant risk factor for increasing DMO incidence in both types of diabetes.[72]

A more recent study group has suggested that maintaining an HbA1c level of <7.0% could build a good "metabolic memory" which reduces the risk of DR progression for up to 4 years.[73] Such a legacy effect results in the retina of an individual with good metabolic memory being able to respond to short term changes in glycaemic levels, helping to prevent any DR from worsening. All of these findings emphasise the importance of maintaining good glycaemic control.

On the other hand, a rapid improvement in blood glucose or HbA1c control can trigger DR worsening, especially in people with a history of poorly controlled diabetes. Although

most cases of progression are only temporary, people who have pre-existing moderate DR can potentially experience sight-threatening progression.[74-76] Performing eye examinations is therefore advised not only during, but also, more importantly, before starting intensive treatment; thus, deliberation can be given as to whether the intensive insulin treatment is suitable (considering the risk of rapid DR progression to STDR), to planning treatment if progression occurs, or to putting in place a plan to monitor patients more closely in situations where rapid improvement is crucial, such as pregnancy.

b. Hypertension

High blood pressure (BP) affects DR through the impacts of stretching the retinal vascular endothelium which triggers a rise in the expression of VEGF and its receptors.[77,78] The UKPDS reported that a reduction in the mean systolic BP of T2DM patients by 10 mmHg could reduce the risk of a 2-step or more deterioration on the ETDRS scale to a relative risk of 0.75. Moreover, those with tight BP control were less likely to need photocoagulation treatment.[79] Tight BP control was proven to reduce 3 or more steps of DR progression by 34%, and DR did not progress if the systolic BP was kept between 120-140 mmHg.[73] A similar effect was reported in T1DM patients by the WESDR group.[80]

In comparison, diastolic BP was an important predictor of DMO development. The WESDR group found that having diastolic BP within the fourth quartile range had a 3.3-fold and 2.1-fold increase in the risk of developing DMO in the subsequent four years in those with T1DM and T2DM, respectively.[81] All of these publications emphasise the importance of controlling BP to reduce DR and DMO development. It should also be noted that in contrast to glycaemic control, it has been suggested that BP control does not have a legacy effect, hence the importance of sustained blood pressure control.[82]

c. Hyperlipidaemia

Many studies investigated the association between hyperlipidaemia (elevated serum lipid levels) and DR. The WESDR group found that an elevated serum total cholesterol was incrementally associated with DR severity and the appearance of hard exudates at the macula (and CSMO) in T1DM patients.[83] Similarly, the ETDRS group found that high total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were correlated with the presence of hard exudates in the posterior pole. Both in T1DM and T2DM,

patients with a total cholesterol level of >6.21 mmol/L were 2.0 times as likely to have hard exudates compared to those who had a total cholesterol level of <5.17 mmol/L. Moreover, an LDL-C level equal to 4.14 mmol/L or more had twice the risk of developing hard exudates compared to an LDL-C level lower than 3.36 mmol/L.[84] Various studies reported comparable findings.[85,86] Other than total cholesterol and LDL-C, DR severity and DMO development were also associated with a higher level of triglycerides and decreased level of high-density lipoprotein cholesterol (HDL-C).[86-88] Administration of lipid-lowering drugs (such as fenofibrate and simvastatin) was associated with a reduction in DMO, exudate formation, and DR progression.[89,90]

d. Body mass index (BMI)

There have been conflicting findings regarding the association between DR and BMI. Several studies found that there was a positive correlation between DR and both BMI and waist to hip ratio, especially in obese individuals (BMI >31 kg/m^2 for men and >32 kg/m^2 for women).[86,91,92] A meta-analysis by Zhu *et al.,* which included only prospective cohort studies, found that obesity increased the risk of DR in patients with T2DM and that obesity was a risk factor for NPDR but not for PDR.[93] In an older population (50-74 years-old), the odds ratio for developing DR was 1.3 (95% CI 1.0 –1.7) per SD increase in BMI, after adjusting for age, sex, and type of diabetes.[86] In contrast, a community-based study in Indonesia found that BMI had an inverse correlation with DR in T2DM[94] which is supported by other Asian population studies.[95,96] Aside from the mentioned studies, there were also studies that found no association between BMI and DR in T2DM patients.[97,98]

Non-modifiable risk factors

a. Duration of diabetes

Extensive studies have consistently shown that duration of diabetes has a strong association with the presence of DR. The WESDR group observed T1DM patients with an age of diagnosis less than 30 years and 30 years or more. In both groups, the prevalence of DR and PDR were significantly higher in those with a diabetes duration of 15 years or more (77.8% - 97.5% had DR and 15.5% - 67% had PDR) compared to those with a diabetes duration of less than 5 years (17% - 28.8% had DR and 1.2% - 2% had PDR).[99,100] A New Zealand study found that for each additional year of diabetes, there was a decrease

of 14% in the expected mean time to development of DR.[101] A similar trend has also been demonstrated for T2DM. The Melbourne Visual Impairment Project reported that the group with DR had a significantly longer duration of diabetes (median 14.0, range 0-44 years) compared to those who did not have DR (median 5.0, range 0–57 years).[102] Likewise, an epidemiological study in Indonesia, which observed T2DM patients aged over 30 years, described that duration of diabetes was an independent risk factor for the presence of DR and STDR.[103]

b. Pregnancy

Despite the debate as to whether DR is more common in males or females, a recent population-based meta-analysis reported that females were at a higher risk of developing visual disturbance or blindness due to DR than men in all age groups, and this risk was aggravated if these diabetic women fell pregnant.[104] The DCCT study group compared pregnant and non-pregnant women with T1DM and found that pregnancy increased the risk of progression of DR by 1.63-fold in women who received intensive treatment and by 2.48-fold in women who received conventional treatment. Although the changes that occurred during pregnancy were mostly temporary, any progression to sight-threatening disease was not reversible and the risk of this persisted for up to 12-months after delivery.[105] Based on this data, it can be concluded that women of reproductive age, which coincides with the working-age group where DR presence peaked, who fall pregnant have a higher risk of developing vision-threatening eye disease.

2.3. Diabetic Retinopathy in Pregnancy

As presented in the previous section, pregnancy can affect diabetes control and its complications, including progression of DR to STDR.[13,106,107] The section below presents a more in-depth discussion of the effect of pregnancy on DR from prevalence and progression rate through to the implications of DR for the mother and baby.

2.3.1. Global reports of diabetic retinopathy in pregnancy

The first reported case of DR and its progression in pregnant women with diabetes was published in 1950. Beetham observed 200 pregnancies with diabetes and found that although the majority of patients had no DR, those who had DR progressed significantly, and 4 out of 44 patients developed proliferative retinopathy during pregnancy. Among 18

pregnancies with PDR in early pregnancy, only one had a successful pregnancy.[108]

Following Beetham's report, many studies have emerged that report DR prevalence and its progression rate among pregnant women with pre-existing diabetes. The reported prevalence varies widely, ranging from 8% to 63%,[109,110] and the reported progression rates similarly vary significantly. Temple *et al.* found that DR progression occurred in only 5% of their cohort study population with type 1 diabetes during pregnancy in the United Kingdom, which is negligible when compared to a progression rate of 41.5% in a study in Israel of which 77.5% suffered sight-threatening progression to PDR.[111,112] There are very few articles reporting the effect of pregnancy on DMO development. Between 5 – 27% of pregnant women with T1DM were reported to have developed DMO in one prospective and one retrospective study in T1DM patients and only one study investigated the presence of DMO in T2DM pregnant women, with a reported rate of 2.5%.[13,110,113]Moreover, since the advent of OCT, there has yet to be a study that has used OCT to assess for DMO in a pregnant population at the time of writing this literature review.

It is clear that DR in pregnancy is a significant clinical issue; however, it is difficult to determine the true disease burden, due to the very wide range of reported DR prevalence in this patient group. Moreover, available publications have mostly only involved women with T1DM, with very few studies reporting the DR status in pregnant women with T2DM.

2.3.2. Data on the prevalence of diabetic retinopathy during pregnancy in Australia

In Australia, only one study has been published in this field.[114] Horvat and colleagues studied pregnant women with "latent" (now known as GDM) and "clinical" (pre-existing) diabetes from the Royal Women's Hospital and performed full routine ocular examinations during pregnancy and after delivery in 1967-1978. This study recruited 107 latent and 172 clinical diabetic women and followed them up over a 12-year period. None of the latent diabetic women had DR at the initial assessment nor developed any DR during pregnancy. These findings are supported by Sugiyama *et al*. in their study which showed none of their 1267 gestational diabetes patients had DR during pregnancy.[115] In contrast, 47 women with clinical diabetes were reported to have had DR early on their pregnancy (40 had background DR, 7 had proliferative DR), and 14.5% of this group

experienced worsening of their DR during pregnancy.

However, despite the stated long follow-up period, most of the participating patients (119 of 172 cases) were followed up for less than 4 years, and the patients' retinas were only assessed using direct ophthalmoscopy, which provides a very limited field of view (10-15 degrees, representing less than 15% of the retina). Most of all, this study was completed more than 40 years ago, and it is most likely that the vast majority of patients had T1DM. **Therefore, more contemporary data on the prevalence of DR and its progression in Australian pregnant women with pre-existing diabetes (both type 1 and type 2) is needed in order to develop robust management guidelines for this growing high-risk group of patients.**

2.3.3. Ophthalmic changes during pregnancy

Various studies have attempted to explain how pregnancy can affect DR progression, and several theories have been proposed. However, the pathogenic mechanism of this relationship is still not fully understood. During pregnancy, a woman's body changes and adapts to allow the foetus to grow while also preparing for delivery and breastfeeding. These changes occur due to the effects of specific hormones which also affect vascular and inflammatory processes throughout the body, including the eye.[116] Although all parts of the eye experience pregnancy-induced changes, the retina, with its dense vascular structure, is particularly vulnerable.

Retinal blood flow

Pregnant women experience an increase in heart rate, cardiac contractility, and plasma volume, and a decrease in peripheral vascular resistance, which results in a rise of approximately 40% in cardiac output.[117] In the non-diabetic eye, these changes are countered by retinal vasoconstriction to maintain constant retinal blood flow (RBF). However, this autoregulatory ability is impaired in a diabetic eye, causing significant changes to the RBF.[118]

Several reports have found conflicting results in RBF changes during pregnancy. Schocket and colleagues found that RBF was significantly decreased during pregnancy and speculated that this change may induce DR progression by exacerbating retinal ischaemia and hypoxia.[119] Although a decrease of RBF in pregnancy also was reported

by Larsen *et al.*, they did not find a correlation between this decrease and DR worsening.[120] On the other hand, Kohner argued that pregnancy induces a worsening of retinopathy by increasing the RBF.[121] This finding is supported by more recent publications which suggest that an increased blood flow adds stress to the retinal circulation, which is already disturbed due to diabetes.[17,122] The hyperdynamic circulatory state of the retina may thus contribute to DR worsening by causing endothelial damage from additional shear stress to the capillary wall.

Hormonal changes and angiopoietic factors

At the beginning of pregnancy, progesterone expression increases to facilitate implantation of the fertilised ovum into the endometrium.[123] Other hormones, such as oestrogen, prolactin, and human placental lactogen (hPL) also markedly increase. These pregnancy hormones regulate maternal physiological changes which facilitate foetal development by indirectly increasing insulin resistance to allow for foetal nourishment.[124] For women who already have diabetes, these hormonal changes magnify the stress of hyperglycaemia.[116] Progesterone and hPL were found at higher levels in pregnant women with DR compared to those without DR. Additionally, among pregnant women with DR, cotton wool spots were most often observed in the second trimester when the concentrations of these hormones were at their highest compared to the other trimesters.[125] Although further studies are required to understand the direct effect of hPL on DR, this hormone can activate prolactin receptors which have pro-angiogenic properties.[126] However, progesterone has been directly correlated with DR progression by upregulating intraocular vascular endothelial growth factor (VEGF), the most potent pro-angiogenic factor for producing new vessels.[127]

VEGF has a key role in the development and maintenance of foetal and placental vasculature in early pregnancy.[128] Systemic VEGF levels are higher in pregnant women compared to non-pregnant women, and reduced VEGF expression has been linked with defective embryogenesis and foetal loss.[129,130] Angiogenesis during pregnancy is tightly regulated by a delicate balance between pro- and anti-angiogenic factors. Unfortunately, some pregnancies undergo pathological angiogenesis which is caused by an unbalanced expression of angiogenic factors.[131,132] This occurs not only systemically, causing preeclampsia, but also in the eye, contributing to the development of PDR. A study in Denmark that observed 103 pregnant women with T1DM found that a higher level of

serum insulin-like growth factor (IGF-1), another pro-angiogenic factor, was associated with a worsening of DR. IGF-1 circulation was also found to be upregulated following a rapid improvement of glycaemic control, a known risk factor for DR progression.[133]

The effect of systemic hypertension in pregnancy

Other than physiological changes, retinal vasculature is also affected by pathological changes that occur in pregnancy. Pregnancy-induced hypertension, which is defined as an elevated BP that develops after 20 weeks of gestation without any history of hypertension before conception,[134,135] affects 6-10% of all pregnancies and it was associated with development of retinopathy.[136-138] Rosenn et al. reported that 50% of their diabetic pregnant cohort that had pregnancy-induced hypertension experienced DR worsening during pregnancy.[138] This finding was supported by a more recent study which found that women with pregnancy-induced hypertension had a significantly higher incidence of severe DR than those without (24% vs 6%).[139] Another study in Malaysia reported that among 154 non-diabetic pregnant women with hypertensive disorder (including pregnancy-induced and chronic hypertension), 32.5% of them were found to have hypertensive retinopathy.[137] Although it has different features than DR, both conditions have similar mechanisms in their pathophysiology that involves inflammation, endothelial dysfunction, and angiogenesis.[140] Hypertensive retinopathy is distinguished by the presence of focal or generalised arteriolar narrowing, which is an early retinal autoregulatory response to control the increased blood flow to the retinal capillaries. It may be accompanied by exudative changes such as retinal haemorrhages, cotton wool spots, or oedema, which represent more severe stages.[141]

Visual impairment from hypertension in pregnancy is mainly seen in pregnant women with severe preeclampsia (BP >160/110 mmHg with involvement of multisystem abnormalities) and eclampsia (preeclampsia with convulsion and/or unexplained coma).[142,143] The visual symptoms may include blurred vision, photopsias, and visual field defects. Although rare, complete blindness has been observed in patients with severe preeclampsia/eclampsia from resultant serous retinal detachments or cortical cerebral oedema. However, most of these cases regressed or reverted to normal without treatment soon after delivery.[143,144] With the improvement of antenatal care and early detection of preeclampsia, such severe cases are now rarely seen (if at all) in current studies.[137,145,146]

2.3.4. Risk factors and predictors of sight-threatening progression during pregnancy

Timely, sight-saving interventions can reduce the risk of blindness and can be delivered most effectively if clinicians are able to predict which patients are most at risk. Currently, the known risk factors that contribute to the progression of DR during pregnancy are similar to the key risk factors in the non-pregnant population, including a longer duration of diabetes,[111,112,138,147] poor metabolic control,[13,148,149] and hypertension.[110,112,150]

On top of this, as explained earlier, being pregnant itself is a strong predictor for DR progression, increasing the risk by nearly 2.5-fold compared to non-pregnant diabetic women.[149] Some studies also reported that a rapid reduction of blood glucose during pregnancy, development of preeclampsia and the baseline severity of DR and/or DMO in early pregnancy were all risk factors for the worsening of DR.[110,112,148,151,152] However, due to a lack of agreement, there is still very limited information available on the predictors of progression towards sight-threatening disease during pregnancy. As a result, it is unclear which pregnant women are most at risk of developing sight-threatening disease and need to be seen more frequently.

2.3.5. Retinal vascular imaging in pregnancy

Other than identifying clinical risk factors for DR progression, we can also potentially predict which pregnant patients are most at risk of developing sight-threatening diseases using retinal imaging techniques. It may be possible to predict the progression risk of DR by assessing the extent of retinal non-perfusion since retinal non-perfusion has been associated with DR progression in non-pregnant populations.[153] In diabetic eyes, non-perfusion can be identified by a loss of previously perfused capillaries, by reduced retinal vessel density and by enlargement of the foveal avascular zone area (FAZ).[154]

As previously stated, the gold standard for assessing ischaemic changes in the retinal vasculature has been fundus fluorescein angiography (FFA), which involves an intravenous injection of dye.[59,155,156] Although dye injections have not been found to have a teratogenic effect in pregnant animals,[156,157] it crosses the placenta and so may cause harm to the foetus.[156,158] Therefore, they are not recommended to be performed during pregnancy unless they are absolutely necessary.[48,156]

Recently, a novel imaging modality that offers similar functionality to FFA was introduced. Optical coherence tomography angiography (OCTA) is an ancillary function of OCT that uses motion contrast to detect blood flow from an analysis of voxel decorrelation in repeated two-dimensional cross-sectional retinal scans (B-scans) of a single location on the retina. This modality is able to map out and reconstruct the three-dimensional retinal vasculature. The flow is the difference in the OCT signal between two sequential B-scans where the non-mobile tissue's signal is stationary and thus looks identical.[159,160] OCTA provides not only structural but also functional information (i.e., blood flow and vessel integrity). Moreover, since it does not require a dye injection, OCTA provides a safer approach for evaluating DR in pregnancy and has a potential role in assisting clinicians in the management of DR during pregnancy.[156,161,162]

Clinical utility of OCTA in Ophthalmology

OCTA has several unique advantages over FFA in the clinical setting. This modality is non-invasive, has a quicker acquisition time, is repeatable, and provides quantifiable, depth-resolved, high-resolution images of the retinal vasculature.[155,156] OCTA allows for separate quantification of the radial peripapillary capillary plexus and the deep and superficial capillary plexuses of the macula.[163]

Although it has a number of advantages, OCTA does have some limitations. It requires a longer fixation time to capture the image and fixation failure results in the presence of motion artefacts. Motion artefacts are seen as a misalignment in the vessel image (**Figure 2-4 D**). OCTA is also more prone to other types of artefacts, such as projection artefacts (where false flow signals are seen deep to true retinal vessels) and blink artefacts (shown as a black line on the OCTA images due to eye blinking) (**Figure 2-4**).[164] As an example, in one study, it was reported that 25.6% of OCTA scans were uninterpretable, mostly due to poor-quality images containing artefacts.[155] This has led to the ongoing development and refinement of OCTA software to eliminate these artefacts.[164,165]

Scan size is another OCTA limitation, as there is a trade-off between scan size and image resolution. Although OCTA can currently be performed with a scan size of up to 12 mm x 12 mm, the best image resolution can only be achieved using a 3 mm x 3 mm scan size at the present time; thus resulting in a smaller field of view.[161,166] However, the use of a wide-field OCTA montage, which is a combination of several OCTA images, has been

proposed to allow for a larger view with the same image resolution.[163] It can be seen that although OCTA has some limitations, ongoing improvements and modifications will further increase its use and application in ophthalmology well into the future.

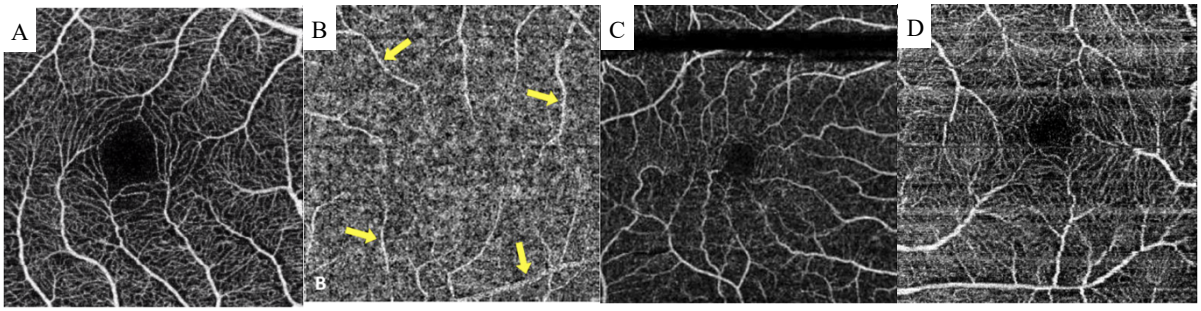


Figure 2-4. Example of optical coherence tomography angiography images

A) High quality image; **B)** Projection artefacts (yellow arrows) in the outer retina layer from the superficial layer; **C)** Blackline of a blink artefact; **D)** Motion artefacts in white arrows. Images courtesy of the Topcon User Manual Ophthalmic Data System and www.opticianonline.net.

Clinical utility of OCTA in diabetic retinopathy

Previous studies have reported OCTA findings in DR. Several biomarkers can be studied using OCTA including vascular remodelling of the FAZ border, FAZ area enlargement, microaneurysms, areas of non-perfusion (capillary dropout), vessel density, and neovascularisation.[154,167,168] Using the in-built software containing automated algorithms, quantitative measurements of several FAZ parameters and vessel density has made it possible to assess vascular changes more objectively and consistently, especially for monitoring DR progression.[154,169] Overall, a larger FAZ area and lower vessel density are associated with a worsening of DR.[167,170] With its ability to distinguish between vascular plexuses, OCTA offers better visualisation of the capillary nonperfusion area that cannot be shown clearly in a whole inner retinal layer image.[171] Al-Sheikh *et al.* found that the superficial capillary plexus (SCP), intermediate capillary plexus (ICP) and deep capillary plexus (DCP) were all affected by DR and suggested that the decrease in the VD was most prominent in the superficial retinal layer.[170] On the other hand, a more recent study reported that changes in the FAZ area and VD were more evident in the DCP compared to the SCP in both types of diabetes.[172] These findings support those of a previous study which suggested that parafoveal VD in the DCP was more representative of NPDR severity compared to the VDs in the SCP and DCP.[173] Despite the conflicting research

findings, OCTA allows a more detailed assessment of DR changes in the retinal vasculature of the posterior pole of the fundus than does FFA.

Another significant aspect of OCTA is its potential use in predicting DR progression. Several authors have found that OCTA could visualise very early signs of diabetic vascular changes around the fovea in diabetic eyes even before DR was clinically apparent.[174-176] Moreover, Sun *et al.* demonstrated that OCTA parameters could be used as a novel predictor for DR worsening. This study group followed a total of 129 patients with diabetes for at least 2 years and routinely examined their eyes using OCTA. Among their study population, 13.7% and 8.8% of them experienced DR progression and DMO development, respectively. The group found that in the eyes with progression, FAZ area, VD, and fractal dimension in the DCP were able to predict DR progression, and the VD in the SCP was able to predict DMO development.[153] Although more studies are needed to support this finding, this imaging modality shows promise in improving DR management in the future.

As explained in the previous section, pregnancy-induced changes can affect the eye; hence appearance of the retinal vasculature during pregnancy may differ from the appearance outside of pregnancy. To the writer's knowledge, there are no OCTA studies on pregnant women with DR, but few studies have compared OCTA parameters between pregnant and non-pregnant women with no prior medical or ophthalmic history and reported conflicting findings. Chanwimol *et al.* found that in their healthy pregnant group (>28 weeks of gestation), the mean VD value in the SCP was lower, but the mean VD in the DCP was higher compared to their healthy non-pregnant group. No difference was found in the size of the FAZ area.[177] Another study by Kızıltunç *et al.* demonstrated that the VD in both the SCP and DCP were significantly higher in the pregnant group than in the non-pregnant group, specifically in the parafovea and perifovea region of the SCP. They also found that in the centre or foveal region, the VD of the SCP in the pregnant group was lower, which was consistent with the finding of an increased FAZ area in the same group compared to the counter group.[178] Despite the dissimilar findings, it can be concluded that the VD of the DCP during pregnancy is relatively higher than the general population.

Thus far, only one study has assessed OCTA parameters in pregnancies with diabetes. Sugimoto *et al.* observed pregnant women with GDM and pre-existing diabetes without

any DR and compared the measurements with healthy non-pregnant controls. They found that the FAZ areas in diabetic pregnant eyes in the SCP and DCP were not significantly different from the control group, but the FAZ area in the SCP was inversely correlated with gestational age. An assessment of VD was not performed.[179] Unfortunately, due to the characteristics of the control group, an assessment of factors that may affect the FAZ (pregnancy or diabetes) could not be performed, thus limiting the interpretation of the results. More importantly, the sample size was small, particularly in the pre-existing diabetes group (n = 13 women) where the most changes were expected to be observed. **Further studies are thus clearly needed to understand the differences in OCTA parameters during pregnancy with diabetes in order to determine the role of OCTA imaging in the management of DR in pregnancy.**

2.4. Impact of Diabetes and Diabetic Retinopathy during Pregnancy

Hyperglycaemia in pregnancy is associated with a higher risk of adverse pregnancy outcomes, both to the mother and the foetus. Moreover, it has been reported that the severity of DR in early pregnancy is a strong predictor of adverse pregnancy outcomes.[180] In this section, the adverse outcomes of pregnancy with pre-existing diabetes and DR are discussed.

Perinatal mortality due to diabetes has decreased enormously after the invention of insulin therapy and dedicated antenatal care program for women with diabetes. Nonetheless, the mortality rate remains higher compared to non-diabetic pregnancies.[181] Furthermore, high blood glucose levels during pregnancy increase the risk of developing complications, such as congenital malformations (by 2-fold) and stillbirth (by 5-fold).[26,182] Maternal outcomes are also affected by diabetes. Women with pre-existing diabetes have a higher risk (3 to 12-fold) of developing pregnancy-induced hypertension (preeclampsia or gestational hypertension) and an increased risk (2 to 4-fold) of needing an emergency caesarean section.[4,26] Although these outcomes occur more frequently in pregnancies with T1DM than T2DM, they still occur in women with T2DM, indicating that equal attention should be given to the clinical management of both types of diabetes in pregnancy.[183]

Adverse pregnancy outcomes can also be associated with the existence of pre-existing diabetes complications, such as nephropathy and DR. Higher rates of preterm birth and preeclampsia were reported in women with either diabetic nephropathy or DR before

pregnancy compared to those without.[184,185] It also has been reported that women with pre-existing PDR, in particular, experienced worse adverse outcomes compared to their counterparts with no DR or mild DR.[109,186,187] Moreover, Klein *et al.* reported that DR severity was a strong predictor of adverse pregnancy outcomes, namely miscarriage, congenital malformation and perinatal mortality.[187] In addition, the incidence of DR progression was also associated with birth weight-related complications.[152] Women with DR progression had 5.4-fold, 2.7-fold, and 0.5-fold higher risk of having babies that were small for gestational age (SGA), that had low birth weight, and that were large for GA (LGA), respectively compared to women with stable DR. These findings might indicate that worsening of the microvascular disease in the eye could reflect the overall microvascular condition.

2.5. Management of Diabetes and Diabetic Retinopathy in Pregnancy

In the 1989 Saint Vincent declaration, it was stated that optimising medical care is important so that pregnant women with diabetes can achieve similar pregnancy outcomes to pregnant women without diabetes.[6] Unfortunately, as discussed in the previous section, this goal was not achieved until recently. Since pregnancy affects not only diabetes complications but also diabetes control, special considerations need to be taken when managing diabetes in pregnancy. This section discusses the steps that need to be executed in the management of pregnancy with pre-existing diabetes to improve pregnancy outcomes, particularly preventing adverse visual outcomes.

2.5.1. Pre-pregnancy care

The adverse pregnancy outcomes of mothers with pre-existing diabetes can be reduced significantly by controlling the appropriate risk factors. Structured pre-pregnancy care and a dedicated multidisciplinary team have been proven to reduce the development of adverse outcomes in women with pre-existing diabetes, both for the mother and the offspring.[4,188] The pre-pregnancy period is a crucial time for addressing blood glucose and blood pressure control, ceasing teratogenic drugs (e.g. lipid-lowering drugs [such as statins], renin-angiotensin system antagonists, and non-insulin glucose-lowering drugs [except metformin]), and commencing folic acid supplementation. Striving for good glycaemic control (HbA1c ≤6.5%) is important when planning for a pregnancy.[189,190] Furthermore, pre-existing diabetes complications should be assessed for and managed

accordingly to reduce the risk of undesirable outcomes, including DR.

Any efforts to optimise control are also beneficial for preventing DR progression. Glycaemic optimisation prior to pregnancy is associated with a tendency towards the reduced DR progression during pregnancy compared to delaying the optimisation of hyperglycaemia until pregnancy occurs.[13,105] Although rapid improvement to euglycaemia before pregnancy or in early pregnancy can trigger DR worsening, such rapid control is imperative in order to reduce the risk of more significant pregnancy complications. Therefore, close monitoring of eye health in this phase is strongly recommended to ensure appropriate treatment can be given if necessary. A dilated eye examination should ideally be done before pregnancy or as early as possible in the pregnancy. Any cases of DR requiring therapy should ideally be treated before pregnancy to reduce the risk of vision loss thereafter.

Counselling on the risk of DR worsening during pregnancy and the importance of routine DR screening during pregnancy is essential and should be explained to women with pre-existing diabetes who are planning a pregnancy. A report from the Atlantic Diabetes in Pregnancy (Atlantic DIP) study showed that among the women who received appropriate eye screening examinations, the proportion who attended pre-pregnancy care was significantly higher than the proportion who did not (58.4% versus 17.2%).[150] This finding might suggest that those who received pre-pregnancy care were more likely to adhere to DR screening recommendations than those who did not. Further investigation is needed to confirm this correlation. Unfortunately, attendance rates for pre-pregnancy care have been relatively low in Australia, with rates of 27.8% and 12% in T1DM and T2DM patients, respectively.[30] The main reasons for non-attendance were lack of awareness about the availability of diabetes-dedicated pre-pregnancy care and unplanned pregnancies.[191]

2.5.2. Antenatal care

As previously discussed, physiological changes in pregnancy induce insulin resistance later on in pregnancy (>16 weeks gestation). This change causes fluctuations in insulin requirements and can worsen the hyperglycaemic state in women with pre-existing diabetes if treatment is not adjusted accordingly.[190] Therefore, once women are pregnant, intensive glycaemic monitoring is required to ensure optimal control.[189,190] The essential

steps are: 1) ensuring the blood glucose targets are achieved; 2) measuring and adjusting the insulin requirement to manage the hormonal milieu of pregnancy; and 3) adjusting meal plans to cope with nausea and vomiting in pregnancy and changes in appetite associated with late pregnancy[5]

Table 2-4 shows the blood glucose target for pregnant women with pre-existing diabetes. Aside from daily blood glucose monitoring, HbA1c measurements are important since they can help to predict outcomes. An assessment of the HbA1c should thus be done in each trimester. Recently, continuous glucose monitoring (CGM) has been introduced to help monitor daily glucose levels, and its use has been shown to create better outcomes than conventional capillary blood glucose monitoring in pregnancies with T1DM.[192] In Australia, the use of CGM in pregnancies with T1DM has increased following the National Diabetes Services Scheme (NDSS) subsidy in April 2017.

Table 2-4. The blood glucose targets for pregnant women with pre-existing diabetes (adapted from the Australasian Diabetes in Pregnancy Society guidelines[189])

	Preconception	**Pregnancy**	
		Trimester 1	**Trimester 2 & 3**
Daily blood glucose monitoring			
Fasting & pre-meal (mmol/L)	<6.0	<5.3	
1-hour post-meal (mmol/L)	<8.5	<7.8	
2-hour post-meal (mmol/L)	<7.5	<6.7	
HbA1c (%)*	≤6.5	≤6.5	≤6.0

* **I**f it can be achieved without causing hypoglycaemia.

During pregnancy, women with pre-existing diabetes are recommended to see a multidisciplinary team more frequently (**Table 2-5**). This may include seeing an obstetrician, endocrinologist, diabetes educator or diabetes nurse practitioner, dietician, midwife, general practitioner (GP) and psychologist. Many pregnancy clinics, especially those who have diabetes-specific care, offer integrated care between these specialists. However, eyecare has not yet been incorporated into this model and therefore, in addition to this care, these women also need to visit an optometrist or ophthalmologist for eye screening examinations to monitor their DR status, as well as other possible complications.

Table 2-5. A sample of diabetic pregnant woman's appointment schedule[193]

	Visit time points
First trimester	Every 4 weeks
Second trimester	Every 2-3 weeks
Third trimester	Every week
After delivery	Around 6 weeks after delivery

2.6. Diabetic Eye Screening Examination

Eye screening examinations have been and continue to be the cornerstone of preventing vision loss from DR. Prevention programs promote regular eye screening examinations to facilitate the detection of early signs of sight-threatening DR. The Diabetic Retinopathy Barometer Study, a global research effort by the International Diabetes Federation involving eight countries, found that 65% of people with diabetes visited an ophthalmologist when they had already experienced some degree of vision alteration, and a further 6.2% presented with PDR, by which stage it was already too late for effective treatment.[194] This report shows that screening examinations are crucial and this program has been proven to reduce the risk of severe vision loss from DR by up to 94%.[195]

There is currently strong international agreement on diabetic eye screening guidelines for the general population with type 1 or type 2 diabetes. It is recommended that all people with diabetes should have dilated fundus examinations at least biennially, or annually for patients at higher risk.[48,196] The International Council of Ophthalmology recently published new recommendations for DR screening programs that varied based on the level of resource available in a given clinical setting. If patients are found to have mild or moderate NPDR in high-resource settings, they are recommended to be re-screened in the following 6-12 months and 3-6 months, respectively. On the other hand, if similar disease is found in patients living in low- to intermediate-resource settings, less frequent examinations are advised.[197] Unfortunately, recent studies have reported low compliance with these recommended guidelines.[198-200] As a result, personalised diabetic eye screening schedules have been introduced to reduce visits for patients at low risk, in the hope that better compliance can be achieved.[201] However, this approach cannot yet be applied to the pregnant population due to the lack of knowledge regarding the identification of high-risk individuals.

2.6.1. Diabetic eye screening examinations in pregnancy

As mentioned previously, prevention programs that encourage regular eye screening examinations to detect early signs of sight-threatening DR have been promoted, including during pregnancy. Due to the risk of more rapid progression, more frequent examinations are recommended for diabetic women who fall pregnant.[48,189,196,197] Unfortunately, there are multiple guidelines on DR screening during pregnancy, and these offer inconsistent recommendations regarding the recommended frequency of follow-up.[9,202] A summary of guidelines that discuss DR in pregnancy can be seen in **Table 2-6**, although it should be noted that these guidelines do not distinguish between women with T1DM and T2DM.

Because of the inconsistency between guidelines and their lack of inclusion of potential clinical risk factors that may indicate a higher risk of developing sight-threatening disease in their recommendations, determining screening intervals for patients with diabetes who become pregnant is challenging. A particular concern is that frequent examinations may place an intolerable burden upon patients who already need multiple health appointments during pregnancy, which may lead to non-attendance. Therefore, determining an appropriate and well-received screening schedule for this population is imperative.

The International Council of Ophthalmology recommends that pregnant women with pre-existing diabetes undergo a retinal screening assessment after their first visit for antenatal care and again at 28 weeks of gestation if no DR is found. An additional retinal assessment at 16-20 weeks is advised for pregnant women with DR in early pregnancy.[197] The American Diabetes Association recommends more general scheduling which involves an assessment of the retina in every trimester and again at 12-months after delivery.[196] In Australia, the Australasian Diabetes in Pregnancy Society (ADIPS) recommends that pregnant women with pre-gestational diabetes have their eyes reviewed at least 3-monthly from the time of conception if risk factors for DR progression are present (including the presence of retinopathy at the first examination, a rapid improvement in glycaemic control, or a long duration of pre-existing diabetes defined as more than 10 years).[203] In comparison to these guidelines, the Australian National Health and Medical Research Council (NHMRC) is less specific and only states that pregnant women with pre-existing diabetes should have their eyes checked in their first trimester and then be followed closely throughout the remainder of their pregnancy (level of evidence: IV).[48] Both of these recommendations were developed based on international data due to a lack of

Australian data.

As discussed previously, DR screening and management guidelines during pregnancy vary significantly due to inconsistencies and gaps in the literature, which has made it difficult to generate suitable local guidelines. Additionally, current follow-up recommendations during pregnancy are based on adaptations of information on the risk of DR progression in non-pregnant women, which may not be entirely appropriate. Therefore, updated data is needed for the development of better Australian DR guidelines to help physicians manage pregnant patients with pre-existing diabetes.

Moreover, the success of a screening program is determined not only by its disease detection rate, but also by its ability to reduce health costs by decreasing unnecessary referrals to eye hospitals. In the United Kingdom, implementation of a DR photographic screening clinic for diabetic eye disease in pregnancy proved to be effective in reducing unnecessary costs.[204] However, two main concerns were found. Firstly, patients were initially screened late in their pregnancy (in the second or third trimester). Secondly, many participants only had one visit and did not attend scheduled follow-up visits. These issues are significant barriers to optimal eyecare in this population.

Patient attendance is crucial for the success of any screening program. Unfortunately, many studies have reported that patient attendance at DR screening programs in the general population have remained suboptimal.[195,198,199,205] Since more frequent DR screening is recommended for pregnant women, it is expected that their adherence may be even less satisfactory. Nevertheless, the Atlantic DIP study cited that the attendance rates in their study population was 70.7% for attending at least one examination during pregnancy and 60.3% for attending an adequate number of eye examinations (defined as having at least two examinations in different trimesters).[150] These numbers have since improved to 74.1% for attending an adequate number of eye examinations during pregnancy following the integration of their eye screening program into their antenatal care visits.[206] This remains the only study to report the adherence rate of a population to eye screening recommendations at the time of writing.

Table 2-6. Recent guidelines for diabetic retinopathy screening in pregnancy

Guidelines	Year of last publication	Recommendations for Pregnancy with Pre-existing Diabetes		
		First assessment	Follow-up examinations during pregnancy	
			No DR in baseline	DR in baseline
American Diabetes Association[196]	2018	Before pregnancy or in the first trimester	Monitor every trimester and for 1 year postpartum as indicated by DR severity	
Australasian Diabetes in Pregnancy Society (ADIPS)[203]	2005	Not stipulated	Review at least 3-monthly if there is a) presence of DR at baseline; b) rapid improvement in blood glucose control; or c) long duration of diabetes	
Australia National Health and Medical Research Council (NHMRC)[48]	2008	In the first trimester	Not stipulated	Followed closely throughout pregnancy
Canadian Ophthalmological Society[207]	2017	Before pregnancy or in the first trimester	Repeat assessments as indicated (based on DR severity and its progression rate) during pregnancy and through the first-year post-delivery	
Danish Ophthalmological Society[208]	2018	As soon as pregnancy is recognised	3-6 months postpartum if no systemic risk factors are found and there is good glycaemic control	Review at between 24-28 weeks of pregnancy, then at 3-6 months postpartum. In patients with severe DR, systemic risk factors, or with rapid DR progression, an additional examination at 32-36 weeks is advised
Hongkong Primary Care[209]	2013	In the first trimester	Close follow-up throughout pregnancy and for one year postpartum	
International Council of Ophthalmology[197]	2018	Before pregnancy or after the first antenatal care appointment	Review at 28 weeks	Review at 16-20 weeks
International Diabetes Federation[210]	2009	At the first prenatal visit	Repeat examinations in each trimester	
Iranian Clinical Practice Guidelines[211]	2016	In the first trimester	Monitor closely throughout pregnancy	

Malaysia Clinical Practice Guidelines[64]	2011	Before pregnancy or in the first trimester	Every 3 months	If mild NPDR, review every 3 months. If worse, refer to an ophthalmologist
National Institute for Health and Clinical Excellence (NICE)[212]	2015	Before pregnancy or in the first trimester (if not performed in the past 3 months)	Review at 28 weeks of pregnancy	An additional retinal assessment at 16-20 weeks, then at 6 months after delivery if referable DR was found during pregnancy
New Zealand Ministry of Health[213]	2016	In the first trimester	If no modifiable risk factors present, continue with normal two- or three-yearly screening	If minimal DR, more frequent screening during their pregnancy needed. If mild or more advanced DR, close monitoring by an ophthalmologist.
Pacific Eye Institute[63]	2009	Early in the first trimester	Continue with annual screening	If DR is detected frequent screening throughout pregnancy. If more than minimal DR, refer to an ophthalmologist.
Royal College of Ophthalmologist[214]	2013	Following the first antenatal check-up	Review at 28 weeks	Review at 16-20 weeks, then again at 28 weeks
Scottish Intercollegiate Guidelines Network (SIGN)[215]	2010	Before pregnancy	Examine in each trimester	
Spanish Society of Diabetes and Spanish Vitreous and Retina Society[216]	2017	Before the end of first trimester	Not stipulated	
Singapore Ministry of Health[217]	2014	Before pregnancy, followed by another one early in the first trimester.	Depends on the results of the first trimester examination	
Sri Lanka College of Obstetricians & Gynecologists[218]		At the first antenatal visit	Examine in each trimester	
The Vision 2020 Program of the IAPB for Latin America[219]	2011	Before pregnancy or in the first trimester	Every 3 months	

2.7. Importance of This Thesis

The data to date regarding the prevalence and incidence of DR during pregnancy varies widely, with most studies predating recent advances in endocrinology management. As a result, the ideal management and follow up of these patients is still largely unknown, as it is hard to draw conclusions from such disparate results. A further limit to the applicability of many of these past studies is their exclusive inclusion of women with type 1 diabetes. Due to changes in diet and lifestyle habits, we will face an increasing number of pregnant women with type 2 diabetes in the future. Thus far, there are only 4 studies in the last 10 years that investigated pregnancy-induced progression of DR in type 2 diabetic patients.[13,109,147,150] Three of these studies had a very small sample size (N= 25-51), and the other did not have any postpartum follow-up. Additionally, we have found that there is no current data on the prevalence and incidence of DR during pregnancy in Australia. More current and higher quality evidence is therefore needed to develop an updated national DR guideline for these patients. **Hence, the purpose of my thesis was to collect and analyse clinical data from pregnant diabetic women who were followed up throughout their pregnancy and up to 3-months postpartum (Aim 1). Moreover, in an effort to utilise the most advanced retinal imaging modality currently available, optical coherence tomography angiography, my thesis also aimed to assess its utility in evaluating changes in the retinal vasculature of pregnant diabetic patients (Aim 2). Information gathered from this prospective study will inform the development of new management guidelines for this unique, but growing, group of patients.**

As discussed earlier, the most significant issue with a diabetic eye screening program is patient non-attendance. Because it affects the outcomes of patient care, we wish to understand the issues behind this non-attendance, especially when patients who do not attend have an increased risk of DR compared to those patients who do.[220] Many studies reported a range of issues relating to patient adherence, from the perspectives of patients and care providers', to system-level issues. Studies with a patient-centred approach have suggested an emphasis on patient knowledge, attitudes, and health beliefs to encourage patient compliance.[221] During pregnancy, the issues raised relating to patient attendance include a lack of knowledge about the risk of DR progression during pregnancy, a lack of pre-pregnancy counselling, and the distance between the antenatal clinic and the eye clinic making it hard for pregnant women to travel alone.[204] **In Australia, no study has yet reported on the factors related to patient adherence to recommended eye screening guidelines during pregnancy; therefore, this**

thesis also aimed to determine the factors related to patient adherence to Australia's recommended eye screening guidelines within our patient population (Aim 3).

CHAPTER 3: GLOBAL ESTIMATES OF DIABETIC RETINOPATHY PREVALENCE AND PROGRESSION RATE IN PREGNANT WOMEN WITH PRE-EXISTING DIABETES

(Systematic Review and Meta-analysis)

3.1. Overview

As presented in the previous section, pregnancy can affect diabetes and its complications. It has also been associated with DR progression including the development of sight-threatening disease. Various authors have tried to report prevalence of DR in pregnancy and its progression – however their differing methods and inclusion criteria have resulted in varied results. These disparate findings have resulted in a world-wide lack of consensus with guidelines regarding the management of DR in pregnancy. More precise estimates from high quality studies are thus needed to inform the development of robust management guidelines on DR in pregnancy. Therefore, a systematic review was conducted which aimed to estimate the prevalence of DR and sight-threatening DR (STDR), and the rates of DR progression in pregnant women with pre-existing diabetes, based upon currently available literature. The findings from this part of the study will not only provide clearer information about the overall burden of DR in pregnancy, but also will show the gaps in the literature in this field so that better research can be conducted to provide more robust evidence.

In this chapter, the materials and methods of the systematic review and meta-analysis are described. Results from two analyses, the pooled prevalence of DR in pregnancy and the progression rate of DR during pregnancy, are presented along with an assessment of heterogeneity within the included studies. This meta-analysis was registered on the PROSPERO database (registration number CRD42020119643).

3.2. Methods

3.2.1. Literature search

Literature search strategies were developed with assistance from Jim Berryman, the

liaison librarian at the Brownless Biomedical Library at the University of Melbourne (**Appendix A1**). The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement was used as guidance for this systematic review.

A systematic search was performed to identify studies that investigated and reported the occurrence of DR in pregnant women with pre-existing diabetes (T1DM or T2DM that was diagnosed before pregnancy). English-language articles were retrieved from three databases (Medline/Ovid, EmBase, and Scopus). The search terms that were used were: "pregnant" or "pregnancy" and "diabetic retinopathy". Further keywords to identify diabetes type were not used because, after reviewing the literature from the 1950s to the present day, it was clear that there has been a great degree of variability in the description and definition of diabetes in pregnancy throughout this time. In an attempt not to omit any publication with relevant data, the type of diabetes was not restricted in search strategies, with the final decision to include or exclude a paper in the meta-analysis being made on the basis of an assessment of either its abstract or full text. The final search was conducted on 18 October 2019.

Elimination of irrelevant citations and duplications was performed by manually screening the title and abstract of the articles using reference managing software (EndNote). Full texts of the remaining papers were screened to assure that the studies met the inclusion criteria. Additionally, manual searches of the reference lists of relevant review articles and major studies also were conducted. These processes were performed by two independent reviewers (FW and Dr Rathika Kandasamy [RK]), and any disagreement regarding whether a paper should be included for review was settled by a third reviewer (LL).

3.2.2. Inclusion and exclusion criteria

Generally, this review made no restrictions on patient setting, time period of study, or geographical location. Any observational study, whether prospective or retrospective, that investigated and reported the number of patients with/without DR during pregnancy, directly or indirectly (investigated as non-primary outcomes) was included. Reviews, books and book chapters, guidelines, conference presentations, editorials, letters, comments, news/ newspaper articles and systematic reviews were excluded.

The final articles that were included were then assessed again for their relevance to each

of this review's aims. Depending on the outcomes reported, some papers contributed to just one of the review objectives whilst others contributed to both.

a) Prevalence of diabetic retinopathy in pregnancy

For this part of the review (objective 1), studies involving pregnant women with pre-existing diabetes (either T1DM or T2DM or both) in whom DR was measured at any trimester up to delivery were included. Studies that did not specifically report the prevalence of DR but presented count data that could be used to calculate prevalence were also included. Studies where the prevalence of diabetic retinopathy could not be calculated were excluded. This particularly pertained to studies where participating women/pregnancies had been included or recruited based on retinopathy status.

b) Progression rate of diabetic retinopathy during pregnancy

For the second part (objective 2), the review included studies involving pregnant women with pre-existing diabetes (either T1DM or T2DM or both) in whom DR was assessed at 22 weeks of gestation or earlier, where there was further reporting of DR status thereafter up to 12 weeks after delivery. Studies that described the interval change in DR status of subjects (stable, progressed or regressed), enabling calculation of progression rate, were included. Studies that recruited women after 22 weeks of gestation and/or only performed one examination during pregnancy were excluded.

3.2.3. Data extraction

A standardised data attributes spreadsheet was used to assess relevant data. From each of included articles, information on study details and methodology were extracted, such as: year of publication, country, study design, participant characteristics (age, ethnicity, type of diabetes, duration of diabetes at baseline), sample size, year/era of participants' first retinal exam, the retinal assessment method utilised and how DR severity/status was graded. This spreadsheet was tested on several selected papers and refined accordingly as needed. Two reviewers assessed the literature and performed data extraction independently (FW and SR). Any disagreement was settled by consensus or another reviewer arbitrated the conflict (LL). Any potential sources of heterogeneity in sampling,

recruitment, clinical examination, definitions of DR progression and reporting of results between studies were noted.

The outcome data of interest were then extracted based on the review's aims. Although most studies reported their sample as the number of women, some reported as the number of pregnancies. Therefore, this review calculated the outcome estimates as the rate per pregnancy. For studies that reported the number of included women only, it was assumed that each woman was studied only once (one pregnancy) in their data.

a) Prevalence of diabetic retinopathy in pregnancy

For this part of the review, the outcomes measured were the number of pregnancies with and without: 1) any DR and 2) PDR. The number of cases and the corresponding total number of pregnancies assessed (the denominator) were extracted from each of the articles. Data was extracted based on gestational age at the examination. Many studies presented DR grading data at multiple timepoints before pregnancy, throughout pregnancy and the post-partum period. However, since very few studies reported data during the second trimester, this review focused on the prevalence at "early pregnancy" (defined as up to 22 weeks pregnant) and "around delivery" (defined as 23 weeks pregnant until 12 weeks after delivery). If a study reported data at more than one timepoint in any of these time categories, data from the first trimester and third trimester were chosen.

b) Progression rate of diabetic retinopathy during pregnancy

Following the previous aim, this review focused on changes that occurred between "early pregnancy" and "around delivery" for this meta-analysis. The outcome measures in this part included the number of pregnancies with: 1) development of any new DR (from a baseline of no DR); 2) progression by the equivalent of 1-step in DR severity as measured on the 5-step scale of ETDRS[49] (from a baseline of NPDR); 3) progression from a baseline of no DR to PDR; 4) progression from a baseline of any NPDR to PDR; and 5) worsened PDR marked by the development of new neovascularisation, new haemorrhages, reactivation of treated-PDR, or requiring laser treatment during pregnancy.

3.2.4. Assessment of methodology, reporting quality, and heterogeneity

Study methodology and reporting quality were assessed independently by two investigators (FW and RK). Any disagreement regarding this part of the assessment was resolved by a third reviewer with biostatistics expertise (SR). Studies were appraised for the quality of their extracted data for the purposes of each meta-analysis aim with respect to a list of attributes (adapted from Yau *et al.*'s meta-analysis[33]) as shown in **Appendix A2,** specific to each meta-analysis aim. Studies with well-described data and rigorous ophthalmic reports were defined by a score of ≥9 (maximum, 13) for prevalence analysis and a score of ≥12 (maximum, 19) for progression analysis.

3.2.5. Data analysis

The Stata SE version 16.1 (College Station, Texas, USA) command *metaprop-one* was utilised for all meta-analyses by which the reported binomial count data was transformed with the Freeman-Tukey double arcsine transformation. The Dersimonian-Laird random-effects model was used to calculate the pooled estimate of prevalence (objective 1) and progression rate (objective 2) with exact 95% confidence intervals (CIs). These pooled rates were estimated using data only from those studies with similar methodologies and reporting quality (i.e., studies with a quality score of ≥9 for objective 1 and ≥12 for objective 2). Furthermore, a subsequent pooled rates calculation was performed of only those studies with similar DR grading schemes (i.e., studies that used the ETDRS grading system or its modifications including modified Airlie House, WESDR, and modified WESDR methods). Pooled estimates of rates and 95% CIs were presented in forest plots.

The presence of heterogeneity was assessed using the chi-squared test and the magnitude of heterogeneity was assessed using I^2 test. A significant and considerable heterogeneity was defined by an I^2 value ≥75% with a corresponding chi-squared $p < 0.05$.[222,223] Sub-group analyses by study region, study era (pre- and post-St. Vincent Declaration [the establishment of a standard of care for diabetes in 1989 which included optimising care for pregnant women with diabetes and in order to reduce the rate of diabetes related blindness]),[6] and DR grading methods were performed to explore some potential causes of considerable heterogeneity.[222]

3.3. Results

3.3.1. Description and characteristics of included studies

Flowchart of the systematic review and meta-analysis was presented in **Figure 3-1**. A total of 1151 articles were identified from the systematic search. After removing the duplicates, 651 articles were screened for the title and abstract, leaving 61 articles for full-text review. Of these, 36 articles met the inclusion criteria. After assessment of the methodology and reporting quality, only 18 studies had well-reported data and rigorous ophthalmic reports (17 studies with a score of ≥9 for prevalence analysis and 16 studies with a score of ≥12 for progression analysis) so that pooled estimates could be calculated. **Table 3-1** and **Supplementary table S3-1** show an overview of the included articles' characteristics and quality scores.

These 18 included studies were undertaken in 12 countries, the majority of which were developed countries. Seven (38.9%) studies were from the United States (U.S.),[138,148,149,152,224-226] three (16.7%) studies were from British Isles,[113,204,227] two (11.1%) studies from Finland,[122,228] three (16.7%) from Denmark,[13,110,133] and one each from Italy,[229] Israel,[112] and Saudi Arabia.[230] In terms of study design, 15 (83.3%) were prospective cohort studies and three were retrospective cohort studies. The majority of studies (16 studies; 88.9%) only observed pregnant women with type 1 diabetes (T1DM); one study observed women with type 2 diabetes (T2DM) only.[13] A further study observed women with either type of diabetes[204] and presented their results so that data could be extracted and analysed separately for women with T1DM and T2DM. Two studies[106,224] recruited their participants based upon the type of insulin used and presented them as two separate groups (insulin lispro group or regular insulin group) allowing these groups to be analysed separately here too, so that the total of 18 included studies provided a total of 21 groups of subjects (hereafter referred to as "subsets") for analysis. Overall, a total of 1464 pregnancies with T1DM, and 262 pregnancies with T2DM were included in the analysis.

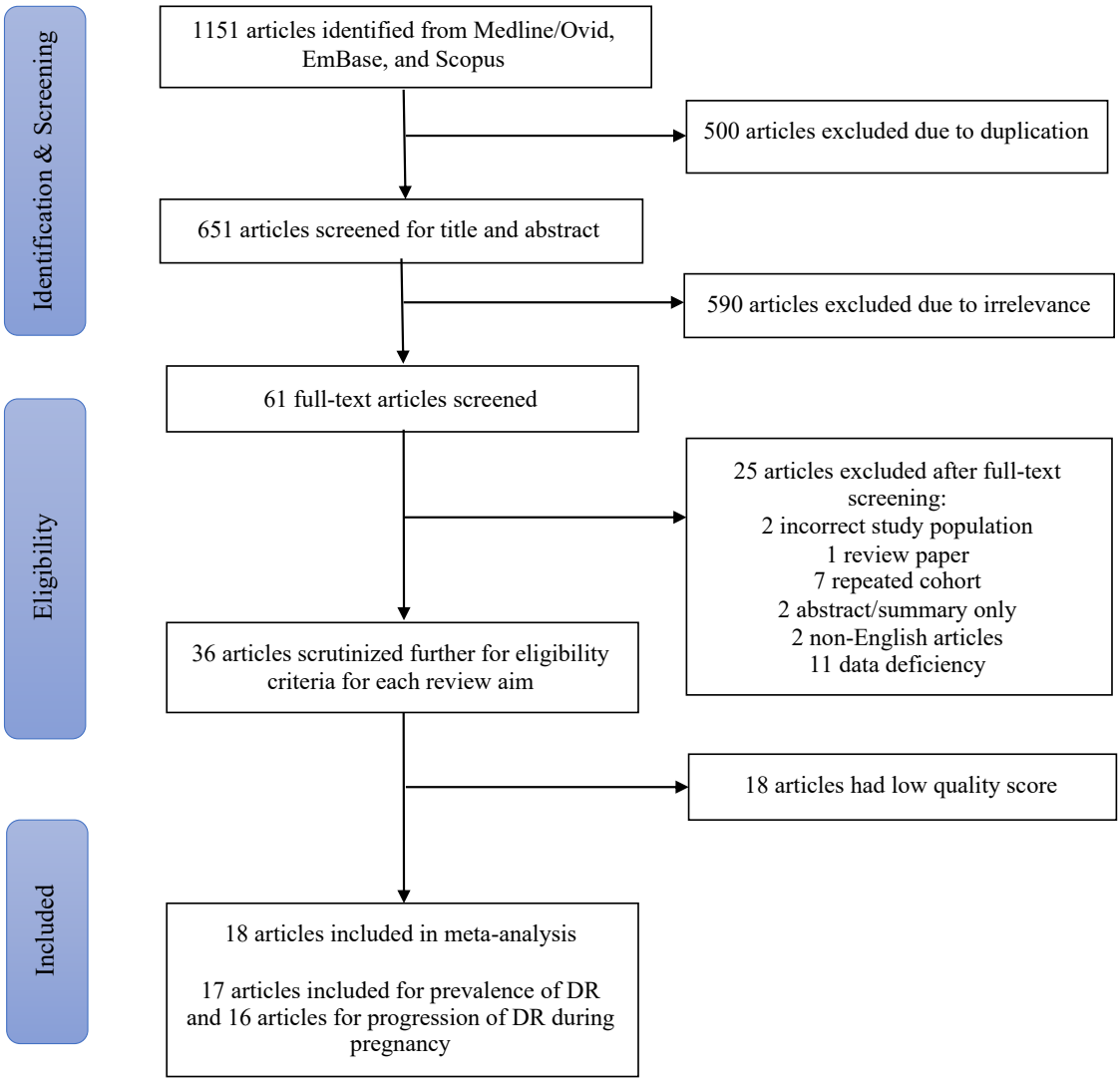


Figure 3-1. Systematic search and selection of eligible literature

Table 3-1. Characteristics of included studies

Study	Subset characteristics	Country	Study Design	Study period	Sample size*	Mean ± SD duration of diabetes (years)	DR Grading Method	Fundus photography	Quality score†	
									1‡	2§
T1DM only										
Arun, 2008[113]		British Isles	RC	1989 – 1998	59	14.4 ± 8	Eurodiab	Yes	**10**	**14**
Axer-Siegel, 1996[112]		Israel	PC	1989 – 1994	65	13.6 ± 6.4 R = 2 - 29	other	Yes	**12**	**16**
Buchbinder, 2000[224]	Insulin lispro group	U.S.	PC	1997 – 1999	12	15.6 ± 8.2	mod Airlie House	Yes	**10**	**12**
	Regular insulin group				42	14.6 ± 8.2				
Chew, 1995[148]		U.S.	PC	1983	155	11.9 ± 7.0	mod Airlie House	Yes	**12**	**17**
Dibble, 1982[225]		U.S.	PC	NR	55	12.44	other	Yes	**10**	**12**
Klein, 1990[149]		U.S.	PC	1982 - 1986	133	11 ± 6.9	mod Airlie House	Yes	**12**	**17**
Laatikainen, 1980[228]		Finland	PC	1978 – 1979	73	R = 1 - 28	other	Yes	**9**	**13**
Lapolla, 1998[229]		Italy	PC	NR	16	11.2 ± 7.1	ETDRS	Yes	**11**	**16**
Lauszus, 2003[133]		Denmark	PC	1993 – 1997	103	NR	WESDR	Yes	**13**	**19**
Loukovaara, 2003[106]	Insulin lispro group	Finland	PC	1998 – 2002	36	16.5 ± 7.9	ETDRS	Yes	**12**	NA
	Regular insulin group				33	14.7 ± 6.2				
McElvy, 2001[152]		U.S.	PC	1978	205	Stable group: 12.4 ± 7.2 Progressed group: 13.8 ± 5.6	mod Airlie House	Yes	**10**	**13**
Moloney, 1982[227]		British Isles	PC	1979 – 1981	53	10.2 ± 0.8	other	Yes	**11**	NA
Phelps, 1986[226]		U.S.	PC	1977 – 1982	38	No DR group: 9.9 ± 2.0 NPDR group: 14.2 ± 1.0 PDR group: 13.6 ± 1.1	mod Airlie House	Yes	**11**	**14**

Rahman, 2007[230]		Saudi Arabia	RC	1998 – 2002	54	12.4 ± 6.4 R = 2 - 24	ETDRS	No or not described	7	**12**
Rosenn, 1992[138]		U.S.	PC	1978	154	Stable group: 10.9 ± 6.8 Progressed group: 13.1 ± 5.8	other	Yes	**9**	**12**
Vestgaard, 2010[110]		Denmark	PC	2004 – 2006	102	Median (R) Stable group: 16 (9–24) Mild progressed group: 16 (11–23) ST progressed group: 17 (15–25)	mod WESDR	Yes	**10**	**14**
T2DM only										
Rasmussen, 2010[13]		Denmark	PC	2003 – 2008	160	Stable group: 3.3 ± 2.8 Progressed group: 6.7 ± 4.6	mod WESDR	Yes	**10**	**16**
Mixture of DM types										
Hampshire, 2013[204]	[T1DM]	British Isles	RC	2006 – 2009	76	NR	UK NSCG	Yes	**10**	**13**
	[T2DM]				102	NR				

* Number of pregnancies.

† Detailed quality scoring was presented in **Supplementary table S3-1**.

‡ Quality score with respect to a prevalence analysis (maximum possible score 13).

§ Quality score with respect to a progression rate analysis (maximum possible score 19).

Graded by 'other' includes trained and accredited grader and diabetes physician.

Abbreviations: DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; mod Airlie House, modified Airlie House classification; mod WESDR, modified Wisconsin Epidemiologic Study of Diabetic Retinopathy; NR, Not reported and could not be deduced; PC, Prospective cohort; PDR, proliferative diabetic retinopathy; R, range; RC, Retrospective cohort; ST, sight-threatening; T1DM, type 1 diabetes; T2DM, type 2 diabetes; UK NSCG, United Kingdom National Screening Committee guidelines; U.S., United States; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

3.3.2. Prevalence of diabetic retinopathy in pregnancy

Eighteen subsets from 16 studies fulfilled the criteria for prevalence analysis of any DR and a similar, but not identical, set of 18 subsets from the same 16 studies (which differed by two subsets from one study that were not included in the first set) fulfilled criteria for prevalence of PDR in pregnancy. The overall prevalence of any DR in early pregnancy was 52.3 per 100 pregnancies (95% CI 41.9 – 62.6; I^2 93.95%), $p < 0.01$) and around delivery was 57.8 per 100 pregnancies (95% CI 45.0 – 70.2; I^2 94.46%, $p < 0.01$). As for PDR, the prevalence in early pregnancy was 6.1 per 100 pregnancies (95% CI 3.1 – 9.8; I^2 83.40%, $p < 0.01$) and around delivery was 8.2 per 100 pregnancies (95% CI 4.3 – 12.9; I^2 84.08%, $p < 0.01$; **Supplementary figure S3-1 and S3-2**).

Figure 3-2 illustrates the pooled prevalence of any DR in early pregnancy and around delivery, limited to studies with a similar DR grading scheme. All of these studies had a prospective cohort design with a sample size ranging from 16 to 205 pregnancies. The pooled prevalences per 100 pregnancies of any DR were 55.5 (95% CI 38.9 – 71.6; I^2 95.97%, $p < 0.01$) and 59.5 (95% CI 36.1 – 80.8; I^2 97.09%, $p < 0.01$) in early pregnancy and around delivery, respectively. There was only one study in a population with T2DM that fulfilled our quality score criteria for these analyses and discernible differences in the prevalences were found between this T2DM study and the T1DM studies (between-group heterogeneity p-values < 0.001). The T2DM study had significantly and substantially lower prevalence of any DR at both timepoints.

The pooled prevalence for PDR in early pregnancy was 6.0 (95% CI 2.2 – 11.2; I^2 85.8%, $p < 0.01$) and around delivery was 6.4 (95% CI 1.7 – 13.4; I^2 87.84%, $p < 0.01$) per 100 pregnancies (**Figure 3-3**). In early pregnancy, the prevalence of PDR in the T2DM study was also much lower than the prevalence in T1DM studies (between-group heterogeneity $p < 0.001$). In contrast, a considerable and significant heterogeneity was observed in the calculation for prevalence of PDR at around delivery within T1DM studies (I^2 80.60%, $p < 0.01$); therefore, subgroup analyses were performed for this outcome. As can be seen from **Table 3-2**, the considerable heterogeneity within T1DM studies in the PDR prevalence (I^2 80.60%) was markedly reduced (I^2 values ≤ 12.3% in all subgroups) after accounting for the study region, study era, and DR grading methods. It is important to note that all three studies with eye exams that predate the St. Vincent Declaration (StVD) were from the U.S. region and all three studies that were performed after the StVD were in Europe; thus, the high heterogeneity within T1DM studies could be ascribed to either of these factors. Given that the pooled prevalence of PDR

around delivery in the U.S. studies that predate the StVD was much higher than in the more recent European studies (16.92 vs 2.30 per 100 pregnancies, $p < 0.001$), this does suggest that the effect of the StVD on patient care may have been a significant factor. With respect to the potential influence of differing DR grading methods, the pooled prevalence in studies that used the Modified Airlie House Classification was significantly higher than in studies that used ETDRS or WESDR (16.9 vs 1.3 vs 3.9 per 100 pregnancies, respectively; $p < 0.001$), suggesting that differing DR grading methods might also play a role in the high heterogeneity within the T1DM studies.

Table 3-2. Pooled prevalence of PDR around delivery (T1DM studies only), by subgroups of interest, using studies with similar quality and DR grading scheme

	N studies	Cases/Total	Prevalence per 100 (95% CI)	I^2 (%)	*p*-value
Study region					
Europe	4 subsets from 3 studies	6/183	2.30 (0.29 – 5.50)	0.0	0.47
United States	3 studies	68/398	16.92 (13.33 – 20.83)	0.0	0.95
Between-group heterogeneity					<0.001
Study era					
Pre-St. Vincent Declaration	3 studies	68/398	16.92 (13.33 – 20.83)	0.0	0.95
Post-St. Vincent Declaration	4 subsets from 3 studies	6/183	2.30 (0.29 – 5.50)	0.0	0.47
Between-group heterogeneity					<0.001
DR grading methods					
Modified Airlie House	3 studies	68/398	16.92 (13.33 – 20.83)	0.0	0.95
ETDRS	3 subsets from 2 studies	2/80	1.28 (0.00 – 6.43)	12.3	0.32
WESDR	1 study	4/103	3.88 (1.07 – 9.65)	NA	NA
Between-group heterogeneity					<0.001

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

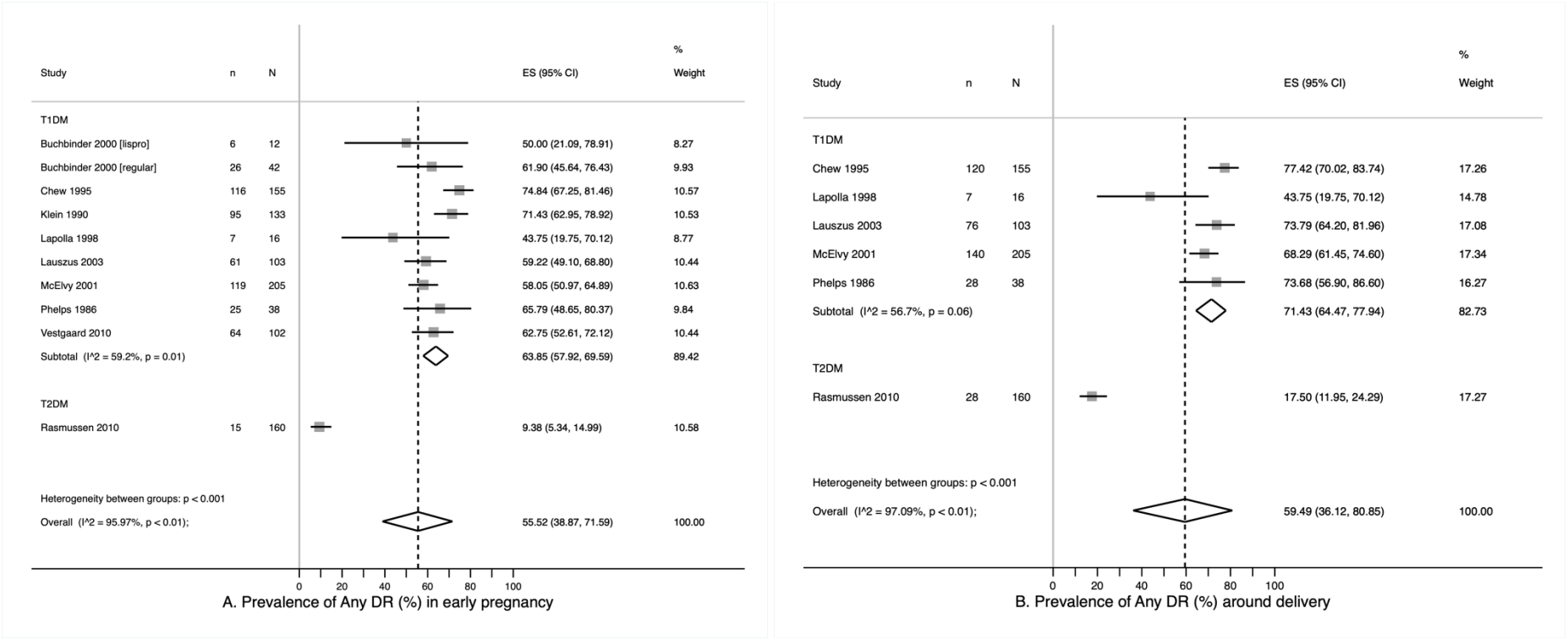


Figure 3-2. Forest plots of prevalence of any DR

A) In early pregnancy and **B)** around delivery using studies with similar quality and DR grading scheme, by type of diabetes. Weights are from random effects analysis. Abbreviations: DR, diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

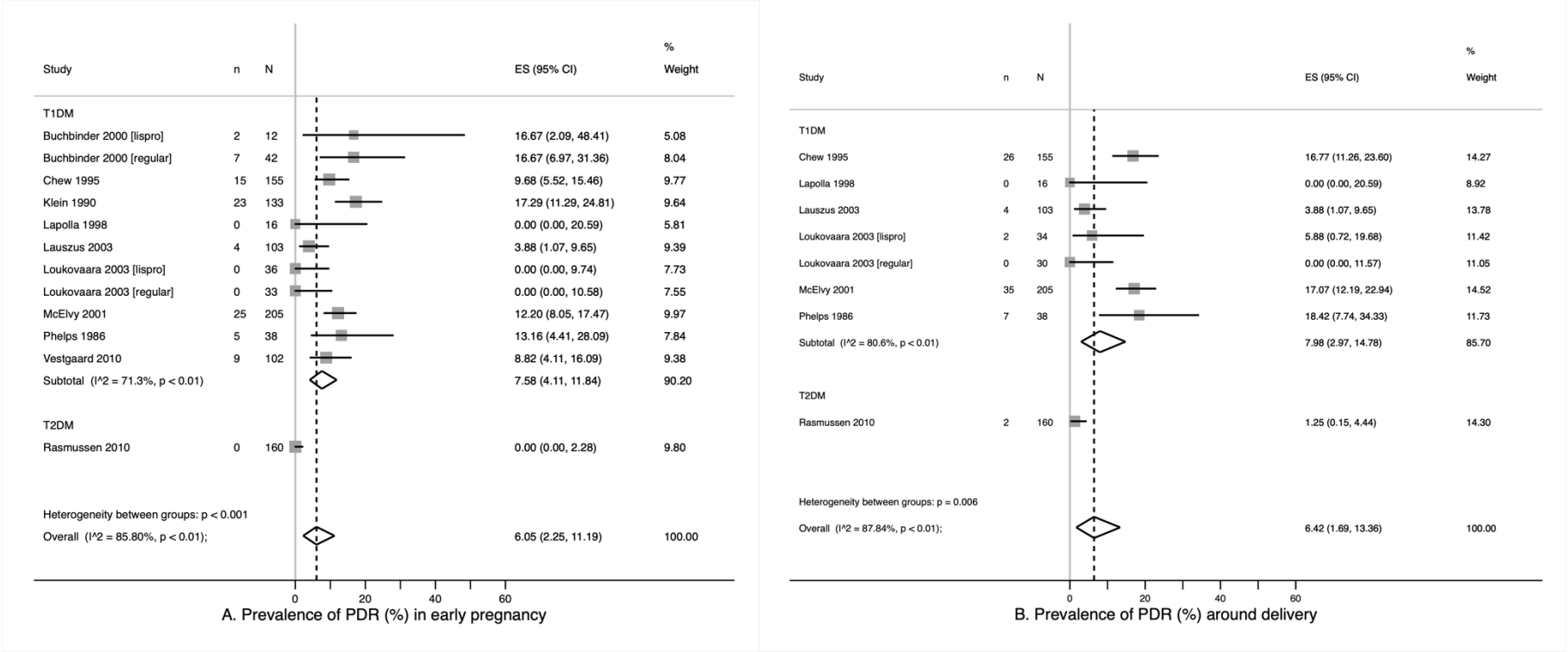


Figure 3-3. Forest plots of prevalence of PDR

A) In early pregnancy and **B)** around delivery using studies with similar quality and DR grading scheme, by type of diabetes. Weights are from random effects analysis. Abbreviations: DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

3.3.3. Progression rate of diabetic retinopathy in pregnancy

There were 16 studies that fulfilled criteria for progression rate analysis. Sixteen subsets from 15 studies provided data for progression from no DR to any DR, 18 subsets from 16 studies provided data for worsened NPDR by at least 1 DR level, 16 subsets from 14 studies for progression from NPDR to PDR, and 12 subsets from 11 studies (all from T1DM studies) for worsened PDR. From early pregnancy to around delivery, the overall progression rate per 100 pregnancies was 15.0 (95% CI 9.9 – 20.8; I^2 67.57%, $p < 0.01$) for no DR to any DR, 30.95 (95% CI 23.2 – 39.2; I^2 75.80%, $p < 0.01$) for worsened NPDR, 6.3 (95% CI 3.3 – 10.0; I^2 37.66%, $p = 0.06$) for NPDR to PDR, and 37.0 (95% CI 21.2 – 54.0; I^2 58.32%, $p = 0.01$) for worsened PDR (**Figure 3-4** and **Figure 3-5**). Among the included articles, only one study[224] observed progression from no DR to PDR (1 out of 16 pregnancies with T1DM in the regular insulin subset).

Among the pooled progression rates above, a high heterogeneity was observed in calculating the progression rate of worsened NPDR (**Figure 3-4B**) that could not be explained by the difference in the type of diabetes and any other subgroup analysis**.** It can be seen from the **Table 3-3** that although significant heterogeneity could be elucidated by the difference in the study region and study era of the included studies, considerable heterogeneity was still observed in the U.S. studies and studies that predate the StVD (I^2 80.1%, $p < 0.01$ and I^2 79.9%, $p < 0.01$, respectively). Meanwhile, heterogeneity between the types of diabetes was only significant for the progression from no DR to any DR ($p = 0.030$). It can be seen that T1DM studies had higher rates of progression compared to the one study with T2DM (**Figure 3-4A**). Heterogeneity between the two types of diabetes was not significant in the worsening of NPDR ($p = 0.660$) and from NPDR to PDR ($p = 0.503$), verifying the decision to pool studies of both types of diabetes into one pooled estimate regardless of the diabetes type (**Figure 3-4B** and **Figure 3-5A**). No T2DM studies were eligible or available to provide data to measure worsening of PDR during pregnancy for comparison.

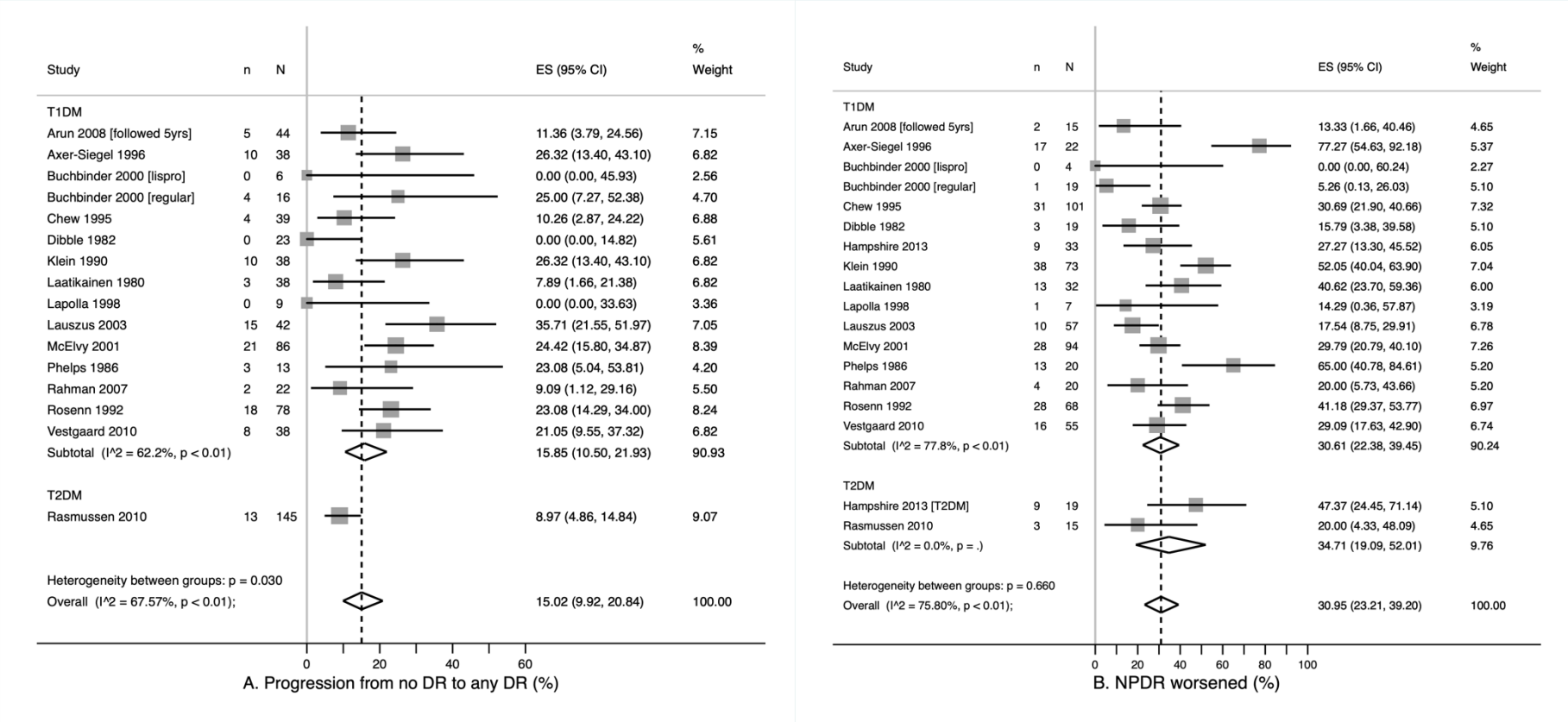


Figure 3-4. Forest plots of pooled progression rate

A) From no DR to any DR and **B**) worsened NPDR by at least 1 DR level from early pregnancy to around delivery using studies with similar quality, by type of diabetes. Weights are from random effects analysis. Abbreviations: DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

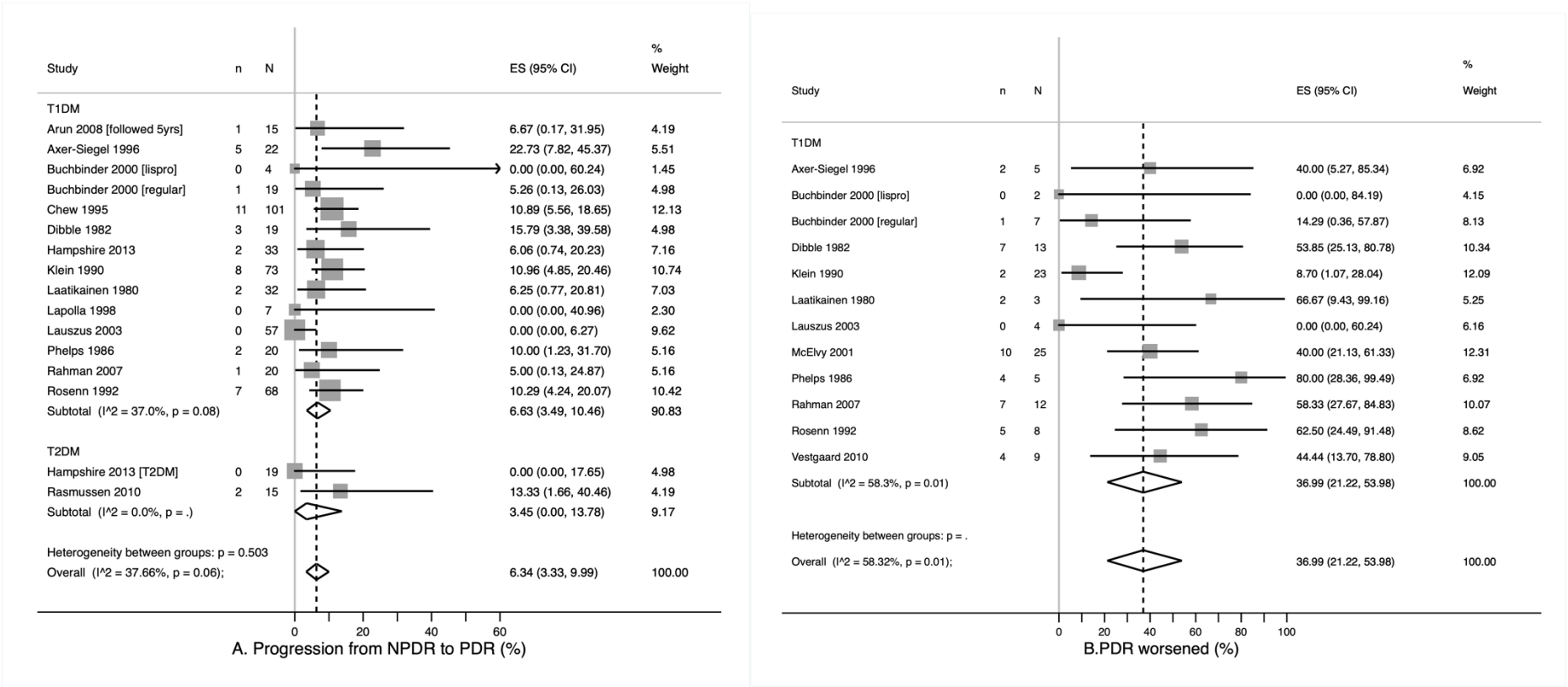


Figure 3-5. Forest plots of pooled sight-threatening progression rate

A) From NPDR to PDR and **B**) PDR that worsened from early pregnancy to around delivery using studies with similar quality, by type of diabetes. Weights are from random effects analysis. Abbreviations: NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 3-3. Pooled DR progression rate of NPDR worsening by at least 1 DR level (in both diabetes type) by subgroups of interest, using studies with similar quality

		Worsened NPDR			
	N studies	**Cases/ Total**	**Progression rate per 100 (95% CI)**	**I^2 (%)**	***p*-value**
Type of diabetes					
T1DM	16 subsets from 15 studies	214/639	30.61 (22.38 – 39.45)	77.8	<0.01
T2DM	2 studies	12/34	34.71 (19.09 – 52.01)	0.0	.
Between-group heterogeneity					0.660
Study region					
Europe	8 subsets from 7 studies*	63/233	26.43 (18.92 – 34.62)	36.4	0.14
Middle East	2 studies	21/42	49.85 (34.45 – 65.26)	0.0	.
United States	8 subsets from 7 studies	142/398	31.42 (20.15 – 43.78)	80.1	<0.01
Between-group heterogeneity					0.031
Study era					
Pre-St. Vincent Declaration	8 studies	170/425	42.77 (31.63 – 54.27)	79.9	<0.01
Post-St. Vincent Declaration	10 subsets from 8 studies*	56/248	20.51 (13.79 – 28.01)	33.7	0.14
Between-group heterogeneity					0.002
DR grading methods					
Modified Airlie House	6 subsets from 5 studies	111/311	31.62 (17.32 – 47.69)	83.8	<0.01
WESDR/ modified WESDR	3 studies*	29/127	22.34 (15.13 – 30.43)	2.9	0.357
ETDRS	2 studies	5/27	17.90 (4.48 – 35.99)	0.0	.
Eurodiab	1 study	2/15	13.33 (1.66 - 40.46)	NA	NA
UK NSCG	2 subsets from 1 study*	18/52	34.26 (21.64 - 48.01)	0.0	.
Other	4 studies	61/141	43.41 (23.20 - 64.76)	82.5	<0.01
Between-group heterogeneity					0.175

* Includes the T2DM study.

Abbreviations: DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NA, not applicable; NPDR, non-proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes; UK NSCG, United Kingdom National Screening Committee Guidelines; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

3.4. Discussion

Pregnancy was reported to increase the risk of DR worsening in women with pre-existing diabetes, which could lead to sight-threatening disease.[105,149] Despite concern regarding the risk of blindness from DR during pregnancy, there has been no agreement on the guidelines of DR management in pregnancy.[9] Uncertainty regarding the magnitude of the impact of pregnancy on DR still exists, mainly due to disparate findings from previous studies. As an attempt to solve this issue, this systematic review and meta-analysis was conducted to estimate the global prevalence and incidence rate of DR progression during pregnancy.

Based on data from high-quality studies, we found that the pooled prevalences of any DR and PDR in early pregnancy were 52.3 (95% CI 41.9 - 62.6) and 6.1 (95% CI 3.1 - 9.8) per 100 pregnancies, respectively. However, considerable heterogeneity was observed in both calculations (I^2 values ≥ 95.97%; *p*-values < 0.01), suggesting that there was clinical or methodological diversity among the included studies. Similar findings were also observed in the prevalences of any DR and PDR around delivery. Analyses limited to studies with similar quality and DR grading scheme showed more homogenous results, especially after categorising the included studies by the type of diabetes of the study population (except for the prevalence of PDR around delivery). We found that the prevalences of any DR and PDR early in the pregnancies of women with T1DM were 63.8 (95% CI 57.9 - 69.6) and 7.6 (95% CI 4.1 - 11.8) per 100 pregnancies, respectively. Around delivery in these pregnancies, the prevalence of any DR was 71.4 (95% CI 64.5 - 77.9) per 100 pregnancies. Unfortunately, only one study could be found with a good quality score and compatible DR grading scheme to provide data for the T2DM population.[13] All calculated prevalences from this study were significantly lower than the pooled prevalences from T1DM studies. This finding aligns with the trend that was observed in the non-pregnant diabetic population which showed that prevalence of any DR and PDR was significantly higher in people with T1DM than T2DM.[33]

From the above, we can see that the high heterogeneity in our estimates was most likely due to the difference in the study methodology (e.g., DR grading schema) and study population characteristics (i.e., type of diabetes). More factors, such as study region and study era, were also observed as the potential cause of the variation in the calculation of pooled PDR prevalence around delivery. Our results revealed that the prevalence in the U.S. prior to the St. Vincent Declaration (StVD) was much higher than in Europe after the declaration (16.9 vs 2.3 per 100 pregnancies). Unfortunately, the interaction between the study region and study era could not be discerned due to the identical contributing data; thus, limiting the interpretation of our findings. However, looking further into the characteristics of the individual study populations, the significant difference in the prevalence might be due to the difference in the study era (pre- and post- StVD) Since the StVD, several improvements have been applied in the management of pregnancy with pre-existing diabetes, such as the implementation of a multidisciplinary team in antenatal clinics and structured pre-pregnancy care.[231] Therefore, it is expected that pregnancy outcomes in the post-StVD era would be better than pre-StVD, including DR. We found

that pregnant women in the U.S. studies seemed to have more severe diabetes, reflected by their relatively higher mean HbA1c and fasting blood glucose, compared to those in the later European studies. Poor glycaemic control is a recognised association with a higher prevalence of PDR in the overall (non-pregnant) diabetic population.[33] Additionally, several other studies have also reported this trend towards reduced adverse pregnancy outcomes in women with pre-existing diabetes since the implementation of the StVD recommendations which support our hypothesis.[4,188,232]

Our meta-analysis also estimated the progression rate of DR from early pregnancy to around delivery. Using studies with similar quality, we found that the pooled progression rate for new DR development was 15.0 (95% CI 9.9 - 20.8), worsened NPDR was 31.0 (95% CI 23.2 - 39.2), progression from NPDR to PDR was 6.3 (95% CI 3.3 - 10.0), and worsened PDR was 37.0 (95% CI 21.2 - 54.0) per 100 pregnancies. Unlike the prevalence, no significant difference was found between the rate of progression in T1DM and T2DM studies, except for the rate for new DR development. The rate for the development of new DR was substantially higher in women with T1DM than T2DM. These may suggest that women with T1DM are at a higher risk to develop new DR during pregnancy, but once women had DR, the risk of DR progression was similar irrespective of the diabetes type. No suitable study was found that reported cases of worsened PDR in the T2DM pregnant population.

High heterogeneity was observed in the pooled progression rate of worsened NPDR, which could not be explained by our predefined subgroup analyses. The reported rate of worsened NPDR ranges widely from 0.0% (95% CI 0.0 - 60.2) in a subset of pregnant women using insulin lispro in U.S.[224] to 77.3% (95% CI 54.6 - 92.2) in an Israeli cohort.[112] The wide variation in the reported rates may be partly attributed to the differing DR grading schemes used by included studies. For example, the Israeli study by Axer-Siegel and associates grouped DR severity into six levels: level 1 (no DR), level 2 (mild NPDR), level 3 (moderate NPDR), level 4 (NPDR), level 5 (PDR), and level 6 (regressed PDR after laser treatment). When we compared its grading definition to the Modified Airlie House Classification that was applied in the U.S. insulin lispro study by Buchbinder *et al.*, the magnitude of difference between DR level in the Israeli study, especially within NPDR severity, was more subtle. Therefore, the study by Axer-Siegel *et al.* had a higher chance of detecting the worsening of NPDR than the other study. However, similar wide

variations was also observed in studies that used similar DR grading schemes (for example, a study by Phelps *et al.* from the U.S. graded DR severity using the Modified Airlie House Classification and reported a progression rate of 65% for worsened NPDR[226]). Another possibility was related to the characteristics of the study cohort. For instance, looking into the proportion of patients with pre-existing DR, Buchbinder's cohort had fewer patients with pre-existing DR than Phelps's; thus, the former study might observe fewer cases of DR worsening, given that the presence of DR before the onset of pregnancy has been associated with an increased risk of DR progression in pregnancy.[112,138]

This review was the first that summarised the prevalence of DR and its progression rate in pregnancy from available studies from around the world. In reviewing the literature, it was evident that the available data in this area is scarce, thus making it hard to assimilate the results and use them to guide our practice. Difference in the study era, study region, or DR grading methods resulted in differing reported results. It was also evident that majority of studies with good methodologies and reporting quality were studies from affluent countries. This discrepancy may highlight the possibility of a higher burden of DR in the actual global population, particularly due to the fact that patients in less affluent settings, in developing countries for example, have limited access to eye health and diabetes care in pregnancy. This lack of access was associated with a more severe diabetes, worse pregnancy outcomes, and higher cases of diabetes-related complications than those patients in affluent settings.[233]

More importantly, most of these studies are outdated and the majority exclusively studied pregnant women with T1DM. Surprisingly, only one study has been conducted in Australia, and this was commenced more than 50 years ago (study period 1967 through 1978), pre-dating many advances in endocrinology and ophthalmology treatment.[114] Due to its low-quality score, this sole Australian study had to be excluded from our meta-analysis. With over half of diabetic pregnant women in Australia having T2DM, the current evidence on DR prevalence and incidence is therefore not reflective of, and may have limited applicability to, the present-day population in Australia. More contemporary evidence is needed to develop updated national DR guidelines for this unique and growing population.

CHAPTER 4: METHODOLOGY

4.1. Overview

In this chapter, the overall methodology for setting up this PhD study, including the research team, ethics approvals, and patient recruitment strategy, is described. Data collection and the process for storing data electronically are also explained. Lastly, the outcomes of patient recruitment are presented. The specific method for each study aim will be covered separately.

4.2. Research Team and Collaboration

The research for this PhD was performed at the Centre for Eye Research Australia/Department of Surgery (Ophthalmology), University of Melbourne (UoM). This study also had the full support of the Department of Optometry and Vision Sciences, UoM and Melbourne Eyecare (MEyecare) Clinic; the Department of Ophthalmology, Royal Melbourne Hospital (RMH) and the Austin-Repatriation Hospital (ARH); the Diabetes and Endocrine Service at the Royal Women's Hospital (RWH); and the Perinatal Department at the Mercy Hospital for Women (MHW).

The main research team consisted of Dr. Felicia Widyaputri (FW), study coordinator; A/Prof. Lyndell Lim (LL), A/Prof. R. C. Andrew Symons (RCAS), and Dr. Xavier Fagan (XF), ophthalmologists; A/Prof. Alexis Shub (AS), an obstetrician; A/Prof. Daryl Guest (DG), an optometrist; A/Prof. Alison Nankervis (AN), A/Prof. Jennifer Conn (JC), and Dr. Christine Houlihan (CH), endocrinologists; and Mrs Sophie Rogers (SR), a statistician. In this thesis, the work that each person has contributed to the study is described by mentioning the person's role followed by their initials, e.g., study coordinator (FW). Further collaborations related to a specific aim will be described in each dedicated chapter.

4.3. Ethics Approval

This study was performed according to the principles of the International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. Research ethics approvals were obtained from the Behavioural and Social Sciences

Human Ethics Sub-Committee, University of Melbourne (Ethics ID: 1749108), the Human Research Ethics Committee (HREC) of the Royal Women's Hospital (Project ID: 17/26), the HREC of Melbourne Health (HREC Reference number: HREC/17/MH/430), and the HREC of Mercy Health (Project ID: 2018-009). Letters of approval can be found in **Appendix A3**.

4.4. Participant Eligibility Criteria

This study aimed to recruit pregnant women with pre-existing diabetes. The inclusion criteria for this study were women who: 1) were pregnant or planning to fall pregnant; 2) had type 1 or type 2 diabetes that had been diagnosed pre-pregnancy (fasting blood glucose >7.0mmol/l or 2-hour plasma glucose > 11.1 mmol/l following a 75g oral glucose load, or HbA1c >6.5%),[7] as confirmed by an endocrinologist (AN, JC, CH) or obstetrician (AS); and 3) provided informed consent.

All eligible women who attended the RWH and the MHW for diabetes care were approached to ask if they wished to participate in the study.

4.5. Recruitment Protocol

Specialist diabetes in pregnancy clinics are run at the RWH every Monday and Wednesday, and every Thursday at the MHW. On the day of these clinics, medical records were screened, and eligible patients were identified from their appointment notes. In addition, patients' barcodes were collected and placed in a record book with information about their diabetes type and estimated gestation to assist with tracking their follow-up. Physicians who saw the patients in the hospital clinics (AN, JC, AS, and CH) identified potential participants from these notes, then invited patients to participate in the study during their consultations with them. After the consultation, patients interested in taking part in the study were referred to the study coordinator (FW) to discuss the aims and requirements of the study in more detail. All patients were given a participant information sheet and consent form (PICF – Appendix A4) and the opportunity to read it thoroughly and discuss it with family or other health care professionals prior to consenting to take part in this study. Patients were made aware that refusal to participate would not affect their relationship with their doctor or their future medical care. One of the three possible outcomes was noted for each patient invitation: the patient agreed to

participate, refused to participate, or considered the invitation without a definite decision. Patients who failed to give a decision were later contacted via a phone call or text message or approached again at their next hospital appointment. Additionally, eligible patients that were referred by their physicians outside of the usual clinic schedule were invited to participate by phone.

All patients who agreed to participate were asked to sign the consent form. A copy of the patient information sheet was given to the patients, and the consent form was scanned and stored on our dedicated, secure electronic database (full details below). Each patient was allocated a unique study ID, which was used for all data collection. After consenting, an eye examination appointment was arranged, which was typically on the same day as their next scheduled hospital appointment. Patients received a text notification confirming their appointment and a text reminder a day before their scheduled visit.

4.5.1. The Royal Women's Hospital site

For patients that were recruited from the RWH, the eye screening appointment was scheduled at the MEyecare Clinic. Patients were booked in and seen as part of the Diabetes Eye Screening and Investigation Clinic (DESIC), where appointments were available at any time between 8.45 am to 3.30 pm on Monday to Thursday (4 timeslots) and on Friday afternoons between 1.30 pm to 3.30 pm (2 timeslots). If the patient was scheduled to have their eye screening examination after their visit at the RWH, they were offered their choice of an escorted service (by car) to the clinic (located 2 km away) or a reimbursement for their parking fee.

4.5.2. The Mercy Hospital for Women site

Patients recruited from the MHW had two options for where they would receive their eye examinations. These were the MEyecare Clinic (as outlined above, 11 km away) and the ophthalmology clinic at the ARH located 1.5 km away. At the ARH, patients were seen as part of a retinal screening clinic, which ran every Thursday and Monday fortnightly from 9 am to 11.40 am (9 timeslots), with a maximum capacity of 4 study patients per day. Transportation assistance or parking fee reimbursement were also offered to patients who attended ARH.

4.5.3. Other recruitment strategies

Aside from recruiting patients from the above specialty clinics, this study also sought participation through advertisements on the Victorian primary care practice-based Research and Education Network's (VicRen) and on Diabetes Australia's websites. Letters of invitation were also sent to general practitioner practices around the Melbourne area notifying them of the study and encouraging them to refer suitable candidates.

4.6. Eye Examination Protocol

4.6.1. The Melbourne Eyecare Clinic

The Melbourne Eyecare Clinic is a student-based optometry clinic. Eye examinations were performed by student optometrists under the supervision of fully qualified optometrist staff. For this study protocol in particular, the examination duration (including obtaining retinal imaging) was up to 2 hours.

Visual acuity was measured in 3-metre-long rooms with mirrors using a LogMar chart that was available in the Medmont AT20R software (Medmont International Pty Ltd., Australia). The chart was calibrated to be at an equivalent distance of 6 metres. Patients were examined for best-corrected visual acuity (BCVA). In the case of a patient being unable to read letters, LEA calibrated symbols (Medmont AT20R, Medmont International Pty Ltd., Australia) were used. If no figure was visible at a distance of 6 metres, finger counting, hand movement, perception of light, and no perception of light were used to record the patient's visual acuity.

An assessment for external eye, anterior segment, and posterior segment abnormalities was performed using a penlight, slit lamp, and fundoscopy. The presence of any other eye pathologies was reported, and the patient was referred to an ophthalmologist at the Royal Melbourne Hospital if needed.

Intraocular pressure was measured using applanation tonometry with a Goldmann tonometer. If another tonometry method was used, the method and reasoning were noted in the patient's record (e.g., Perkins or I-care). If the initial examination showed no risk of acute angle glaucoma, the patient's pupils were then dilated using 1% tropicamide eye drops (one drop per eye). Patients were asked to close their eyes and occlude their lacrimal

duct (by pressing the medial corner of their eyes), shortly after the eye-drops had been administered to minimise the systemic absorption. If any contraindication for pupil dilation was found, the patient was referred to an ophthalmologist for further assessment.

Fundus photos of each patient's eye were taken using standardised retinal photography with a DRI OCT Triton, Swept Source OCT (Topcon Corp., Tokyo, Japan). The DRI OCT Triton is a multi-modal OCT with a non-mydriatic colour fundus camera. Two-field (macula and optic disc centred), 45°, colour fundus photographs were captured (**Figure 4-1 A, B**).[49] The OCT scan was taken with the same camera and consisted of a 3D horizontal scan, 7.0 x 7.0 mm, centred onto the macula (**Figure 4-1 C**).

Figure 4-1. Retinal photos macula-centred (A) and disc-centred (B); OCT scan area (C)

4.6.2. The Austin Repatriation Hospital

The same protocol was applied when performing eye examinations at the ARH. Visual acuity was measured using a Snellen chart at a distance of 3 metres with a mirror (equivalent to 6 metres of distance), and the BCVA was recorded. Intraocular pressure was measured using a Perkins tonometer. Fundus photography was taken using a VISUCAM$^{PRO\ NM}$ fundus camera (Carl Zeiss, Oberkochen, Germany) and the OCT scan was obtained using an OCT Spectralis (Heidelberg Engineering Inc., Massachusetts, USA). Although this clinic uses different cameras, the images from both sites were comparable.[234]

4.6.3. Patient's local eye clinic

For patients who preferred to have eye examinations at their local clinic due to travel and time restrictions (shared care participants), similar data was collected from the respective

clinic. After discussing the arrangement with the patient, the study coordinator (FW) sent reminders when the next eye examination was due. Once the patient confirmed that she had attened the examination, the study coordinator contacted the eye clinic to get the results. The collected data included BCVA, IOP, the presence of any ocular pathology (if any), and DR status. If available, any fundus photographs and OCT scan reports were also collected.

4.7. Diabetic Retinopathy and Diabetic Macular Oedema Grading

4.7.1. Diabetic retinopathy grading

At each eye examination visit, the DR severity was graded by experienced optometrists or ophthalmologists who regularly see patients for their routine clinical care. This clinical grading was based upon the International Clinical Disease Severity Scale (ICDSS), the widely accepted clinical grading scheme in Australia.[62]

For the purpose of this thesis, DR severity was also graded by an independent, trained grader (masked to the patient's clinical details; Dr. M. Bayu Sasongko [MBS]) from the fundus photographs taken as part of this study. DR was classified into five severity levels according to the modified Airlie House Classification.[49] The severity of DR was assigned for each eye-visit. If no fundus photography was taken during the eye examination or the photography was ungradable, DR severity was assigned using the available clinical grading.

4.7.2. Diabetic macular oedema grading

A diagnosis of diabetic macular oedema (DMO) was made based on the OCT scan (quantitative data and morphology assessment). The quantitative data from the in-built software within OCT devices were collected, namely central subfield thickness (CSFT) and total retinal volume within the ETDRS grid area (**Figure 4-2**). CSFT is defined as the distance between the inner limiting membrane (ILM) and the boundary of the outer layer and the retinal pigment epithelium (OS/RPE) within a 1-mm diameter of an ETDRS grid.[234] A normal mean CSFT is 239.62 ± 21.16 μm and 281.3 ± 23.1 μm with the DRI OCT Triton and the OCT Spectralis, respectively.[234,235] The structural appearance on the OCT scan was also assessed manually by RCAS (at the MEyecare Clinic) and XF (at the ARH) for any morphology changes. The presence of DMO was defined as having a CSFT

value two standard deviations beyond the normal mean or the presence of intra-retinal fluid or sub-retinal fluid within the OCT scan, regardless of the CSFT.[69] DMO diagnoses for visits at local clinics were made based upon the shared OCT results (**Table 4-1**) and the clinical diagnosis.

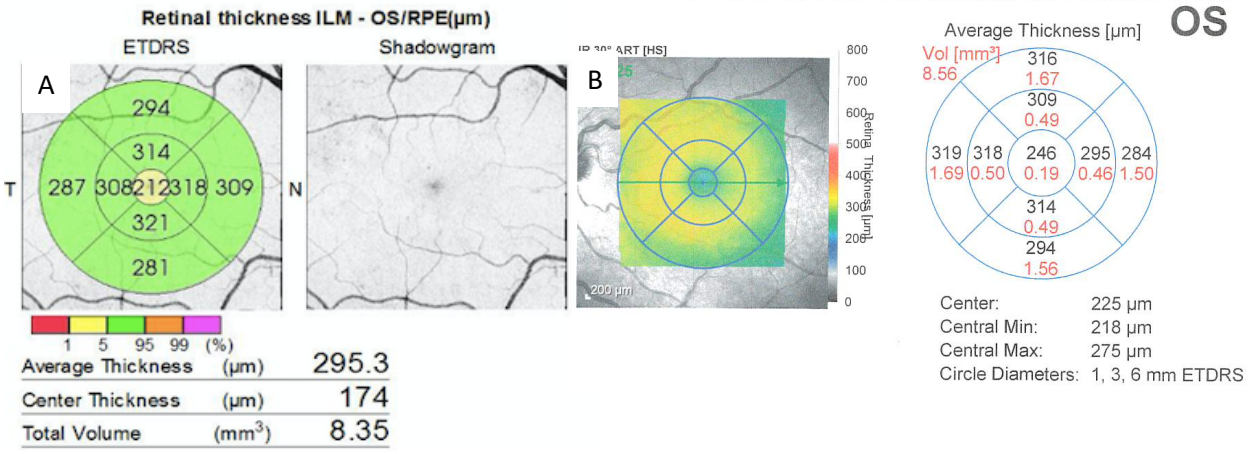


Figure 4-2. Optical Coherence Tomography report from the DRI OCT, Topcon (A) and the Spectralis, Heidelberg (B)

Table 4-1. CSFT cut-offs for several OCT machines that were used at participating clinics for diagnosing DMO

Parameters	CSFT (µm)
DRI-OCT, Topcon[234]	≥282
3D OCT-1, Topcon[236]	≥310
Spectralis, Heidelberg[68]	≥320
Cirrus HD-OCT, Zeiss[237]	≥295

Abbreviations: CSFT, central subfield thickness; DMO, diabetic macular oedema; OCT, optical coherence tomography.

4.8. Demographics and Clinical Data Collection

Once patients signed the consent form, the study coordinator (FW) asked them to complete the "basic medical data and risk factors" questionnaire (**Appendix A5**) on the same day. Moreover, clinical data were continuously collected from patient's medical records during the study period. For this study, data collection ceased on 7 November 2019.

4.8.1. Basic medical data and risk factors questionnaire

A structured questionnaire was constructed to identify risk factors that may be related to the development of DR during pregnancy ("Basic medical data and risk factors"). This

questionnaire gathered information on their demographics, educational background, diabetes history, general health and eye health history, and obstetrics history. Information from this questionnaire was then entered into the electronic database.

Patient's contact details

The patient's name, date of birth, and contact details (address, phone number, and email address) were recorded.

Ethnicity

Patients were asked to identify their ethnicity from seven different options listed in the questionnaire, namely 1) Aboriginal and Torres Strait Islander People; 2) South Pacific Islanders; 3) Caucasian (North-west European, Southern and Eastern European); 4) North African and Middle Eastern; 5) Asian; 6) Peoples of the Americas; and 7) Sub-Saharan African. These ethnicity groups were based upon the Australian Bureau of Statistics Data and were similar to that used in other studies.[198,238,239] Due to small numbers in groups 4, 6 and 7, these groups were combined as "other" in the data analysis.

Level of education

A patient's level of education was defined as the highest level of education achieved. Patients were asked to choose between five options: 1) primary school; 2) secondary school; 3) trade certificate; 4) diploma; and 5) university degree.

Diabetes status

Patients were asked about their diabetes history: type of diabetes, duration of diabetes, diabetes medication (including dosage and duration of use), and family history of diabetes. Moreover, a list of possible diabetes complications was provided. Patients were asked to tick "Yes" if they had ever experienced any of these conditions (diabetic ketoacidosis, hypoglycaemia, heart disease, neuropathy, and nephropathy).

Eye health history

Any past and current eye diseases and any treatment related to these conditions were explicitly asked about and recorded. Self-reported attendance at diabetic eye screening examinations was obtained by asking "How often do you have your eyes checked?" with

six frequency options and “When was your last eye check?” as an open question.

Any history of diabetic eye disease, and DR in particular, was asked about, and if patients answered in the affirmative, the time of diagnosis and treatment details were recorded.

Maternity status

Current pregnancy details were collected including the agreed expected due date, gestational age at the time of study recruitment, and attendance at pre-pregnancy care. The gestational age was determined using an obstetric ultrasound examination at the patient’s booking visit and recorded in their medical records.

A history of prior pregnancies was obtained, including the number of prior pregnancies, number of previous deliveries or miscarriages, any complications of earlier pregnancies, and the patient’s attendance at eye screening examinations.

General medical history

A detailed history of smoking and alcohol consumption was recorded, including their current or past smoking status, number of years as a smoker, number of cigarettes smoked per day and, where applicable, when the patient quit smoking.

Other comorbidities were also recorded, including a history of hypertension, ischemic heart disease, kidney disease, dyslipidaemia, neuropathy, and thyroid problems.

4.8.2. Clinical Data Collection

Height and weight

All patients had their height and weight measured at their first pregnancy visit using a wall-mounted, adjustable tape measure and a calibrated digital weight scale, respectively. Body mass index (BMI) in early pregnancy was calculated using the formula (BMI = weight [kg]/height [m^2]) and categorized as underweight (BMI <18.5kg/m^2), normal (BMI 18.5-24.9kg/m^2), overweight (BMI 25-29.9kg/m^2), or obese (BMI >30kg/m^2).[240] As well as the first measurement, the weight of each patient was also measured at every eye examination visit and recorded in the patient’s follow-up data collection form.

Blood pressure

Blood pressure (BP) was measured during each pregnancy clinic visit based on the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines.[135] A mercury sphygmomanometer was used to record the BP in a sitting position after 5-10 minutes of rest.

Pathology results

Pathology test results were collected from the patient's medical records. These included HbA1c levels and urine albumin/creatinine ratios or protein/creatinine ratios in their pre-pregnancy (if any), in each trimester, and up until 6-weeks postpartum, as per routine clinical care. All blood and urine analyses were done at the pregnancy clinic as ordered by the physicians as part of their standard care.

Pregnancy outcomes

Pregnancy outcome data were collected from patient's records in the relevant hospital system (Clinical Lookup and Results Acknowledgement [CLARA] in the RWH; Birthing Outcomes System [BOS] in the MHW). Gestational age (GA) at birth, birth weight, and mode of delivery were recorded. The birth weight was defined as small for GA (SGA) if the birth weight was below the 10th percentile for that GA for the Australian population[241] and large for GA (LGA) if the birth weight was above the 90th percentile for that GA. Moreover, neonatal outcomes of interest were also recorded, such as the occurrence of respiratory problems (including respiratory distress, respiratory distress syndrome, or transient tachypnoea of the newborn), hypoglycaemia (blood glucose <2.6 mmol/L),[26] sepsis (including any risk of, suspected, and definite sepsis), jaundice and the requirement for phototherapy, birth asphyxia, cardiac abnormalities (including anatomical and functional defects), and any other abnormalities.

Hypertensive disorders in pregnancy (HDiP) were defined as either having hypertension during pregnancy or the need for any BP-lowering drugs.[135] This includes conditions such as: 1) chronic hypertension (essential hypertension or pre-gestational hypertension) if there was a history of anti-hypertensive drug use before pregnancy or BP was ≥140/90 mmHg before pregnancy or prior to 20 weeks of gestation; 2) gestational hypertension if the patient's BP was ≥140/90 mmHg on at least two different measurements during

pregnancy (>20 weeks of gestation) with normal BP at the booking visit or pre-conception; 3) preeclampsia that was diagnosed when the patient's BP rose to ≥140/90 mmHg after 20 weeks of gestation and was accompanied by significant proteinuria (a spot urine protein/creatinine ratio ≥30 mg/mmol); 4) eclampsia that was diagnosed because of seizures that occurred in the context of pre-eclampsia; and 5) preeclampsia superimposed on chronic hypertension if the patient had chronic hypertension and developed significant proteinuria accompanied by an abrupt increase of ≥15% in either systolic or diastolic BP.[4,135,242] Other maternal complications were also noted, such as polyhydramnios, oligohydramnios, cholestasis of pregnancy, and urinary tract infection.

Post-delivery follow-up

At the post-delivery visit, information on the mother's and baby's general health was collected, particularly any abnormal conditions (i.e., follow-up of birth complication and maternal adverse condition).

4.9. Data Entry and Storage

A longitudinal database was created which incorporated the clinical records obtained from the pregnancy clinic (as mentioned above) and diabetic eye clinics (including ophthalmic findings, visual function tests, and ocular imaging). Study data was collected and managed using the Research Electronic Data Capture tool (REDCap version 8.8.0, Vanderbilt University, Tennessee) hosted at the University of Melbourne. REDCap is a secure, web-based application designed to support data capture for research studies. Details of the REDCap options and set-up are explained below.

Main Project Settings and Design Data Collection

A longitudinal study design with survey data collection was chosen, which best suited this PhD study. This developed database had ten instruments for data collection. There were: 1) Demographics data (consisted of 23 fields for data entry including the scanned consent form for each patient); 2) Baseline data (38 fields); 3) Pre-pregnancy data (2 fields); 4) Pregnancy data (52 fields); 5) Eye examinations (109 fields, including attachments of fundus photographs and OCT reports); 6) Pathology results, as described above (20 fields); 7) Pregnancy outcomes, as described above (15 fields); 8) Post-delivery follow-up (9 fields); 9) Completion data (11 fields); and 10) Survey data (see chapter 7)

(62 fields). The contents and settings of each instrument can be seen in **Appendix A6**.

Defined Events and Designated Data Entry Forms for The Events

Nine events defined the follow-up time points of this project, namely enrolment, pre-pregnancy (where applicable), first trimester, second trimester, third trimester, 6-week to 3-month postpartum, 6-month postpartum and 12-month postpartum, and final follow-up. Each event consisted of several instruments, as shown in **Figure 4-3**.

Data Collection Instrument	Enrolment (1)	Pre pregnancy (2)	Trimester 1 (3)	Trimester 2 (4)	Trimester 3 (5)	6 week - 3 month postpartum (6)	6 month postpartum (7)	12 month postpartum (8)	Final follow-up (9)
Demographics	✓								
Baseline Data	✓								
Pre-pregnancy Data	✓								
Pregnancy Data	✓								
Examinations		✓	✓	✓	✓	✓	✓	✓	
Pathology Results		✓	✓	✓	✓	✓	✓	✓	
Pregnancy Outcomes						✓			
Post Delivery Follow-up						✓	✓	✓	
Completion Data									✓
SURVEY DATA (survey)									✓

Figure 4-3. Designated events and forms in REDCap for data collection

Optional Modules

In REDCap, additional features can be activated to assist with data collection. For this project, repeatable instruments and events were enabled to allow more than one data entry for the same event (for example: entering pathology data which was collected more than once in each trimester, in comparison to only one eye examination per trimester).

Data Entry Log

Data entry was only performed by the study coordinator (FW) and a fellow student who joined the research team in 2019 (Edmund Khong). The study coordinator (FW) was responsible for re-checking and verifying any changes in the records. These changes were recorded in the system and can be tracked.

To ensure the confidentiality and privacy of patient data, all paperwork (including consent forms, questionnaires, and laboratory results) were stored in document folders and kept in a secure storage locker at the Clinical Trials Research Unit, Centre for Eye Research Australia. Paper forms were also scanned and uploaded into the REDCap database. All information will be kept for the period required by applicable regulations and guidelines,

which, in Victoria, is 15 years (minimum) after the completion of this study. Each investigator is responsible for ensuring the maintenance and retention of the database. At the end of the required retention period, or if the investigator retires or relocates, the investigator will contact the University of Melbourne, allowing the University the option of permanently retaining the study records.

The results of this study may be shared with other researchers who aim to research the same topic. The information shared with these researchers will be anonymised, and any information which can identify patients shall be removed to protect their privacy.

4.10. Patient Recruitment Outcomes

Figure 4-4 shows the flowchart of patient recruitment and their final status. During the recruitment period (November 2017 – September 2019), the study coordinator (FW) approached 221 patients (36 who were planning to fall pregnant and 185 who were pregnant) across both pregnancy clinics at the RWH and the MHW. One hundred and seventy-seven patients (n=177) agreed to participate (participants), yielding a participation rate of 80.1%. No patients were recruited outside of the specialist pregnancy clinics.

Patients who declined to participate did so for the following reasons: lack of time for additional appointments (n=24); no interest in participating in any study (n=13); already participating in another study (n=11); living too far away (n=13); caring for young children (n=12); could not or did not want to travel to another clinic (n=11); did not want the dilating eyedrops or had no one to drive them (as driving post pupil dilation is not recommended) (n=4); unsure about the time commitment in the study (n=2); and imminent delivery of the baby (n=2).

Participants were divided into three groups based on their preferred participation type. The first was the participants who agreed to participate in the full study (n=156). In this group, patients attended the eye screening examinations at the study's eye clinics. The second group was those participants who preferred to have eye-checks at their local clinic and share their demographic and clinical data (shared care participants; n=16). This group was also followed until they gave birth, and the examination results were collected from their local clinic. The third and final group was those participants who agreed to only

complete the survey (n=5). For this group, participants only completed the survey questionnaire on the same day that they consented and did not participate in any of the testing parameters set out for the full study. Additionally, details on their last or any prior eye-check during pregnancy were collected at the time of the survey (self-reported data).

Six pre-pregnant participants fell pregnant during the study period, and 10 participants were excluded due to either miscarriage (n=8) or because they moved residence (n=2), resulting in a final study number of 147 pregnant women with 147 pregnancies. During the follow-up period, five participants amended their participation type from full study to shared data participation due to time commitment issues, such as the long examination period (at the MEyecare Clinic) and the unsuitability of the eye clinic's schedule (at the ARH). Five participants withdrew from the study: three without any eye-checks and two with one eye-check. Those with an eye-check agreed to include their data in the study for prevalence analysis. Each participant may or may not be eligible for all study aims, depending on the inclusion criteria for each aim (this will be outlined and presented in the chapter relating to each specific aim).

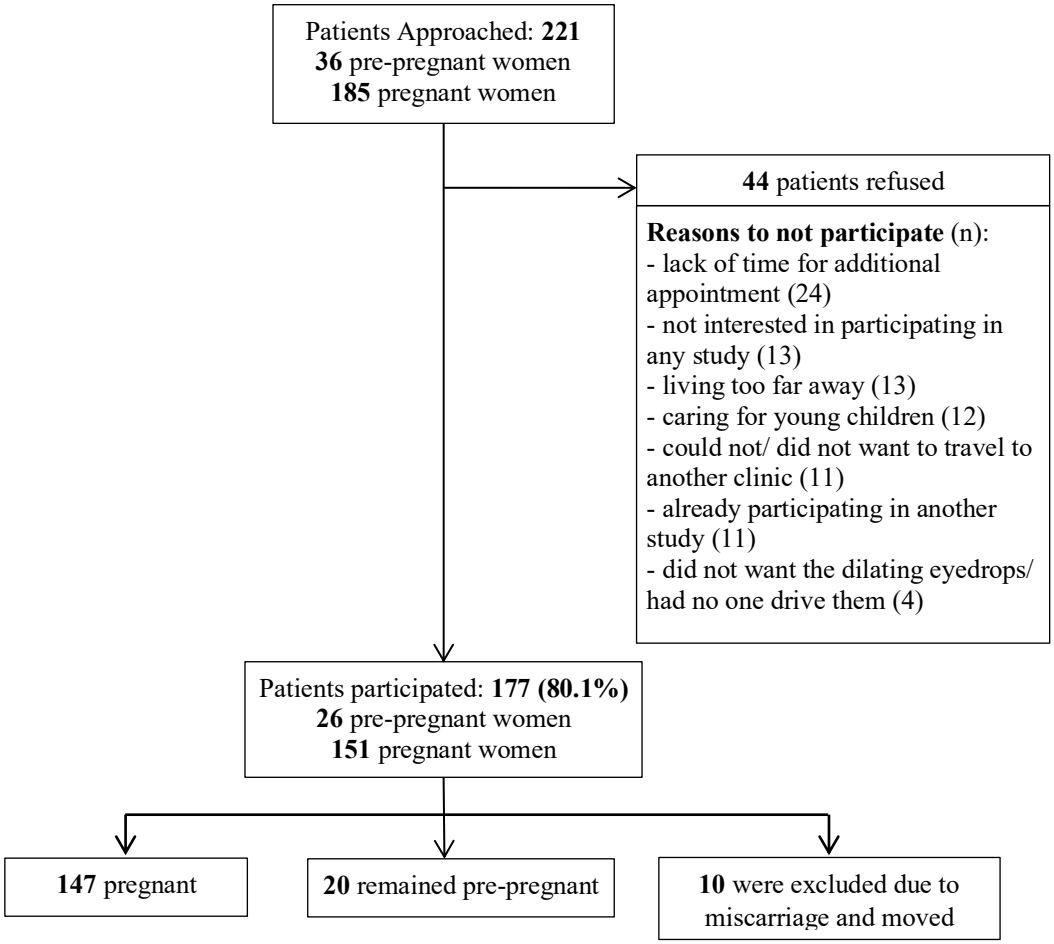


Figure 4-4. Flowchart of patient recruitment and patient's final status

CHAPTER 5: DIABETIC RETINOPATHY IN PREGNANCY IN METROPOLITAN MELBOURNE (AIM 1)

5.1. Overview

As discussed in Chapter 2 and 3, Australia is lacking current data on the prevalence of diabetic retinopathy (DR) in pregnant women with type 1 (T1DM) and type 2 diabetes (T2DM). More importantly, there is no updated data on the rate of DR progression during pregnancy since the advent of contemporary diabetes management guidelines. These gaps in our knowledge limit clinicians in their management of DR in pregnant women with pre-existing diabetes. This part of the study was designed to determine the prevalence of DR, sight-threatening DR (STDR), and its progression rate during pregnancy and the early postpartum period in metropolitan Melbourne.

In this chapter, the methods and results of the first aim of the study are presented, followed by a discussion and comparison to previous studies. Specifically, this present study aimed to:

Aim 1.1: Determine the prevalence of DR and STDR during pregnancy and the early postpartum period from 2 large quaternary subspecialist hospitals in Metropolitan Melbourne - the Royal Women's Hospital and the Mercy Hospital for Women.

Aim 1.2: Determine the rate of progression (if any) of DR during pregnancy and, if it does progress, whether it may then regress post-delivery.

Aim 1.3: Identify risk factors that play a role in the development or progression (if any) of DR and STDR in pregnancy.

5.2. Methods

This part of the study was a prospective cohort study which aimed to follow study participants from their first trimester of pregnancy through to 12 weeks postpartum. Detailed information on the eye examination protocol, clinical data collection and DR grading process has been presented in **Chapter 4**. Briefly, all participants were scheduled

to have diabetic eye screening examinations in the first, second and third trimester, then again at between 6 weeks to 3 months postpartum. Eye examinations were performed at one of two study-site clinics to accommodate the different geographic areas of recruitment. In each visit, 2-field (optic disc-centred and macula-centred) fundus photography and an optical coherence tomography (OCT) scan centred on the macula were obtained from each eye (total of four fundus photos and two OCT images per participant).

DR was graded from the fundus photos by an independent grader (MBS) masked to the participant's details. DR severity was assigned for each eye-visit according to the modified Airlie House Classification, and categorised as follows[49]:

No DR	ETDRS levels 10 and 15
Mild non-proliferative DR (NPDR)	ETDRS levels 20 to 35
Moderate NPDR	ETDRS levels 43 to 47
Severe NPDR	ETDRS level 53
Proliferative DR (PDR)	ETDRS levels 61 to 85

If no fundus photography was taken during the eye examination or the photographs were ungradable, DR severity was assigned using clinical grading from the optometrist or ophthalmologist who saw the participant as part of their routine clinical care. The presence of diabetic macular oedema (DMO) was graded from the quantitative data and morphology assessment of the OCT scan by two ophthalmologists (RCAS – Melbourne Eyecare Clinic; XF – Austin Repatriation Hospital). The presence of DMO was defined as having central sub-field thickness (CSFT) value two standard deviations beyond the normal mean or the presence of intra-retinal fluid (IRF) or sub-retinal fluid (SRF) within the OCT scan, regardless of the CSFT.[69] In situations where participants attended their local clinic, a diagnosis of DMO was made based upon the shared OCT results and the clinical diagnosis.

At each baseline visit, the participant's demographic and clinical data regarding general health, history of diabetes and pregnancy was collected through a structured questionnaire (**Appendix A5**). Blood pressure (BP), height and weight measurements were performed at the first antenatal visit using a standardised method. BP was also recorded at each eye-exam visit. Pathology tests, including glycated haemoglobin A1c (HbA1c) and albumin/creatinine ratio (ACR) or protein/creatinine ratio (PCR), were performed as per routine clinical care. A diagnosis of hypertensive disorders in pregnancy (HDiP), which

is either chronic hypertension, gestational hypertension, preeclampsia, or eclampsia was made according to criteria detailed in **section 4.9 (Chapter 4)**. Pregnancy outcomes, including details regarding birth, maternal and neonatal complications, were collected from each participant's medical records.

5.2.1. Determining the prevalence of diabetic retinopathy and its change over the pregnancy timeline

Calculating the prevalences

Three outcomes of interest were assessed: 1) prevalence of "any DR", including any cases with ETDRS level 20 to 85; 2) prevalence of DMO; and 3) prevalence of STDR, defined as the presence of PDR or DMO. Each prevalence was calculated at four time periods: 1) Trimester 1 (from around conception to 13 weeks of gestation); 2) Trimester 2 (from 14 weeks to 27 weeks of gestation); 3) Trimester 3 (from 28 weeks of gestation to delivery); 4) Postpartum (from delivery to 13 weeks after delivery).

Data from eye-visits within each time period was used for the calculation of prevalence for each period of interest (as detailed above). In situations where there was more than one eye-visit for a particular participant within the time period of interest (e.g., within a particular trimester), the worst (i.e., most severe) eye-visit contributed to the prevalence calculation. This approach was also applied for calculating the prevalence across the entire study period, using the most severe grading per woman at any eye exam from around conception to 3 months after delivery. There were five participants who had more than one eye-visit during their first trimester, and nine participants and one participant with more than one eye-visit in their second and third trimesters, respectively.

Determining the progression and regression

To assess the changes in DR and DMO during pregnancy, we required at least two eye examinations to be performed: one in early pregnancy (from around conception to 22 weeks of gestation) and one in late pregnancy (23 weeks of gestation to delivery). Any progression was defined as: 1) deterioration by one or more levels of DR severity; or 2) development of new DR (from no DR in early pregnancy); or 3) development of DMO; or 4) requiring laser treatment during the observed period in keeping with the composite outcome definitions used by Rasmussen *et al.*[13] Sight-threatening (ST) progression was

defined as: 1) any development of PDR or DMO; or 2) requiring laser treatment during pregnancy due to proliferative changes.[13,197] Meanwhile, regression was defined as: 1) improvement by one or more levels of DR; or 2) resolution of DMO.[149]

For the calculations of progression rate, the eye-visit with the least severe grading at early pregnancy was compared with the eye-visit with the worst grading in late pregnancy if more than one eye-visit from each time period was available. There were 15 participants with more than one eye-visit in early pregnancy and 17 participants with more than one eye-visit in late pregnancy, which includes those women who had more than one eye-visit in each trimester mentioned earlier. Women with regression of DR were counted in the group with no progression. Changes in DR levels were also assessed in the postpartum for those women who returned for an eye examination after delivery.

5.2.2. Statistical analysis

Statistical analyses were carried out using Stata IC 15.1 for Windows (College Station, TX, USA). The normality of the distribution of each continuous variable was tested with the Skewness and kurtosis test for normality, the Shapiro-Wilk test and the Shapiro-Francia test to reach a consensus before presenting the summary statistics as means and 95% confidence intervals (CI), or medians and interquartile ranges (IQR), as appropriate. Demographic characteristics were compared between dichotomous analytical groups of interest, such as diabetes type or women who did and did not have STDR at any time in the study, using the unpaired t-test, Wilcoxon rank-sum test, or Fisher's exact test. Differences were considered to be statistically significant at a two-sided p-value of <0.05.

Prevalence and rates of change in DR were calculated and presented as the number of cases per 100 eyes, with 95% CIs for these rates calculated using the Agresti-Coull, Wilson, or Hanley and Lippman-Hand methods, as appropriate. Risk ratios (RR) for progression of DR were calculated. Mantel-Haenszel stratified RRs were then calculated to adjust for factors of interest, individually: (A) type of diabetes, (B) a diabetes duration longer than the median for their respective diabetes type (as calculated from the women with at least one eye exam during pregnancy), and (C) the presence of any DR in early pregnancy. RRs were considered to be statistically significant if the 95% CI did not include the null value, a RR=1.0. Lastly, DR changes in the postpartum were descriptively presented.

5.3. Results

5.3.1. Study participants' demographics

Overall, 130 out of 147 pregnant women had at least one eye examination during pregnancy and were eligible for the final analysis. Participant characteristics are shown in **Table 5-1**. Mean maternal age was 33.7 years (95% CI 32.8 – 34.5), median diabetes duration was 7.0 years (IQR 3.0 – 17.0), and median HbA1c at the first measurement during pregnancy was 6.4% (IQR 5.8 – 7.4). A history of hypertension, nephropathy, thyroid problems, and dyslipidaemia before pregnancy was found in 15, 2, 32, and 26 women, respectively. Two women (four eyes) had a history of treated PDR before pregnancy.

This cohort comprised 62 (47.7%) participants with T1DM and 68 participants with T2DM. The majority of women with T1DM were of Caucasian ethnicity (79.0%), whereas women with T2DM were mostly Asian and Indian (61.8%). The median diabetes duration of T1DM and T2DM women was 16.5 years (IQR 8.0 - 23.0) and 4.0 years (IQR 2.0 - 6.0), respectively. Participants with T1DM were slightly but significantly younger ($p = 0.002$), had a much longer duration of diabetes ($p < 0.001$), had a higher HbA1c at first measurement during pregnancy ($p = 0.042$) and had a lower early pregnancy BMI ($p = 0.019$) compared to participants with T2DM. The timing of the first measurement of HbA1c during pregnancy was earlier in pregnancy for women with T1DM than the T2DM group (median 8 weeks [IQR 6 – 12.5] vs 11 weeks [7 – 19]; $p = 0.003$).

Across all eye-visits, fundus photography was not taken or ungradable in 75 eye-visits (out of 542 eye-visits), most of which were eye examinations performed at local eye clinics and the DR grading for these visits was assigned based on the clinical diagnosis. Three ungradable photos were from a woman who had a congenital cataract in her left eye and attended three eye-exams during the study period. The characteristics of eye-visits with no photos or ungradable photos compared to eye-visits with gradable fundus photos can be seen in **Supplementary table S5-1**. Eye-visits without fundus photos had more severe DR grades and had a higher proportion of DMO compared to eye-visits with gradable photos (p-values < 0.001).

Table 5-2 shows the maternal and neonatal outcomes of all participants. Among the 130

eligible participants, pregnancy outcome data was not available in five participants because they gave birth in a private hospital. The offspring of mothers with T1DM had a significantly higher mean birth weight ($p < 0.001$) and a correspondingly higher proportion of large for gestational age (LGA) cases ($p < 0.001$) compared to mothers with T2DM. Respiratory problems ($p = 0.027$), neonatal hypoglycaemia ($p = 0.004$), and cardiac abnormalities ($p = 0.001$) were also more prevalent in babies from T1DM pregnancies. Lastly, more babies from mothers with T1DM were admitted to a neonatal intensive care unit (NICU) or special care nursery (SCN) compared to babies from T2DM mothers (67% vs 35%; $p < 0.001$), although the duration of stay was similar once admitted.

5.3.2. Prevalence of DR and STDR during pregnancy and postpartum

Table 5-3 and **Figure 5-1** present the prevalence of DR, DMO and STDR per 100 eyes. Four eyes (from two women) were excluded from the analysis regarding DMO and STDR prevalence because their DMO status could not be confirmed as they had no OCT scans nor any mention of the presence/absence of DMO clinically. The overall prevalence of DR, DMO and STDR at the worst eye-visit per eye at any exam between conception to 3 months postpartum was 20.8 (95% CI 16.3 – 26.1), 5.9 (95% CI 3.5 - 9.5) and 6.6 (95% CI 4.1 - 10.4) per 100 eyes, respectively. Prevalence per woman in the same order was 21.5% (95% CI 15.3 – 29.4), 7.8% (95% CI 4.1 – 13.9), and 9.4% (95% CI 5.3 – 15.8). Among the 17 eyes (from 12 women) with a worst eye-visit grade of STDR, 2 eyes had PDR only, 11 eyes had DMO (9 of these with mild NPDR, and 2 eyes with severe NPDR), and 4 eyes had PDR and DMO.

Characteristics of women with at least one eye-visit with DR compared to women without DR, as well as between women with at least one eye-visit with STDR and without are presented in **Table 5-4**. HbA1c data was not available for eight women (one of whom had STDR) and pregnancy outcome data was not available in five women. Early pregnancy BMI data was also incomplete in 16 women (three of whom had STDR and two had DR). Women with DR or STDR at any time during the study, compared to those without, were more likely to have T1DM (p-values ≤ 0.013), more likely to deliver via caesarean section (C-section; p-values ≤ 0.036), and had significantly longer durations of diabetes (p-values < 0.001). However, once adjusted for DM type, only women with STDR were significantly more likely to have a DM duration longer than median for their

DM type compared to women who did not have STDR (p = 0.012). Furthermore, a significantly higher HbA1c at the first measurement during pregnancy (p = 0.024) and a higher proportion of Caucasian women (p = 0.001) were evident in the DR group compared to the no-DR group.

Table 5-1. Demographic characteristics of participants with at least one eye exam during pregnancy, by type of diabetes

	Overall (N=130)	**T1DM (N=62)**	**T2DM (N=68)**	***p*-value***
Age at enrolment [years], mean (95% CI)	33.7 (32.8 -34.5)	***32.3 (31.0 - 33.7)***	***34.9 (34.0 - 35.8)***	***0.002***
Gestational age at first exam [weeks], median (IQR)	14 (11.0 – 22.0)	14 (10.0 - 19.0)	16 (11.0 - 24.0)	0.123
Time of first eye exam in pregnancy, n (%)				0.366
Trimester 1	58 (44.6)	29 (46.8)	29 (42.6)	
Trimester 2	51 (39.2)	26 (41.9)	25 (36.8)	
Trimester 3	21 (16.2)	7 (11.3)	14 (20.6)	
Duration of diabetes at enrolment [years], median (IQR)	7.0 (3.0 – 16.5)	***16.5 (8.0 - 23.0)***	***4.0 (2.0 - 6.0)***	***<0.001***
Duration longer than median for DM type, n (%)	60 (46.9)	31 (50.0)	29 (43.9)	0.595
HbA1c at the first measurement in pregnancy† [%], median (IQR)	6.4 (5.8 – 7.4)	*6.7 (6.0 - 7.5)*	*6.1 (5.7 - 7.3)*	*0.024*
Ethnicity, n (%)				***<0.001***
ATSI	1 (0.8)	***0***	***1 (1.5)***	
South Pacific Islanders	4 (3.1)	***0***	***4 (5.9)***	
Caucasian	58 (44.6)	***49 (79.0)***	***9 (13.2)***	
Asian	48 (36.9)	***6 (9.7)***	***42 (61.8)***	
Other	19 (14.6)	***7 (11.3)***	***12 (17.6)***	
Education, n (%)				0.363
Primary school	3 (2.3)	0	3 (4.4)	
Secondary school	17 (13.1)	8 (12.9)	9 (13.2)	
Trade certificate	15 (11.5)	10 (16.1)	5 (7.4)	
Diploma	14 (10.8)	5 (8.1)	9 (13.2)	
University degree	81 (62.3)	39 (62.9)	42 (61.8)	
BMI at early pregnancy‡ [kg/m^2], n (%)				***0.019***
<25	39 (34.2)	***23 (44.2)***	***16 (25.8)***	
25 – 29 (overweight)	26 (22.8)	***14 (26.9)***	***12 (19.4)***	
≥30 (obese)	49 (43.0)	***15 (28.8)***	***34 (54.8)***	
Current smoker [yes], n (%)	3 (2.4)	1 (1.6)	2 (3.1)	1.000
Past smoker [yes], n (%)	20 (16.4)	12 (20.0)	8 (12.9)	0.334
History of medical condition [present]:				
Chronic hypertension, n (%)	15 (11.5)	5 (8.1)	10 (14.7)	0.281
Nephropathy, n (%)	2 (1.5)	2 (3.2)	0	0.226
Neuropathy, n (%)	6 (4.6)	4 (6.5)	2 (2.9)	0.424
Other conditions§, n (%)	54 (41.5)	23 (37.1)	31 (45.6)	0.375

* *p*-value relates to the difference between two groups examined using t-test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.

† Not all women had pathology results; Contributed data: 60 women with T1DM and 62 with T2DM.

‡ BMI was measured at the first antenatal visit; Contributed data: 52 women with T1DM and 62 women with T2DM.
§ Includes thyroid conditions, heart disease, dyslipidaemia.
Abbreviations: ATSI, Aboriginal & Torres Strait Islander People; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; IQR, interquartile range; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 5-2. Maternal and neonatal outcomes of included participants, by type of diabetes

	Overall (N=125 women)	**T1DM** (N=61 women)	**T2DM** (N=64 women)	***p*-value***
GA at birth [week], median (IQR)	37 (36, 38)	37 (35, 37)	37 (36, 38)	0.031
GA at birth, [weeks]				0.490
Extreme preterm (≤33)	12 (9.6)	6 (10)	6 (9)	
Preterm (34-36)	31 (24.8)	18 (30)	13 (20)	
At term (37+)	82 (65.6)	37 (61)	45 (70)	
Baby's birthweight [grams], mean (95% CI)	3336 (3188 - 3483)	***3590 (3376 - 3803)***	***3094 (2904 - 3283)***	***<0.001***
Small for GA [yes], n (%)	7 (5.6)	1 (2)	6 (9)	0.115
Large for GA [yes], n (%)	65 (52.0)	***45 (74)***	***20 (31)***	***<0.001***
Neonatal complications†:				
Respiratory problems, n (%)	26 (20.8)	***18 (30)***	***8 (13)***	***0.027***
Hypoglycaemia, n (%)	49 (39.2)	***32 (53)***	***17 (27)***	***0.004***
Suspect Sepsis, n (%)	8 (6.4)	4 (7)	4 (6)	1.0
Jaundice, n (%)	31 (24.8)	19 (31)	12 (19)	0.147
N (%) required phototherapy, for babies with jaundice	20 (64.5)	13 (68)	7 (58)	0.705
Birth asphyxia, n (%)	4 (3.2)	2 (3)	2 (3)	1.0
Cardiac abnormalities‡, n (%)	9 (7.2)	***9 (15)***	***0***	***0.001***
Other abnormalities‡, n (%)	11 (8.8)	2 (3)	9 (14)	0.055
Admitted to NICU/SCN, n (%)				***<0.001***
No	62 (49.6)	***20 (33)***	***42 (66)***	
NICU	41 (32.8)	***24 (39)***	***17 (27)***	
SCN	22 (17.6)	***17 (28)***	***5 (8)***	
Duration of NICU/SCN stay [days], median (IQR)	6 (4 - 10)	6.5 (4 - 10)	6 (3.5 - 12)	0.687
Pregnancy complications† [present]**:**				
Hypertensive disorder in pregnancy, n (%)	33 (26.4)	17 (28)	16 (25)	0.840
Other‡, n (%)	15 (12.0)	8 (13)	7 (11)	0.787
Delivery method, n (%)				0.254
Vaginal birth	39 (31.2)	16 (26)	23 (36)	
Caesarean section	86 (68.8)	45 (74)	41 (64)	

* *p*-value relates to the difference between two groups examined using t-test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.
† A mother or baby could have multiple problems.
‡ Details on the included conditions were presented in **Supplementary table S5-2.**
Abbreviations: CI, confidence interval; GA, gestational age; IQR, interquartile range; NICU, neonatal intensive care unit; SCN, special care nursery; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 5-3. Prevalence of any DR, DMO and STDR during pregnancy and early postpartum

Outcome	Pregnancy status	Overall			T1DM			T2DM		
		N case, eye	N at risk, eye	Prevalence per 100 eyes (CI*)	N case, eye	N at risk, eye	Prevalence per 100 eyes (CI*)	N case, eye	N at risk, eye	Prevalence per 100 eyes (CI*)
Any DR	Entire study†	54	260	20.8 (16.3 - 26.1)	43	124	34.7 (26.9 - 43.4)	11	136	8.1 (4.4 - 14.0)
	Trimester 1	25	116	21.6 (15 - 29.9)	21	58	36.2 (25.1 - 49.1)	4	58	6.9 (2.7 - 16.4)
	Trimester 2	35	176	19.9 (14.6 - 26.4)	26	92	28.3 (20.1 - 38.2)	9	84	10.7 (5.7 - 19.1)
	Trimester 3	28	154	18.2 (12.8 - 25.1)	24	70	34.3 (24.2 - 46)	4	84	4.8 (1.9 - 11.6)
	Postpartum‡	9	61	14.8 (8.0 - 25.7)	9	36	25 (13.8 - 41.1)	0	25	0 (0 - 14.0)
DMO	Entire study†	15	256	5.9 (3.5 - 9.5)	12	122	9.8 (5.6 - 16.5)	3	134	2.2 (0.5 - 6.7)
	Trimester 1	5	114	4.4 (1.6 - 10.1)	5	58	8.6 (3.7 - 18.6)	0	56	0 (0 - 6.3)
	Trimester 2	6	170	3.5 (1.5 - 7.7)	3	88	3.4 (1.2 - 9.5)	3	82	3.7 (1.3 - 10.2)
	Trimester 3	7	138	5.1 (2.3 - 10.3)	7	60	11.7 (5.8 - 22.2)	0	78	0 (0 - 4.5)
	Postpartum‡	3	58	5.2 (1.8 - 14.1)	3	34	8.8 (3.0 - 23.0)	0	24	0 (0 - 14.6)
STDR	Entire study†	17	256	6.6 (4.1 - 10.4)	14	122	11.5 (6.8 - 18.5)	3	134	2.2 (0.5 - 6.7)
	Trimester 1	5	114	4.4 (1.6 - 10.1)	5	58	8.6 (3.7 - 18.6)	0	56	0 (0 - 6.3)
	Trimester 2	8	170	4.7 (2.3 - 9.2)	5	88	5.7 (2.5 - 12.6)	3	82	3.7 (1.3 - 10.2)
	Trimester 3	10	138	7.2 (3.8 - 13.0)	10	60	16.7 (9.3 - 28)	0	78	0 (0 - 4.5)
	Postpartum‡	3	58	5.2 (1.8 - 14.1)	3	34	8.8 (3.0 - 23.0)	0	24	0 (0 - 14.6)

* 95% CI was estimated using the Agresti-Coull, the Wilson, or the Hanley & Lippman-Hand methods, as appropriate depending on the numbers of cases and at risk eyes.
† From trimester 1 to postpartum (6-weeks to 3-months postpartum)
‡ 6-weeks to 3-months postpartum
Abbreviations: CI, confidence interval; DMO, diabetic macular oedema; DR, diabetic retinopathy; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

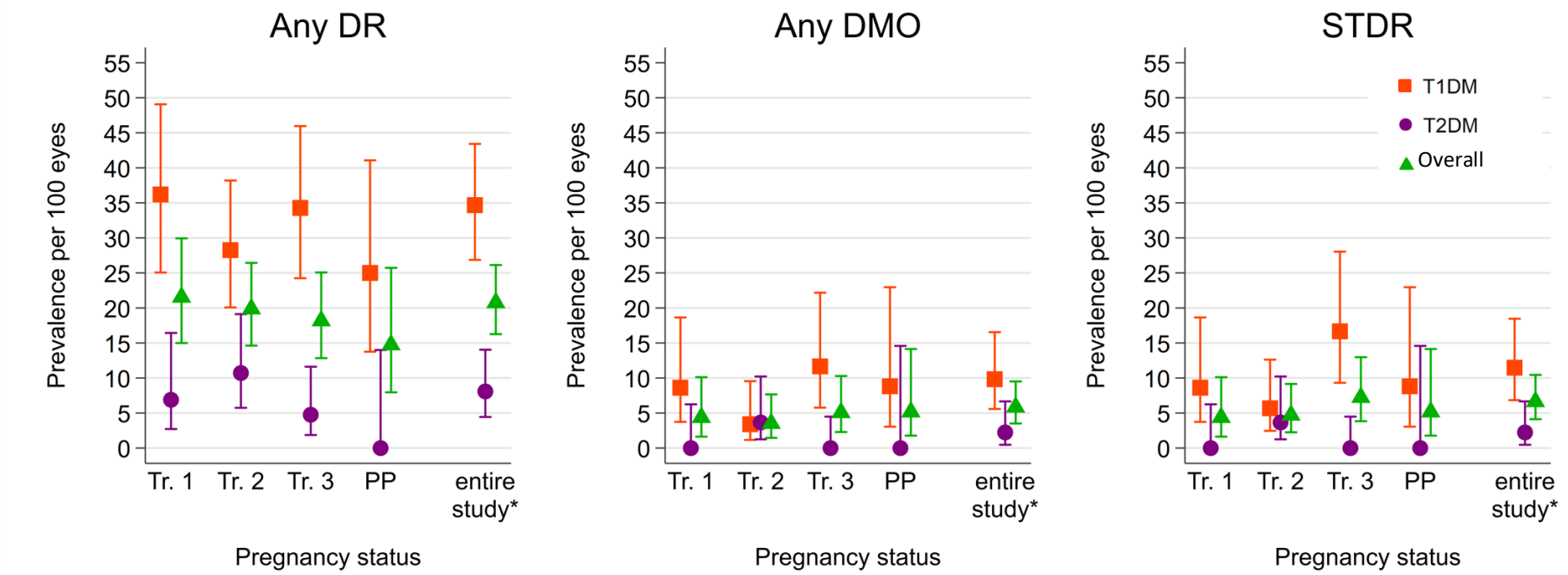


Figure 5-1. Prevalence of any DR and STDR during pregnancy and early postpartum

Filled shapes indicate the crude prevalence rate; error bars indicate 95% CIs for the crude rate. *Entire study prevalence is estimated based on the worst grading per eye at any eye-visit during the study period (Trimester 1 to 3-month postpartum). Abbreviations: DMO, diabetic macular oedema; DR, diabetic retinopathy; PP, postpartum; STDR, sight-threatening diabetic retinopathy; Tr.1, trimester 1; Tr. 2, trimester 2; Tr. 3, trimester 3.

Table 5-4. Characteristics of women who did and did not have DR or STDR in at least one eye-visit

	Any DR*			Sight-threatening DR (STDR)*		
	DR absent (N= 102 women)	**DR present** (N=28 women)	***p*-value†**	**STDR absent** (N=116 women)	**STDR present** (N=12 women)	***p*-value†**
Age at enrolment [years], mean (95% CI)	33.7 (32.8 - 34.6)	33.4 (31.4 - 35.5)	0.784	33.8 (32.9 - 34.7)	32.8 (29.7 - 35.8)	0.485
Type of diabetes, n (%)			***<0.001***			***0.013***
T1DM	***40 (39.2)***	***22 (78.6)***		***51 (44.0)***	***10 (83.3)***	
T2DM	***23 (60.8)***	***6 (21.4)***		***65 (56.0)***	***2 (16.7)***	
Duration of diabetes at enrolment [years], median (IQR)	***5.7 (2.5 - 10.0)***	***19.5 (10.5 - 25.5)***	***<0.001***	***6.0 (3.0 - 13.3)***	***22.5 (18.5 - 27.5)***	***<0.001***
Duration longer than median‡ for DM type, n (%)	42 (42.0)	18 (64.3)	0.053	***49 (43.0)***	***10 (83.3)***	***0.012***
HbA1c at first measurement during pregnancy§ [%], median (IQR)	***6.3 (5.8 - 7.3)***	***7.1 (6.0 - 8.0)***	***0.024***	6.4 (5.8 - 7.5)	6.9 (5.8 - 7.2)	0.756
Systolic BP‖ [mmHg], mean (95% CI)	112.3 (109.8 -114.8)	113.6 (107.9 - 119.2)	0.678	112.3 (110.0 - 114.6)	116.7 (104.8 - 128.5)	0.425
Diastolic BP‖ [mmHg], mean (95% CI)	67.4 (65.2 - 69.6)	66.5 (62.9 - 70.0)	0.649	67.0 (65.1 - 69.0)	67.9 (60.2 - 75.6)	0.816
Ethnicity, n (%)			***0.001***			0.100
ATSI	***1 (1.0)***	***0***		1 (0.9)	0	
South Pacific Islanders	***4 (3.9)***	***0***		4 (3.4)	0	
Caucasian	***36 (35.3)***	***22 (78.6)***		47 (40.5)	10 (83.3)	
Asian	***43 (42.2)***	***5 (17.8)***		45 (38.8)	2 (16.7)	
Other	***18 (17.6)***	***1 (3.6)***		19 (16.4)	0	
Current smoker [yes], n (%)	1 (1.0)	2 (7.4)	0.117	2 (1.8)	1 (8.3)	0.267
Past smoker [yes], n (%)	15 (15.5)	5 (20.0)	0.556	17 (15.6)	2 (18.2)	0.685
History of medical condition [present]**:**						
Chronic hypertension, n (%)	12 (11.8)	3 (10.7)	1.000	13 (11.2)	1 (8.3)	1.000
Nephropathy, n (%)	1 (1.0)	1 (3.6)	0.386	1 (0.9)	1 (8.3)	0.179
Neuropathy, n (%)	5 (4.9)	1 (3.6)	1.000	6 (5.2)	0	1.000
Obesity¶, n (%)	41 (45.1)	8 (34.8)	0.481	45(43.7)	3 (33.3)	0.730
Other conditions#, n (%)	41 (40.2)	13 (46.4)	0.666	49 (42.2)	4 (33.3)	0.760
Hypertensive disorder in pregnancy^ [present], n (%)	24 (24.7)	9 (32.1)	0.470	27 (24.3)	5 (41.7)	0.296
Delivery method^, n (%)			***0.036***			***0.009***
Vaginal birth	***35 (36.1)***	***4 (14.3)***		***39 (35.1)***	***0***	
Caesarean section	***62 (63.9)***	***24 (85.7)***		***72 (64.9)***	***12 (100.0)***	

* Women were categorised based on the most severe grading seen in their worst eye at any time in the study period.

† *p*-value relates to the difference between two groups examined using t-test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.

‡ as calculated from all women with at least one eye exam during pregnancy (n = 130).

§ Contributed data: 95 women in DR absent group, 27 women in DR present group, 110 women in STDR absent group and 11 women in STDR present group.
‖ Measured at the first eye-exam in pregnancy. Contributed data: 91 women in DR absent group, 21 women in DR present group, 102 women in STDR absent group and 9 women in STDR present group.
¶ Contributed data: 91 women in DR absent group, 23 women in DR present group, 103 women in STDR absent group and 9 women in STDR present group.
# Includes thyroid conditions, heart disease, dyslipidaemia.
^ Contributed data: 97 women in DR absent group, 28 women in DR present group, 111 women in STDR absent group and 12 women in STDR present group.
Abbreviations: ATSI, Aboriginal & Torres Strait Islander People; BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; DR, diabetic retinopathy; IQR, interquartile range; STDR, sight-threatening diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

5.3.3. Diabetic retinopathy changes during pregnancy and early postpartum

Among the 130 women who had at least one eye-exam during pregnancy, only 72 women (144 eyes) provided sufficient data to assess DR change. The 58 women from whom there was insufficient data for DR change assessment had their first eye-exam later in pregnancy than those women who provided sufficient data (median [IQR], 23.5 [15-30] weeks vs 12 [10-15.5] weeks, $p < 0.001$). No significant difference was found in DR severity or presence of DMO at the first eye-exam in pregnancy between the groups (p-values ≥ 0.250). However, amongst the women with insufficient data for progression analysis, there were significantly higher proportions of obesity and previous smoking, whilst the proportion of current smokers was significantly lower.

Table 5-5 and **Figure 5-2** show rates of DR progression during pregnancy in the subset of participants with sufficient data. A detailed breakdown of DR and DMO status at early pregnancy compared to late pregnancy is presented in **Table 5-6.** From early to late pregnancy, 9.7 per 100 eyes (a total of 14 eyes from 9 women; 12.5% of women with sufficient data [95% CI 6.7 – 22.1]) showed any progression of DR. Of these 14 eyes showing progression, five eyes (from four women) developed new DR, another eye from one of these women developed new DR and DMO, three eyes (from two women) progressed within NPDR grades and another eye progressed from NPDR to PDR. A further two eyes (from two women) developed new DMO and two eyes (one woman) with treated-PDR required further laser during pregnancy.

The two women with proliferative changes during pregnancy are briefly described below. The first woman was a patient with T1DM who had pre-existing mild NPDR in both eyes seen around 3 weeks before conception. At 30 weeks of gestation, progression was observed where her right eye had progressed to moderate NPDR and her left eye had progressed to PDR. Her HbA1c ranged between 5.4% and 5.6% throughout pregnancy. Later, she was diagnosed with severe preeclampsia at week 35 and had an emergency C-section at week 37 due to a failed induction of labour and foetal distress. Ten weeks after delivery, her left eye had regressed from PDR to moderate NPDR without treatment while her right eye remained unchanged with moderate NPDR.

The second woman with T1DM had pre-existing bilateral PDR and DMO with partial retinal traction in her right eye. She was treated with laser photocoagulation (both eyes), vitrectomy in her right eye, and anti-VEGF injections in her left eye around 6 months before conception.

Her HbA1c was very high (13.4%) at 4 months before conception and when she was about 4 weeks pregnant, she developed vision loss in her right eye due to vitreous haemorrhage that improved without treatment by her next eye-visit (10 weeks pregnant). At 24 weeks of gestation, new neovascularisation was observed in both eyes and laser treatment was administered. Her HbA1c was 8.4% at early pregnancy which reduced to 6.6% at 22 weeks and rose back to 7.4% at 32 weeks. She developed severe preeclampsia at 32 weeks of gestation and delivered her baby at 35 weeks through emergency C-section.

Table 5-5. Overall rates of DR progression during pregnancy

Outcome (Early to late pregnancy*)	**N eyes progressed**	**N eyes at risk**	**Rate per 100 eyes (95% CI†)**
Any progression‡			
Overall	14	144	9.7 (5.8 - 15.8)
T1DM	10	76	13.2 (7.3 - 22.6)
T2DM	4	68	5.9 (2.3 - 14.2)
Progression ≥1-step on 5-level DR severity scale			
Overall	12	144	8.3 (4.7 - 14.1)
T1DM	8	76	10.5 (5.4 - 19.4)
T2DM	4	68	5.9 (2.3 - 14.2)
Progressed from no DR to any DR			
Overall	6	114	5.3 (2.2 - 11.2)
T1DM	4	52	7.7 (3.0 - 18.2)
T2DM	2	62	3.2 (0.9 - 11.0)
Progressed from NPDR to PDR			
Overall	1	22	4.5 (0.8 - 21.8)
T1DM	1	16	6.3 (1.1 - 28.3)
T2DM	0	6	0.0 (0.0 - 58.3)
Sight-threatening progression§			
Overall	6	134‖	4.5 (1.9 - 9.6)
T1DM	5	70	7.1 (3.1 - 15.7)
T2DM	1	64	1.6 (0.3 - 8.3)

* early pregnancy (≤22 weeks of gestation) and late pregnancy (≥23 weeks of gestation up to birth).
† 95% CI was estimated using the Agresti-Coull, the Wilson or the Hanley & Lippman-Hand method, as appropriate depending on the number of cases and at-risk eyes.
‡ Includes progression by at least 1 step on DR severity scale, requiring laser treatment, development of new PDR or DMO.
§ Includes progression that required laser treatment, or development of new PDR or DMO.
‖ DMO status was unknown in 10 out of 144 eyes.
Abbreviations: CI, confidence interval; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

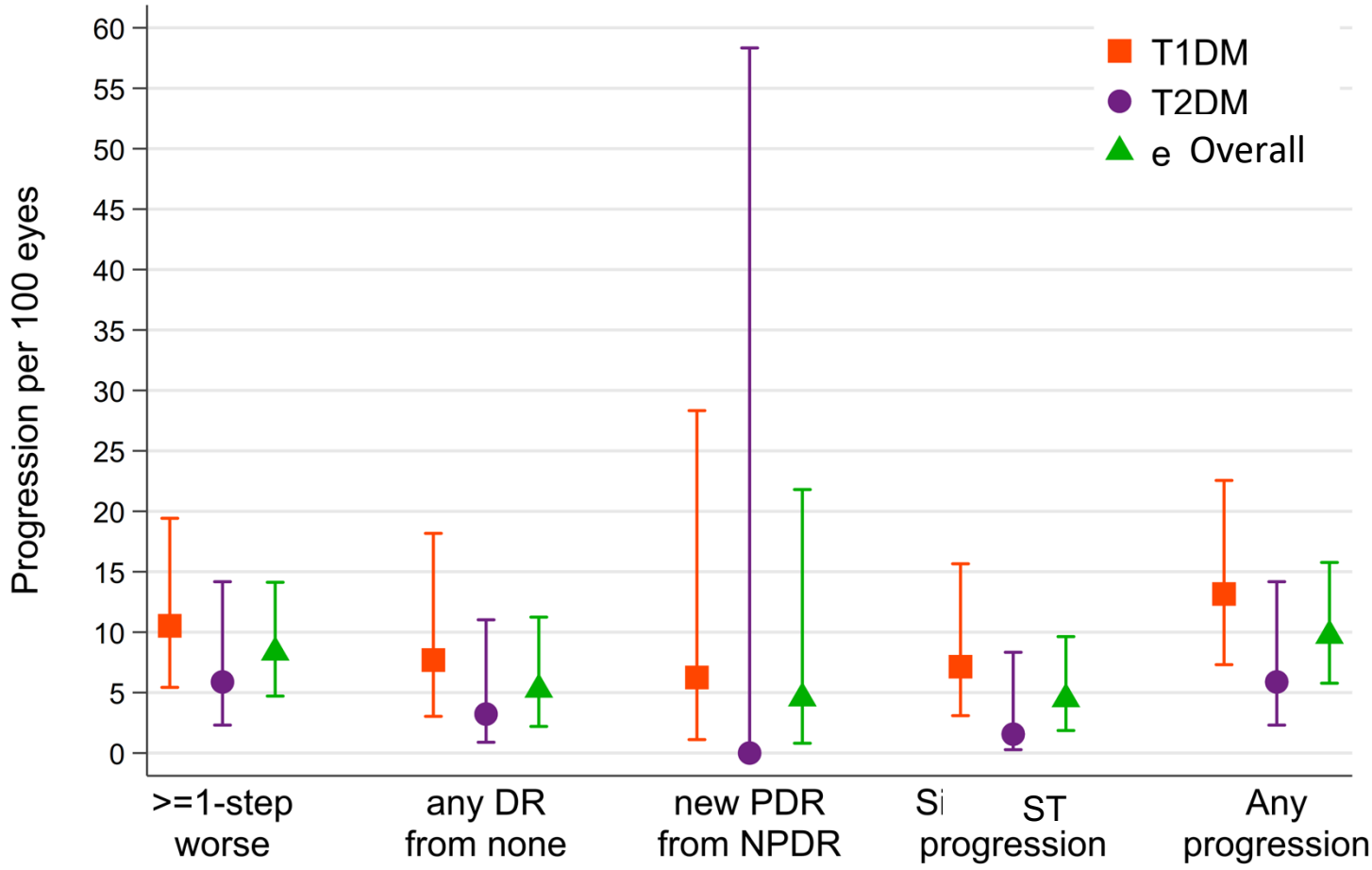


Figure 5-2. Diabetic retinopathy progression from early to late pregnancy

Filled shapes indicate the crude progression rate; error bars indicate 95% CIs for the rate. Abbreviations: DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; ST, sight threatening; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 5-6. DR severity and DMO status in early pregnancy compared to late pregnancy, by eye

			Late pregnancy*										
			No DMO					DMO present					
			No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	No DR	Mild NPDR	Moderate NPDR	Severe NPDR	PDR	TOTAL
Early pregnancy*	No DMO	No DR	100	**5**	.	.	.	.	**1**	.	.	.	106
		Mild NPDR	*3*	11	**1**	.	**1**	.	**1**	.	.	.	17
		Moderate NPDR	.	.	3	.	.	.	.	.	.	.	3
		Severe NPDR	.	.	.	.	.	.	.	.	.	.	0
		PDR	.	.	.	.	1	.	.	.	.	**1**	2
	DMO present	No DR	0	.	.	.	.	.	.	.	.	.	0
		Mild NPDR	.	1	.	.	.	1	.	.	.	.	2
		Moderate NPDR	.	.	.	.	.	.	.	.	**2**	.	2
		Severe NPDR	.	.	.	.	.	.	.	.	.	.	0
		PDR	.	.	.	.	.	.	.	.	.	**2**†	2
		TOTAL	103	17	4	0	2	1	2	0	2	3	134

Numbers in bold are eyes with progression in any form.
* early pregnancy (≤22 weeks of gestation) and late pregnancy (≥23 weeks of gestation up to birth).
† required laser in late pregnancy.
Abbreviations: DMO, diabetic macular oedema; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 5-7. Characteristics of women with and without at least one eye that progressed or experienced sight-threatening progression during the study period

	Any progression			Sight-threatening progression		
	Not progressed (N= 63 women)	**Progressed** (N=9 women)	***p*-value**[*]	**No** (N=62 women)	**Yes** (N=5 women)	***p*-value**[*]
Age at enrolment [years], mean (95%CI)	34.1 (33.1 - 35.2)	31.4 (27.8 - 35.1)	0.140	34.0 (32.8 - 35.2)	32.6 (27.9 - 37.3)	0.469
Type of diabetes, n (%)			0.158			0.358
T1DM	31 (49.2)	7 (77.8)		31 (50.0)	4 (80.0)	
T2DM	32 (50.8)	2 (22.2)		31 (50.0)	1 (20.0)	
Duration of diabetes at enrolment [years], median (IQR)	***7.0 (3.0 - 17.0)***	***20.0 (11.5 - 23.0)***	***0.047***	8.0 (3.0 - 17.8)	23.0 (21.0 - 28.0)	0.088
Duration longer than median[†] for DM type, n (%)	29 (46.0)	5 (55.6)	0.727	29 (46.8)	4 (80.0)	0.197
HbA1c at the first measurement in pregnancy[‡] [%], median (IQR)	6.5 (5.9 - 7.5)	7.0 (6.4 - 7.4)	0.556	6.8 (5.9 - 7.5)	6.6 (5.5 - 7.0)	0.573
Systolic BP[§] [mmHg], mean (95%CI)	110.2 (107.2 - 113.1)	124.4 (106.0 - 142.8)	0.097	***110.9 (107.8 - 113.9)***	***134.0 (120.9 - 147.1)***	***0.006***
Diastolic BP[§] [mmHg], mean (95%CI)	65.8 (63.3 - 68.3)	71.0 (58.3 - 83.7)	0.326	***65.7 (63.1 - 68.4)***	***78.3 (71.2 - 85.5)***	***0.002***
Ethnicity, n (%)			0.779			0.619
ATSI	0	0		0	0	
South Pacific Islanders	2 (3.2)	0		2 (3.2)	0	
Caucasian	30 (47.6)	6 (66.7)		29 (46.8)	4 (80.0)	
Asian	21 (33.3)	2 (22.2)		21 (33.9)	1 (20.0)	
Other	10 (15.9)	1 (11.1)		10 (16.1)	0	
Current smoker [yes], n (%)	2 (3.2)	1 (12.5)	0.309	2 (3.3)	0	1.000
Past smoker [yes], n (%)	4 (6.7)	0	1.000	4 (6.9)	0	1.000
History of medical condition [present]**:**						
Essential hypertension, n (%)	6 (9.5)	0	1.000	5 (8.1)	0	1.000
Nephropathy, n (%)	0	1 (11.1)	0.125	0	1 (20.0)	0.104
Neuropathy, n (%)	5 (7.9)	0	1.000	4 (6.5)	0	1.000
Obesity[‖], n (%)	23 (39.0)	1 (14.3)	0.408	22 (38.6)	1 (25.0)	1.000
Other conditions[¶], n (%)	24 (38.1)	4 (44.4)	0.728	25 (40.3)	1 (20.0)	0.075
Hypertensive disorder in pregnancy [present], n (%)	18 (28.6)	4 (44.4)	0.441	18 (29.0)	3 (60.0)	0.315
Delivery method, n (%)			0.429			0.311
Vaginal birth	19 (30.2)	1 (11.1)		19 (30.6)	0	
Caesarean section	44 (69.8)	8 (88.9)		43 (69.4)	5 (100.0)	

[*] *p*-value relates to the difference between two groups examined using t-test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each

variable.

† as calculated from all women with at least one eye exam during pregnancy (n = 130).

‡ Contributed data: 60 women in the not progressed group, 9 women in the progressed group, 59 women in the “No” ST progression group and 5 women in the “Yes” ST progression group.

§ Measured at the first eye-exam in pregnancy. Contributed data: 60 women in the not progressed group, 5 women in the progressed group, 57 women in the “No” ST progression group and 3 women in the “Yes” ST progression group.

‖ Contributed data: 59 women in not progressed group, 7 women in progressed group, 57 women in “No” ST progression group and 4 women in “Yes” ST progression group.

¶ Includes thyroid conditions, heart disease, dyslipidaemia.

Abbreviations: ATSI, Aboriginal & Torres Strait Islander People; BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; IQR, interquartile range; ST, sight-threatening; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Characteristics of women with or without any DR progression and ST progression are presented in **Table 5-7**. The median duration of diabetes at enrolment was significantly higher in women with any DR progression compared to those without progression (p = 0.047). However, after adjusting for the type of diabetes, a higher median duration for each respective diabetes type was no longer significantly associated with any DR progression (p = 0.727). Meanwhile, the mean systolic BP (SBP; p = 0.006) and diastolic BP (DBP; p = 0.002) were significantly higher in women who had ST progression compared to those without. Similar trends were also observed between women with any progression versus women without, but these differences were not statistically significant.

A per-eye multivariate analysis (**Table 5-8**) showed that the presence of any DR (crude risk ratio [RR] 5.07; 95% CI 1.90 - 13.49) or SBP > 120 mmHg (crude RR 10.36; 95% CI 3.14 - 34.12) in early pregnancy significantly increased the risk of any DR progression. These results persisted even after adjusting for type and duration of diabetes. Similar findings were found for the risk of ST progression as shown in **Table 5-9**. The presence of any DR in early pregnancy was associated with an increased risk of ST progression compared to eyes with no DR (crude RR 18.93; 95% CI 2.30 - 155.54). Meanwhile, the risk of ST progression in eyes from women with SBP > 120 mmHg in early pregnancy was 28.6% (95% CI 4.9 - 52.2) but the risk in eyes from women with SBP ≤ 120 mmHg in early pregnancy was 0% (95% CI 0 - 3.5) so a risk ratio could not be calculated.

Among nine women who had DR progression during pregnancy, three women attended follow-up exams after delivery. One woman was stable, one woman had partial regression (one eye that developed PDR at the third trimester regressed to moderate NPDR without treatment), and the remaining woman who developed new mild NPDR in her left eye at the third trimester later developed new mild NPDR in her right eye after delivery (**Table 5-10**). Aside from this woman, there was another woman that was stable during pregnancy but experienced DR progression at postpartum. Her left eye developed DMO at 7 weeks postpartum, suggesting that progression towards STDR can still occur even after delivery.

Table 5-8. Risk factors associated with any DR progression in pregnancy

Factor of interest	Adjusted for:		Risk ratio (95% CI)
Type 1 diabetes (vs T2DM)		Crude RR	2.24 (0.74 - 6.80)
	Longer DM duration for DM type*	M-H adjusted	2.11 (0.70 - 6.43)
	Presence of any DR at early pregnancy	M-H adjusted	1.34 (0.48 - 3.73)
Longer than median duration of diabetes for diabetes type*		Crude RR	1.49 (0.54 - 4.08)
	DM type	M-H adjusted	1.32 (0.48 - 3.58)
	Presence of any DR at early pregnancy	M-H adjusted	0.69 (0.13 - 3.68)
Presence of any DR in early pregnancy (vs no DR in early pregnancy)		Crude RR	***5.07 (1.90 - 13.49)***
	DM type	M-H adjusted	***4.12 (1.55 - 10.91)***
	Longer DM duration for DM type*	M-H adjusted	***10.93 (1.66 - 71.83)***
HbA1c >6.5% at first measurement during pregnancy (vs HbA1c ≤ 6.5%)		Crude RR	1.75 (0.62 - 4.95)
	DM type	M-H adjusted	1.46 (0.58 - 3.70)
	Longer DM duration for DM type*	M-H adjusted	1.72 (0.61 - 4.86)
	Presence of any DR at early pregnancy	M-H adjusted	1.30 (0.50 - 3.42)
Systolic BP >120 mmHg measured at the first eye-exam during pregnancy (vs SBP ≤ 120 mmHg)		Crude RR	***10.36 (3.14 - 34.12)***
	DM type	M-H adjusted	***10.43 (3.20 - 33.99)***
	Longer DM duration for DM type*	M-H adjusted	***10.11 (3.03 - 33.75)***
	Presence of any DR at early pregnancy	M-H adjusted	***8.69 (2.79 - 27.05)***

* A duration of diabetes > median vs ≤ median (T1DM median duration = 16.5 years; T2DM median duration = 4.0 years).

Abbreviations: BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; DR, diabetic retinopathy; M-H, Mantel-Haenszel; RR, risk ratio; SBP, systolic blood pressure; T2DM, type 2 diabetes.

Table 5-9. Risk factors associated with sight-threatening progression in pregnancy

Factor of interest	Risk ratio (95% CI)
Type 1 diabetes (vs T2DM)	4.57 (0.55 - 38.09)
Longer than median duration of diabetes for diabetes type* (vs median or shorter duration)	5.15 (0.62 – 42.92)
Presence of any DR in early pregnancy (vs no DR in early pregnancy)	***18.93 (2.30 - 155.54)***
HbA1c > 6.5% at first measurement during pregnancy (vs HbA1c ≤ 6.5%)	1.76 (0.34 - 9.30)
Systolic BP > 120 mmHg measured at the first eye-exam during pregnancy (vs SBP ≤ 120 mmHg)	***Risk of 28.6% vs 0%*** **[Fisher exact *p* <0.001]**

* T1DM median duration = 16.5 years; T2DM median duration = 4.0 years.

Abbreviations: BP, blood pressure; CI, confidence interval; DR, diabetic retinopathy; SBP, systolic blood pressure; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 5-10. Summary of cases with postpartum DR changes

	Age (years)	Type, duration of diabetes, and comorbidities	Glycaemic control during pregnancy	Status of DR during and after pregnancy	Pregnancy outcomes
Regressed postpartum					
Patient 1	35	T1DM, 21 years, hypothyroidism.	Good control (HbA1c 5.4% - 5.6%).	Pre-existing mild NPDR in both eyes. At week 30, her right eye progressed to moderate NPDR and left eye progressed to PDR. Five weeks after delivery, her left eye regressed to moderate NPDR without treatment. BCVA maintained at 6/4.8 in both eyes throughout study period.	Emergency C-section at 37 weeks due to severe preeclampsia and foetal distress. Baby was admitted to SCN for 7 days for hypoglycaemia monitoring.
Progressed postpartum					
Patient 2	26	T1DM, 8 years, thyroid disease.	Poor control (HbA1c 7.4% - 8.1%).	No DR in both eyes, first examined at early second trimester. Mild NPDR developed in the left eye at the third trimester and in the right eye later in the postpartum. BCVA maintained at 6/6 in both eyes throughout study period.	Severe preeclampsia, polyhydramnios. Preterm birth at 34 weeks via emergency C-section.
Patient 3	33	T1DM, 22 years, dyslipidaemia.	Good control (HbA1c 5.5% - 5.9%).	Mild NPDR in both eyes, first examined at early second trimester and stable through to the end of pregnancy. DMO was observed in the left eye at 7 weeks postpartum. BCVA maintained at 6/4.5 in both eyes during pregnancy but decreased to 6/6 in both eyes after delivery.	Planned C-section at 37 weeks. Baby experienced respiratory distress.

Abbreviations: BCVA, best corrected visual acuity; DMO, diabetic macular oedema; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SCN, special care nursery; T1DM, type 1 diabetes.

5.4. Discussion

We found that the prevalence of DR and STDR per eye during the entire study in our cohort was 20.8% and 6.6%, and the prevalence per woman was 21.5% and 9.4%, respectively. Between early to late pregnancy, DR progression was observed in 9.7 per 100 eyes, of which almost half of these developed STDR. This progression rate was equivalent to 12.5 per 100 women in this study cohort. Even though the DR status in some eyes regressed, sight-threatening progression was still observed in other eyes after delivery. A new development of DMO contributed to half of the sight-threatening progression cases but impaired vision was observed only in one woman with reactivated-PDR. In this population, DR and STDR were more common in women with T1DM, a longer diabetes duration, and a higher HbA1c in early pregnancy, which is expected since these three factors are well-known DR risk factors. Interestingly, overall DR progression and progression to STDR were associated only with the presence of DR and a higher SBP in early pregnancy.

A wide range of studies have reported the prevalence of DR in early pregnancy; however, very few observed T2DM patients. Globally, it has been estimated that 25% to 72% of pregnant women with T1DM[113,149] and 14% to 33% of those with T2DM[13,204] have DR in early pregnancy. In our study, the prevalence of DR per eye in the first trimester was 36.2% in T1DM and 6.9% in T2DM, with an overall prevalence of 21.6%. These prevalence rates seem lower than the majority of earlier studies. This difference could be due to the fact that our patients' eye examination attendance in the first trimester was low (29 women from each diabetes type; the lowest attendance among three trimesters); thus, our prevalence rate may be an underestimate. However, most previous studies mainly aimed to assess progression rate rather than prevalence; thus, a proportion of women with less than two eye exams during pregnancy (the required number to make a comparison for change) was excluded. Consequently, women with no DR who were more likely to have only one exam were likely underrepresented in their estimations. Interestingly, our prevalence of DR in early pregnancy is similar to that reported in a previous Australian study by Horvat *et al*.[114]

Regarding DR progression rate, a marked decrease in the DR progression rate during pregnancy in Australia is documented (14.5% in the previous Australian study[114] vs 9.7% in the current study) which may suggest an improvement in the DR or diabetes

management, in general. This trend of improvement was also reflected in the overall improved pregnancy outcomes of Australian diabetic women that was reported by Shand and associates.[29] The rate of progression in our cohort was also lower than those reported by the majority of the available literature globally, even after accounting for type of diabetes. For instance, Axer-Siegel *et al.* reported that 36.7% of their T1DM population experienced mild progression and a further 8.3% developed PDR during pregnancy,[112] whilst Rosenn *et al.* observed progression in 33% of their 154 women.[138] Rasmussen *et al.,* who exclusively studied T2DM women, reported a progression rate of 14% for their 80 women.[13] A possible explanation for these discrepancies may be that our cohort had better diabetes control in early pregnancy, as shown by the median HbA1c of 6.4%, and had fewer diabetes complications compared to the previous studies with higher reported rates. Although Axer-Siegel *et al.*'s cohort was younger and had a shorter median duration of diabetes (13 years), their mean HbA1c in the first trimester (8.2%) and proportion of women with hypertension were both higher compared to ours.[112] Similar high-risk factors were also found in Rosenn *et al.*'s cohort (mean HbA1c in the first trimester was 9.3% in the non-progression group and 10.3% in the progression group; hypertension was recorded in 45% and 55% of the groups, respectively).[138] Our progression rate is consistent with that of Toda *et al.*'s well-controlled cohort (mean HbA1c 7.1% ± 0.8).[147] They reported that DR worsening occurred in 17% of their Japanese patients and 3% of them developed sight-threatening disease (two patients lost their vision and one received laser treatment due to severe NPDR). A similar progression rate (15.6%) was also reported by the Atlantic Diabetes in Pregnancy (Atlantic DIP) study, a more recent study that observed mostly Caucasian pregnant women with both types of diabetes (mean HbA1c 7.2% ± 1.48).[150] These findings highlight the imperative of achieving a good glycaemic control in early pregnancy.

We observed sight-threatening progression in a woman with extremely poor glycaemic control. This woman, who had T1DM, experienced rapid improvement in her HbA1c during pregnancy. This single case suggests that poor glycaemic control and rapid HbA1c improvement may be associated with an increased risk of DR progression in pregnancy. This phenomenon of early worsening of DR due to rapid correction of blood sugar levels has been previously reported[74-76] and has been postulated by some to account for the increased progression of DR during pregnancy,[111,148,230] where a rapid improvement in blood sugar control is required to ensure the well-being of both the mother and foetus

during this time. Unfortunately, as we were unable to collect HbA1c data from a sufficient number of women from our cohort prior to pregnancy and in late pregnancy, we were unable to determine if this was a factor in the eyes that progressed.

Diabetic macular oedema (DMO) is the most common cause of vision loss due to DR. It has been postulated that the increased retinal vascular permeability during pregnancy can result in the development of DMO.[107] Surprisingly, a very limited number of studies have assessed DMO progression during pregnancy. Arun *et al.* reported that 5.1% of their T1DM patients had laser treatment in pregnancy for DMO.[113] Two other studies documented that 13.7% of pregnant women with T1DM experienced DMO progression (11 women developed DMO, and three who had pre-existing mild-to-moderate DMO developed clinically significant macular oedema [CSMO], a form of DMO that involves the centre of macula)[110] and 1.2% of T2DM pregnant women developed CSMO.[13] These women with CSMO had loss of visual acuity. The Atlantic DIP study recorded nine cases (4.9%) of DMO progression in their mixed diabetes type cohort (6 women developed new DMO and 3 women had a worsening of their pre-existing DMO).[150] All of these studies diagnosed DMO using fundus photographs. No previous studies have utilised optical coherence tomography (OCT) to diagnose DMO, the current gold standard that is the most sensitive means of diagnosing DMO.[9,243,244] Our present study utilised OCT and we found that among women with sufficient eye exams and OCT data, 2.2 per 100 eyes (two eyes from two women with T1DM and an eye from a woman with T2DM) which represents 4.5% of our population developed DMO during pregnancy. Unfortunately, we did not assess for worsening of pre-existing DMO which might have resulted in the lower rate in our study. Interestingly, sight-threatening progression during pregnancy was more commonly due to the development of DMO than PDR (DMO vs PDR, 3 vs 2 women). This trend was also documented in the Atlantic DIP study (9 vs 6 women, respectively)[150] and three other studies.[13,110,245] Although no visual impairment was observed in our participants who developed DMO, these findings highlight the importance of DMO assessment during pregnancy since worsening of DMO, particularly with central macula involvement, has been associated with vision loss.

Several studies have shown that a worsening of DR during pregnancy was most likely to regress spontaneously after delivery.[112,246,247] However, other studies have had contradictory results.[105,248] Among women who attended postpartum visits, one woman

in our study had partial regression, one woman who had progression during pregnancy remained stable, and two other women progressed after delivery, one of whom developed DMO. Although our case numbers are inadequate, the risk of DR progression appeared to persist in the postpartum. This observation further supports the concept that DR progression can still occur after delivery and spontaneous regression after delivery should not always be expected.

Many studies reported different risk factors that influence the risk of DR progression in pregnancy. Similar to the non-pregnant population, a longer duration of diabetes and poor glycaemic control were mentioned multiple times as the most common risk factors for the presence of DR and its worsening in pregnancy.[13,105,112,148] In contrast, we found that both risk factors were associated with the presence of DR during pregnancy, but not with the risk of progression in this study population. This inconsistency is likely due to a lack of power caused by very small case numbers of progression in our cohort. We observed only 9 women with DR progression while most previous studies recorded more than 20 cases of progression in their cohort. Among those who had less than 10 cases of progression, only baseline retinopathy status was identified as a risk factor for DR progression in pregnancy.[113] When we performed a per-eye multivariate analysis (n = 14 eyes with progression), we similarly found that the presence of DR in early pregnancy increased the risk of DR progression during pregnancy. Similarly, an Israeli study in the early 1990s reported that pregnant women with pre-existing DR were at a higher risk of progression than those without. Moreover, those with NPDR in early pregnancy were more likely to develop PDR than women with no DR.[112] Two other studies have also confirmed this association.[111,230] Furthermore, we found that eyes from women with a higher SBP also had an increased risk of progression. Overall, our findings are in line with those of the Atlantic DIP study, which is one of the most recent prospective cohort studies in this field that similarly demonstrated that a higher SBP at the time of booking increased the odds of retinopathy progression; and that the diabetes type, duration of diabetes and HbA1c in the first trimester did not increase this risk.[150]

Interestingly, we found that women with DR or STDR were more likely to deliver by C-section. In general, it has been well documented that diabetes in pregnancy increases the risk of C-section delivery.[249-252] The rate of C-sections in Australian women with pre-existing diabetes has increased, and are markedly higher than in non-diabetic women (in

2005 - 2007: pre-existing diabetes 41% vs non-diabetic 28%; in 2014 - 2015: pre-existing diabetes 49.1% vs non-diabetic 33%).[249,253] This high C-section rate was also associated with an increased rate of macrosomia, poor diabetes control, unplanned pregnancy and maternal obesity.[250] Additionally, women with T1DM had a higher rate of C-sections than those with T2DM.[253] In our study, women with DR or STDR were more likely to have T1DM, which may explain the high C-section rate in these groups, although, we found no significant difference in the proportion of women with maternal obesity or large for GA (LGA) babies between those with or without DR/STDR. However, women with DR had a significantly higher HbA1c early in pregnancy than those without DR which potentially increased the risk of LGA or macrosomia; this may have increased the proportion of C-section cases, supporting previous findings. However, this association was not observed in women with STDR, although the number of women in this group was likely to have been too small to achieve significance. We did not collect data on unplanned pregnancies; thus, its relationship with the high C-section rate in this cohort could not be assessed. Further studies exploring the relationships between DR progression and pregnancy outcomes might help predict unfavourable outcomes in pregnant women with pre-existing diabetes.

More than half of our cohort of pregnant women had T2DM. T2DM is becoming increasingly common in Australian women of reproductive age and has relatively similar maternal and foetal adverse outcomes to T1DM.[30,254] Unfortunately, there appears to be a comparative lack of attention given to those with T2DM due to the perception that T2DM does not result in STDR to the same extent as T1DM. In Ophthalmology, this is reflected in the limited number of studies that have presented data regarding DR progression during pregnancy in T2DM women.[9] Consequently, there is a lack of specific recommendations regarding the management of DR in this rapidly increasing demographic. In keeping with previous findings,[30,181,255] our study showed that pregnant women with T2DM had slightly lower rates of, but similarly significant, adverse pregnancy outcomes compared to T1DM. Likewise, although the presence of DR was significantly higher in women with T1DM, we found that the risk of progression during pregnancy once DR was present was equal between both types of diabetes. This trend was also observed in more recent studies.[147,150] Therefore, it has been suggested that women with T2DM should follow the same eye screening recommendations as women with T1DM.[13,254] Despite this equivalent risk, worryingly, women with T2DM were less

likely to attend an eye screening examination during pregnancy.[256]

This study has several strengths. It provides contemporary evidence on the prevalence of DR and STDR, its progression rate and the risk factors related to the progression in pregnant women with pre-existing diabetes. Rather than just reporting the prevalence of DR at early pregnancy, we reported the prevalence of DR across the entire study period (from conception up to 3-months after delivery), demonstrating a clearer picture of this disease's burden in the pregnant population. More importantly, with just over half of our participants having T2DM, this study cohort is a good representation of the present-day Australian diabetic pregnant population. This study also provides data on the prevalence and incidence of DMO during pregnancy, a crucial condition in DR that has been understudied in pregnant women. Moreover, the duration of diabetes was analysed based on the median value of each diabetes type. With this approach, the interaction between the type and duration of diabetes could be discerned and enabled the actual effect of each variable to be presented. We found that T1DM was associated with the presence of DR and STDR, but a longer duration of diabetes was only related to the presence of STDR.

However, there are some limitations. There was a tight correlation between diabetes type and ethnicity in this study population, where most of the women with T1DM were Caucasian, and those with T2DM were Asian. Therefore, the effect of ethnicity on the DR prevalence and incidence in this study could not be separated from type of diabetes. Another limitation was that only 88.4% of our participants had at least one eye exam during pregnancy, and just under half had at least two eye examinations available for progression analysis. Therefore, our findings might have underestimated the actual progression rate in the population. However, no significant difference was found in the baseline demographic characteristics between women who were included or excluded from the progression analysis, except for duration of diabetes, smoking history, and those with obesity. Women who were less likely to attend more than one eye exam had a shorter duration of diabetes and a higher rate of obesity, which may be reflective of the characteristics of women with T2DM. A higher rate of previous smoking and lower rate of current smokers was also related to women with insufficient exams. Despite these differences, none of these factors were found to be associated with the risk of DR progression in our cohort, in line with the findings from other studies.[111,147,150] Lastly, due to the limited number of observed cases, we calculated our prevalence and progression

rate as rates per eye rather than rates per woman to achieve better precision. Nonetheless, our rate per eye is quite similar to that per woman, except for the rate of DMO, as women in our cohort were more likely to have unilateral DMO; hence, the rate per eye for DMO is lower than the DMO rate per woman. Therefore, the interpretation of our findings should be made cautiously, although it is worth nothing that DR is generally not a unilateral disease.[257]

To conclude, our prevalence rates of any DR and STDR in pregnancy and in the early postpartum were relatively lower than those reported in former studies. Sight-threatening progression was found to be more commonly due to the development of DMO than PDR. This risk of progression to DMO may still occur even after delivery, emphasising the need for retinal evaluation in the postpartum period. Women with T1DM, who were more likely to have long-standing diabetes and poorer glycaemic control, were more likely to have DR in pregnancy. However, once DR was present, the risk of progression depended only on the level of DR found and the SBP, regardless of diabetes type. Our findings emphasise the importance of achieving good glycaemic control early in pregnancy to reduce the risk of DR progression during pregnancy. Worryingly, one-fifth of our participants failed to attend any eye examinations during pregnancy and women with T2DM were more likely to only attend once. Given our findings, special attention should be given to reverse the misperception that eye screening in T2DM patients is less important than in T1DM patients, highlighting the need to address barriers to eye screening adherence given the significant risk of vision loss from DR in this population.

CHAPTER 6: OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY USE FOR DIABETIC RETINOPATHY SCREENING IN PREGNANCY (AIM 2)

6.1. Overview

Optical Coherence Tomography Angiography (OCTA) is a new, non-invasive imaging modality and its ability to visualise retinal vasculature is equivalent to that of fundus fluorescence angiography (FFA), the current gold standard for assessing ischemic changes in the retina. Since it is not recommended to perform FFA during pregnancy due to the requirement of an intravenous dye injection, OCTA provides a safer way to assess the vasculature of the retina and has a potential role in the monitoring of diabetic retinopathy (DR) during pregnancy. Physiological changes during pregnancy also affect the eye; hence there might be differences in the appearance of the retinal vasculature compared to the non-pregnant population. Since the introduction of this advanced modality, a very limited number of studies have reported its use in assessing DR in pregnancy and correlated OCTA parameters with the DR status of pregnant women with pre-existing diabetes. We hypothesised that OCTA parameters, such as vessel density and parafoveal avascular zone area, in women with diabetes would differ with each stage of pregnancy (non-pregnant, pregnant, and postpartum).

In this chapter, the methods and results of the second aim of the study are presented, which aims to assess the use of OCTA in evaluating retinal vascular changes in diabetic patients during the different stages of pregnancy. Specifically:

Aim 2.1: To compare and correlate Vessel Density (VD) with DR severity and pregnancy status (non-pregnant, pregnant, and postpartum).

Aim 2.2: To compare and correlate the Foveal Avascular Zone (FAZ) area with DR severity and pregnancy status (non-pregnant, pregnant, and postpartum).

Aim 2.3: To assess the predictors of DR progression using OCTA parameters (FAZ area and VD).

6.2. Methods

For this part of the study, an additional OCTA examination was performed at the Melbourne Eyecare (MEyecare) Clinic using the DRI OCT Triton (Topcon Corp., Japan) at every scheduled visit. Vessel density (VD) and FAZ area from the superficial capillary plexus (SCP) of the retina were assessed to evaluate vascular changes in the retina. Although there are plans to assess the VD and FAZ area in the deep capillary plexus (DCP), there are no readily available, validated software packages to perform image analysis on this layer for scans obtained using the Topcon DRI OCT Triton at the time of writing this thesis. Therefore, for this thesis, only the SCP was analysed and presented.

6.2.1. OCTA imaging protocol

Two OCTA scans (macula-centred) were taken from each eye with a 3.0 mm x 3.0 mm scan mode. The 3.0 x 3.0 mm scan was chosen because it gives a better image resolution for assessing VD changes and delineates the FAZ more precisely compared to the 6.0 mm x 6.0 mm, 9.0 mm x 9.0 mm, and 12.0 mm x 12.0 mm scans.[155,166,258] In cases of insufficient image quality, additional scans were taken based on the operator's judgment. If the participants experienced discomfort during the scans, re-scanning was not performed. Good-quality images were defined as having an image quality of ≥40% as determined by the OCT manufacturer,[153,259] with minimal image artefacts that distorted retinal features (manually reviewed by RCAS and FW). Any poor-quality images were excluded and were documented as such (**Figure 6-1**).

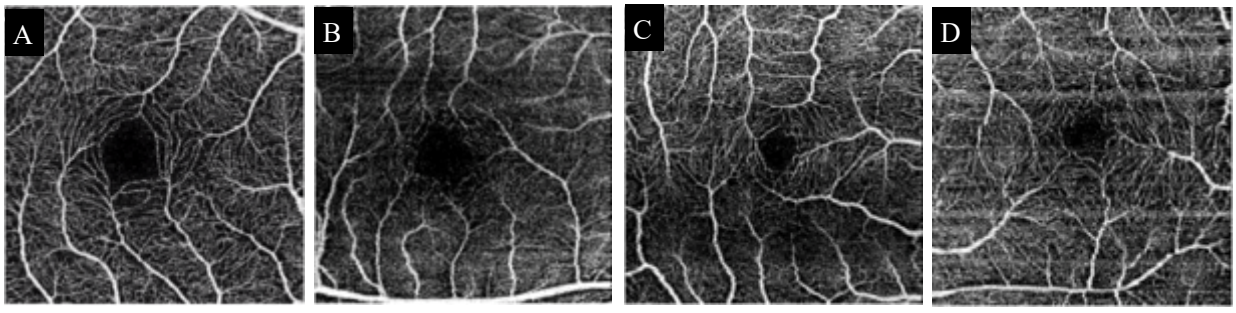


Figure 6-1. Example of OCTA images with high quality (A) and low quality (B-D)

Source: Topcon User Manual Ophthalmic Data System.

From each OCTA image, four 'en-face' OCT layers were automatically generated by the in-built software (IMAGEnet 6 ver.1.21.11783) as shown in **Figure 6-2**. These layers, in the central macular area, include the [40]:

A. **Superficial Capillary Plexus (SCP)** located between 2.6 µm below the internal limiting membrane (ILM) to 15.6 µm below the boundary of inner plexiform layer and inner nuclear layer (IPL/INL). This plexus is mainly supplied by the central retinal artery.

B. **Deep Capillary Plexus (DCP)** located between 15.6µm below the IPL/INL to 70.2 µm below the IPL/ INL. This plexus is supplied by the vertical anastomoses from the SCP.

C. **Outer Retinal Layer (ORL)**, a physiologically avascular area, is located between 70.2 µm below the IPL/ INL to the Brunch's membrane (BM). This layer consists of photoreceptors.

D. **Choriocapillaris Layer**, located between the BM to 10.4 µm below the BM. The choroid receives up to 85% of the ocular blood circulation and is the main supply for the ORL and the FAZ.

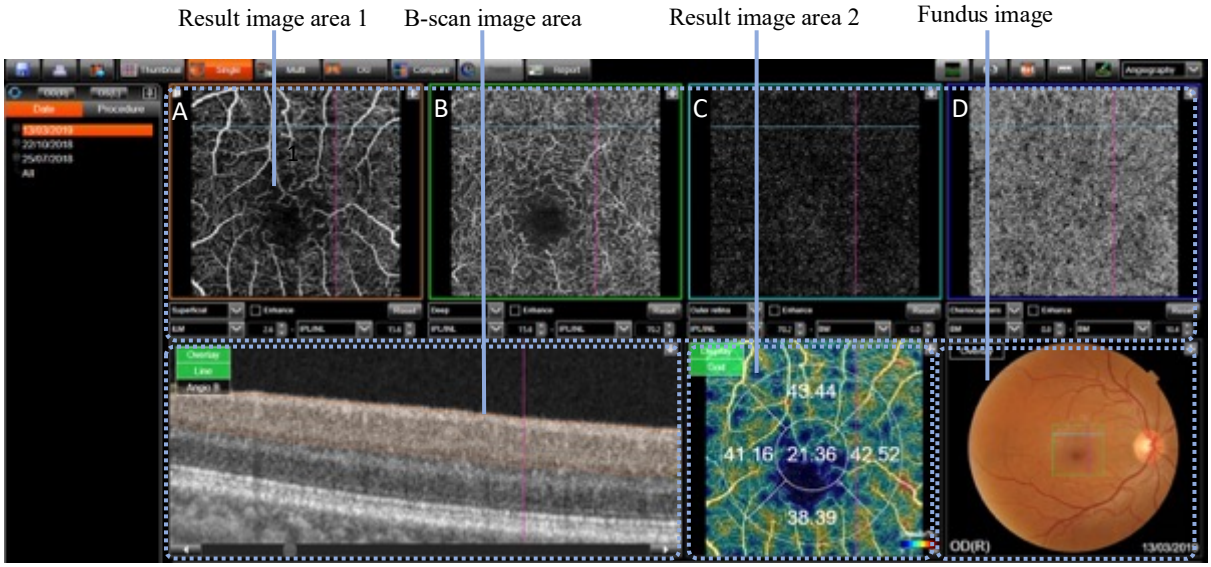


Figure 6-2. The layout of the IMAGEnet 6

Four different retinal layers in the "Result image area 1". The superficial capillary plexus (**A**), deep capillary plexus (**B**), outer retinal layer (**C**), and choriocapillaris layer (**D**).

As mentioned in **Chapter 2**, this segmentation has become one of the advantages of OCTA over the current angiographic gold standard, fundus fluorescein angiography (FFA).

6.2.2. Vessel density measurement

Vessel density (VD) measurements of the SCP were generated automatically by IMAGEnet 6. The VD data was obtained from the software by following these steps:

1) Select the "Display" button in the "Result image area 2" (**Figure 6-2**) and choose "Density Map".

2) Select the "Grid" menu that will be shown under the "Display" menu and choose "ETDRS (Density)". The vessel density data of five areas within the ETDRS grid (central, superior, nasal, inferior and temporal) were then recorded.

3) If the image was not well-centred, a manual adjustment was performed to relocate the grid locations using the B scan for reference, as shown in **Figure 6-3**. It was performed by selecting "Grid" then "Reposition". If, after repositioning the grid, an area was cut-out, the incomplete measurement from that truncated area was excluded from the dataset.

4) Press [ ] button to save the changes that were made.

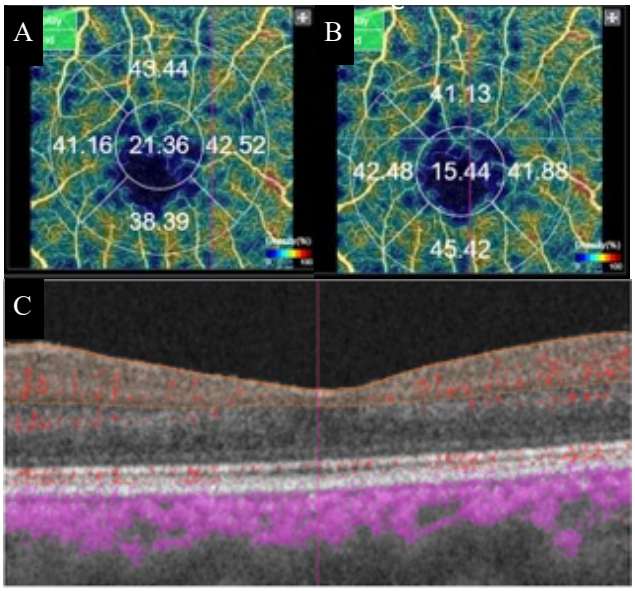


Figure 6-3. Repositioning of the ETDRS grid (A to B) based upon OCT B-scan (C)

All of the above steps were performed for every included SCP image by two reviewers (FW and RCAS) simultaneously. The mean VD value of two OCTA scans from the same eye on the same visit (eye-visit) was calculated for each ETDRS grid area and was used

for data analysis. In cases where only one VD value was available from an eye-visit (for example if only one good-quality image was obtained or there were missing values due to image offsets or movement artefacts), the VD value from the available data was used for analysis in place of a mean. In addition to the five areas of VD described above, a pericentral VD (the mean of all four pericentral subfield VDs [i.e., superior, inferior, temporal and nasal VD]) was also calculated for eye-visits at which there was data available for each of the four subfields. If data from one or more of these subfields was missing, the pericentral VD was not able to be calculated.

6.2.3. Foveal avascular zone area measurement

Because IMAGEnet 6 did not have a system to measure the FAZ area in an automated fashion, the FAZ area was initially obtained by manually defining the FAZ border using the available measurement tool within the software. This tool then calculated the area in μm^2. The measurement was performed following these steps:

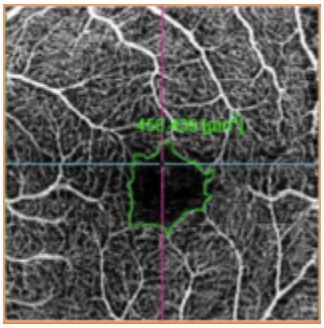


Figure 6-4. Measuring the foveal avascular zone area

1) Activate the desired image (The SCP) in the "Result image area 1". The image was then enlarged by pressing the [Whole screen display] button at the top right corner of each image.

2) Select the [Tool] button and choose 'Free Measurement". Then, drag the cursor to delineate the border of the FAZ area, as shown in **Figure 6-4**.

Two independent graders (FW and Dr Mali Okada) manually measured the FAZ area for each image as described. The quality of the grading was validated by ongoing standardised assessments of inter-grader agreement. Inter-grader agreement was assessed for the first 43 patients (84 eyes, 160 OCTA images) at the baseline visit and an intraclass correlation coefficient (ICC) of 0.998 (95% CI 0.997 - 0.999), indicating an almost perfect agreement, was achieved.[260]

Limitations with this manual measurement methodology were encountered when attempting longitudinal image analysis. Delineating the same FAZ border from the same eye at follow-up visits was challenging with the manual FAZ measurement on the DRI

OCT Triton. Inter-visit measurements could thus be inconsistent, thereby complicating our aim to assess the change in FAZ between visits during pregnancy. Due to this limitation, a new method was developed to provide an automatic measurement utilising independent software (ImageJ, version 2.0.0-rc-69/1.52n). To achieve this, an algorithm was developed and tested in the "FAZ Pilot Study".

FAZ pilot study (ImageJ algorithm development and validation)

In collaboration with A/Prof. Bang Bui and Dr Jeremiah Lim from the Department of Optometry and Vision Sciences, we developed an algorithm to measure the FAZ area of an OCTA image automatically. Using ImageJ, this algorithm created a vessel map by binarizing the pixels in the image into those showing evidence of flow and those not showing evidence of flow. This binarization was determined using a "threshold" which was applied to pixel-level data where each pixel represented segmented data from one B scan. Each pixel had a value, which could be graphed on a grayscale (**Figure 6-5**), indicative of the probability that a flow signal had been detected in the corresponding retinal position. The developed algorithm can be found in **Appendix A7**.

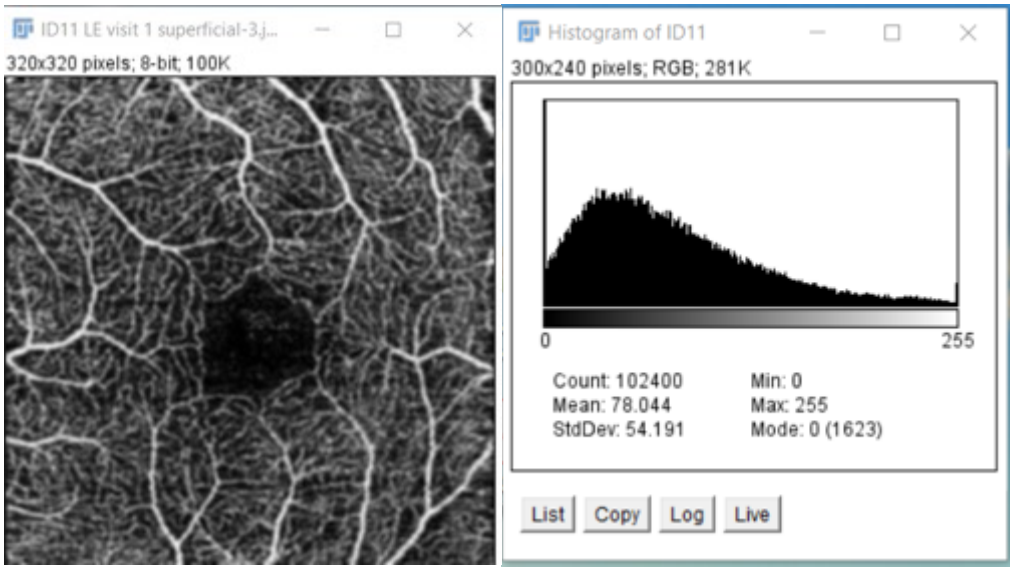
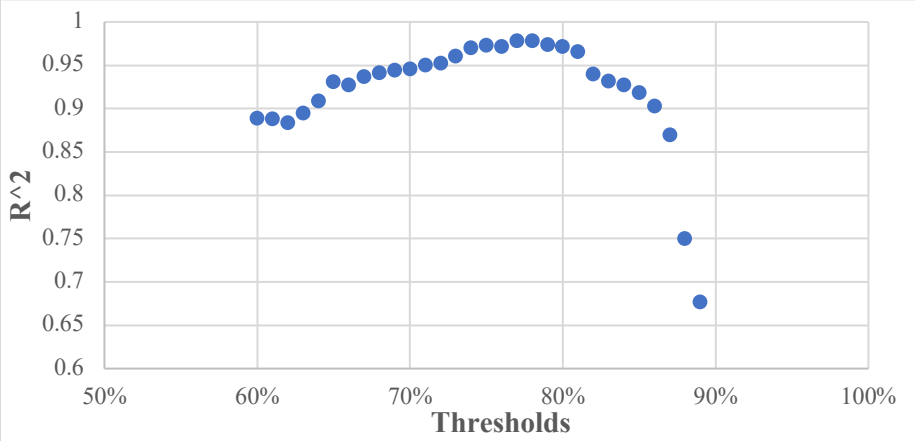


Figure 6-5. Histogram of pixel-level data of the optical coherence tomography angiography image

To determine an optimal threshold for binarization of the OCTA images, we measured a random sample of 20 images from baseline visits with the developed algorithm and then compared these measurements with our manual measurement data (the gold standard).

Thresholds between 60% and 90% were tested for each image, and the coefficient of variance was calculated to determine the optimum threshold value for capturing the best FAZ area measurement in the samples.

Figure 6-6 shows the result of the FAZ pilot study. The best correlation with the gold standard for a fixed threshold across all images was 77% with a coefficient of determination (R^2) of 0.98. However, the optimum threshold varied between images. The mode was 76% (R^2 = 0.97; not dissimilar to 77%) and the mean was 80%. Therefore, 77% was selected as the default threshold for binarization with the option to use a range of thresholds between 65% and 85%, which had similar acceptable coefficients of determination (R^2 > 0.90), if necessary. **Figure 6-7** shows an illustration of the FAZ area that was automatically delineated and measured by the algorithm in ImageJ.



The optimal threshold for each				
min	max	median	average	mode
70	90	82	80.5	76

Figure 6-6. Coefficient of determination for each tested threshold in the foveal avascular zone pilot study

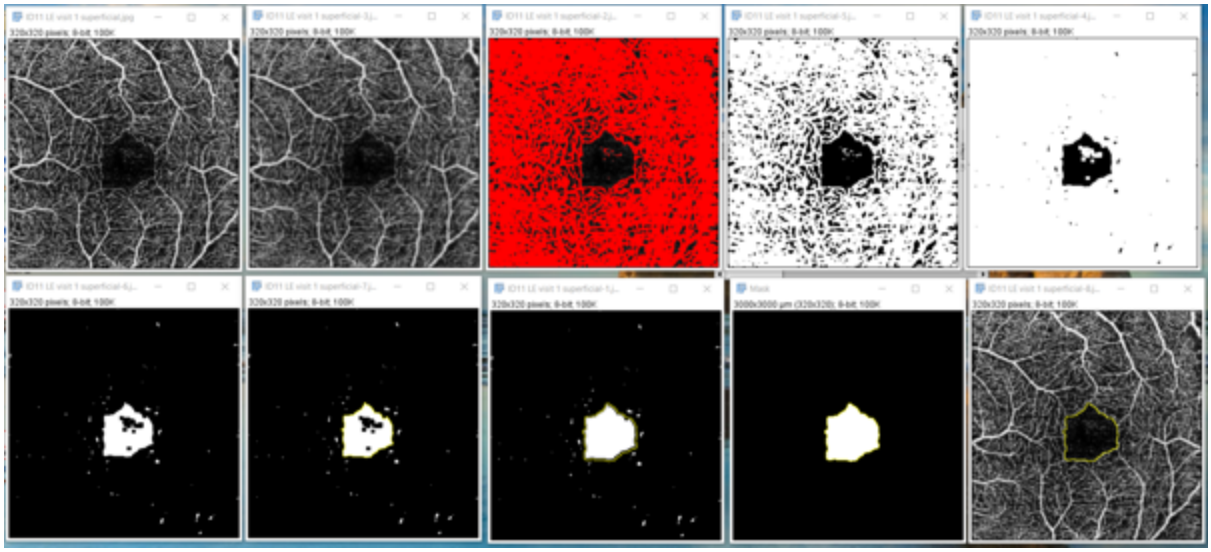


Figure 6-7. Illustration of automated foveal avascular zone measurement using our algorithm in the ImageJ

Automated FAZ measurement

For the FAZ analysis, all OCTA images were exported from IMAGEnet 6 as JPEG files with a resolution of 320 x 320 pixels and subsequently imported into ImageJ to obtain the FAZ area value. The data output was automatically saved as "FAZ ROI compilation.zip" and could be accessed through the image source folder. FAZ data was collected under the "Area" variable (**Figure 6-8**).

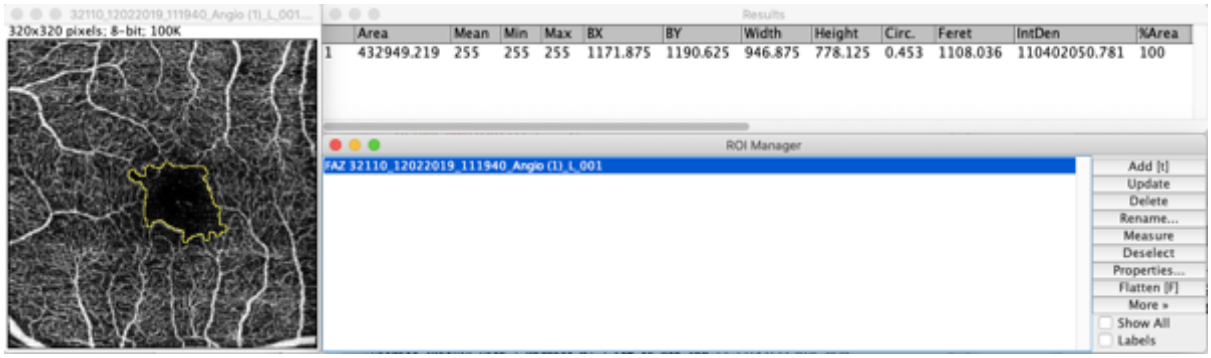


Figure 6-8. Result of foveal avascular zone area measurement using ImageJ

If the algorithm failed to delineate the correct FAZ border in an image (refer to the example situation in **Figure 6-9)**, the image was reviewed by human graders (FW and JL) and adjusted as follows:

1) If the algorithm selected the wrong area (**Figure 6-9 A-B**), the program was re-

run by activating the manual mode ("manualmode = 1", default: "manualmode = 0"), then manually selecting the desired area (FAZ) to be measured.

2) If the algorithm selected the correct area but did not correctly define the FAZ border (**Figure 6-9 C-D**), the algorithm was re-run with an adjusted threshold ("desiredpercent = XX"; default: "desiredpercent = 77"). A threshold between 65% to 85% was applied so that the computed FAZ border agreed with the graders' assessment of the FAZ border.

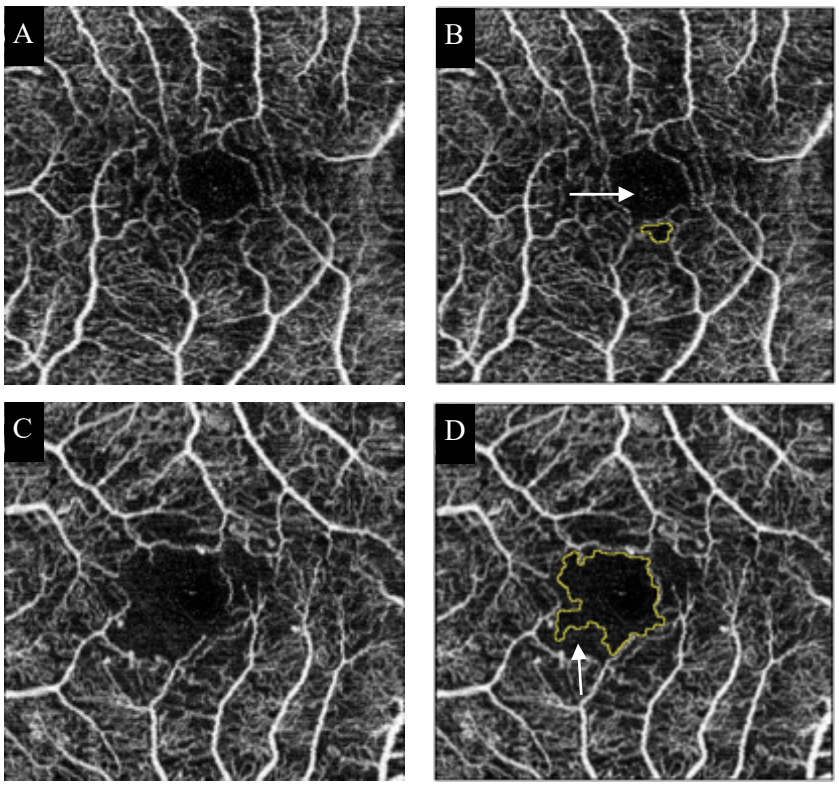


Figure 6-9. Automated FAZ area measurement failures

Raw OCTA images (**A** & **C**) and automated FAZ border delineation (yellow line) using the default algorithm (**B** & **D**). White arrows show the FAZ area that was supposed to be measured. Abbreviations: FAZ, foveal avascular zone; OCTA, optical coherence tomography angiography.

The adjustment steps described above were performed by the two graders and any disagreement was settled by the third adjudicator (RCAS). To further control the measurement quality, measurements were only automatically included when the FAZ area difference between two images from the same eye-visit did not exceed 10%. For images with a greater than 10% difference, the third adjudicator re-assessed the image quality and decided whether the image needed to be measured manually or excluded due

to poor-quality. From the total number of scans acquired, 8.8% were excluded. Similar to VD, the mean FAZ value from the same eye-visit was calculated and used for data analysis. In cases with only one FAZ value, the available FAZ value was used for analysis.

6.2.4. Determining the change in diabetic retinopathy status

To compare and correlate OCTA parameters with the change in DR status over the study period, eyes with multiple visits were categorised into: "eyes with no change" and "eyes with change". Eye changes at any OCTA eye-visit during follow-up were defined as follows: 1) **any progression** (defined as a 1-step increase in DR severity or development of DMO or pre-existing PDR requiring further treatment during study period); 2) **any improvement** (defined as a 1-step reduction in DR severity or resolved DMO); or 3) both progression and improvement during follow-up.

6.2.5. Statistical analysis

All statistical analyses were performed using Stata IC version 15.1 for Windows (College Station, Texas, USA). Participating women were categorised as either non-pregnant, pregnant or postpartum based upon their status at their first eye-visit with the most complete OCTA data (including FAZ area, central, superior, inferior, nasal, and temporal VD). If an eye had an eye-visit during pregnancy with multiple missing data (e.g., missing inferior VD and nasal VD) but had another eye-visit in the postpartum with only one missing datum (e.g., missing only inferior VD), then the eye-visit included in the analysis would be the postpartum visit and the eye would be allocated to the postpartum group.

Descriptive analysis was used to present the baseline characteristics of the included participants and their eyes. The normality of the continuous variable was tested with the Shapiro-Wilk test before presenting the summary statistics as means and 95% confidence intervals (CI) for variables showing a suitably normal distribution, or medians and interquartile ranges (IQR) for variables that did not. Demographic and clinical characteristics were compared between the three analytical groups using the Kruskal-Wallis or one-way ANOVA test.

The included eye-visits were then categorised into "eyes without DR" and "eyes with any DR" depending on their DR status at that first, most complete OCTA eye-visit. Pairwise comparisons between the pregnancy status groups and between the DR status groups were

performed using a Student t-test or Wilcoxon rank-sum test, as appropriate. Spearman correlation coefficients (rho) were also calculated to assess the relationship between the FAZ area and central and pericentral VDs. Finally, longitudinal data per eye was plotted to assess each eye's trajectory over time and compare the OCTA parameters with DR status longitudinally. For all tests, a *p*-value of <0.05 was considered to be statistically significant.

6.3. Results

A total of 64 women had at least one visit with OCTA imaging. **Table 6-1** demonstrates demographic characteristics of these included women; their median age was 34.0 years (IQR 31.0 – 36.0), 38 women (59.4%) had T1DM, and there were 33 (51.6%) Caucasian and 24 (37.5%) Asian women. These women were categorised into three groups based upon their pregnancy status at their first eye-visit with the most complete OCTA data, as described earlier. No statistically significant difference was found between the three groups, except for a history of neuropathy where women in the non-pregnant group more commonly reported neuropathy compared to other groups ($p = 0.001$). **Table 6-2** shows characteristics of included eyes from 64 women at the first visit with the most complete OCTA data. Overall, 125 eyes contributed at least one OCTA measurement (either FAZ or VD data); 21 of these eyes were from the non-pregnant group, 96 eyes from the pregnant group, and 8 eyes from the postpartum group. Both eyes from one non-pregnant woman and both eyes from one pregnant woman had a history of retinal laser treatment. Overall, eyes in the non-pregnant group had more severe DR compared to eyes in the pregnant and postpartum groups ($p = 0.031$) at their first most complete OCTA exam.

6.3.1. Vessel Density

After an assessment of image quality, three women were excluded from the VD analysis. Overall, 117 eyes (from 61 women) contributed measurements of central, superior, and temporal VD, 116 eyes (from 61 women) contributed nasal VD data, and 111 eyes (from 58 women) contributed inferior VD data. Because of some missing values for nasal and inferior VD, pericentral VD could only be calculated in 110 eyes (57 women). Inferior VD data was missing from six eyes (five women) of which five eyes had no DR and one eye had mild NPDR at the exam, while another eye with no DR had missing data for nasal VD.

Table 6-1. Demographic characteristics of included participants with OCTA imaging

	Overall	**Non-pregnant**	**Pregnant**	**Postpartum**	***p*-value***
Participants [women], n (%)	64	11	49	4	
Age at enrolment [years], median (IQR)	34.0 (31.0 - 36.0)	35.0 (33.0 – 37.0)	33.0 (31.0 – 35.0)	35.5 (32.5 – 36.0)	0.303
Time of first eye exam with most complete OCTA data, n (%)					
Non-pregnant	11 (17.2)				
Trimester 1	21 (32.8)				
Trimester 2	19 (29.7)				
Trimester 3	9 (14.1)				
Postpartum	4 (6.2)				
Type of diabetes, n (%)					0.280
T1DM	38 (59.4)	9 (81.8)	27 (55.1)	2 (50.0)	
T2DM	26	2 (18.1)	22 (44.9)	2 (50.0)	
Duration of diabetes at enrolment in T1DM [years], median (IQR)	20.5 (9.0 - 23.3)	22.0 (21.0 - 24.0)	17.0 (8.0 - 23.0)	25.5 (24.0 - 27.0)	0.111
Duration of diabetes at enrolment in T2DM [years], median (IQR)	2.5 (1.0 - 5.0)	1.0 (0.2 - 1.8)	3.5 (1.8 - 5.0)	3.6 (0.1 - 7.0)	0.450
HbA1c around the included eye-visit† [%], mean (95% CI)	6.6 (6.3 - 7.0)	7.3 (6.8 - 7.9)	6.5 (6.2 - 6.9)	-	0.071
Ethnicity, n (%)					0.836
ATSI	1 (1.6)	0	1 (2.0)	0	
South Pacific Islanders	1 (1.6)	0	1 (2.0)	0	
Caucasian	33 (51.6)	8 (72.7)	24 (49.0)	1 (25.0)	
Asian	24 (37.5)	3 (27.3)	18 (36.7)	3 (75.0)	
Other	5 (7.9)	0	5 (10.1)	0	
Current smoker [yes], n (%)	0	0	0	0	NA
Past smoker [yes], n (%)	8 (13.1)	2 (20.0)	6 (12.8)	0	0.786
History of medical condition [present]:					
Chronic hypertension, n (%)	5 (7.8)	2 (18.2)	3 (6.1)	0	0.444
Nephropathy, n (%)	1 (1.6)	0	1 (2.0)	0	1.0
Neuropathy, n (%)	***4 (6.3)***	***4 (36.4)***	***0***	***0***	***0.001***
Obesity (BMI ≥ 30 kg/m^2 at pre-pregnancy or early pregnancy)‡	22 (44.0)	0	20 (45.5)	2 (66.7)	0.295
Other conditions§, n (%)	26 (40.6)	5 (45.5)	19 (38.8)	2 (50.0)	0.907

* *p*-value relates to the difference between the three groups examined using Kruskal-Wallis or one-way ANOVA test as appropriate to the distribution of each variable.

† Not all women had pathology results; Contributed data: 7 women in the non-pregnant group, 40 women in the pregnant group, and none in the postpartum group.

‡ Contributed data: 47 women

§ Includes thyroid conditions, heart disease, dyslipidaemia

Abbreviations: ATSI, Aboriginal & Torres Strait Islander People; BMI, body mass index; CI, confidence interval; IQR, interquartile range; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 6-2. Baseline characteristics of included eyes with OCTA imaging

	Non-pregnant (N = 21)	**Pregnant** (N = 96)	**Postpartum** (N = 8)	***p*-value***
DR severity, n (%)				***0.031***
None	***12 (57.1)***	***83 (86.5)***	***7 (87.5)***	
Mild NPDR	***7 (33.3)***	***10 (10.4)***	***1 (12.5)***	
Moderate NPDR	***0***	***2 (2.1)***	***0***	
Severe NPDR	***0***	***0***	***0***	
PDR	***2 (9.5)***	***1 (1.0)***	***0***	
DMO [present], n (%)	0	2 (2.1)	1 (12.5)	0.249
BCVA [logMar], median (IQR)	0 (0 to 0)	0 (-0.1 to 0)	0 (-0.1 to 0)	0.243

* *p*-value relates to the difference between the three groups examined using Kruskal-Wallis or one-way ANOVA test as appropriate to the distribution of each variable.

Abbreviations: BCVA, best-corrected visual acuity; DMO, diabetic macular oedema; DR, diabetic retinopathy; IQR, interquartile range; OCTA, optical coherence tomography angiography.

Figure 6-10 and **Table 6-3** present the comparison of VDs between eyes with no DR and with any DR across different pregnancy status groups. The pericentral VD and the VD in the superior, temporal, and nasal subfields were statistically significantly higher in eyes with no DR compared to eyes with any DR in the non-pregnant and pregnant groups (p-values ≤ 0.039). A similar but non-significant relationship was observed in the inferior VD of eyes in the non-pregnant and pregnant groups. No significant difference was found between eyes with and without DR in the postpartum group. Additionally, there was a statistically significant difference in nasal VD between eyes without DR in the pregnant vs postpartum group (p = 0.010). However, this difference was not found in eyes with DR in the pregnant and postpartum groups. No other statistically significant difference was found in the rest of VDs between three groups.

Although not statistically different, interestingly, the pericentral VD in the pregnant group was higher than in the non-pregnant group in eyes with DR and without DR. Additionally, the VD in superior, inferior, and nasal subfields were higher and the VD in the temporal subfield was lower in the pregnant group compared to the non-pregnant group, both in eyes with and without DR. The figure also shows that the magnitude of the difference between VD in eyes with no DR versus any DR was smaller in the pregnant group than in the non-pregnant group for the superior, inferior, and nasal, but that there was a larger difference in the temporal subfield.

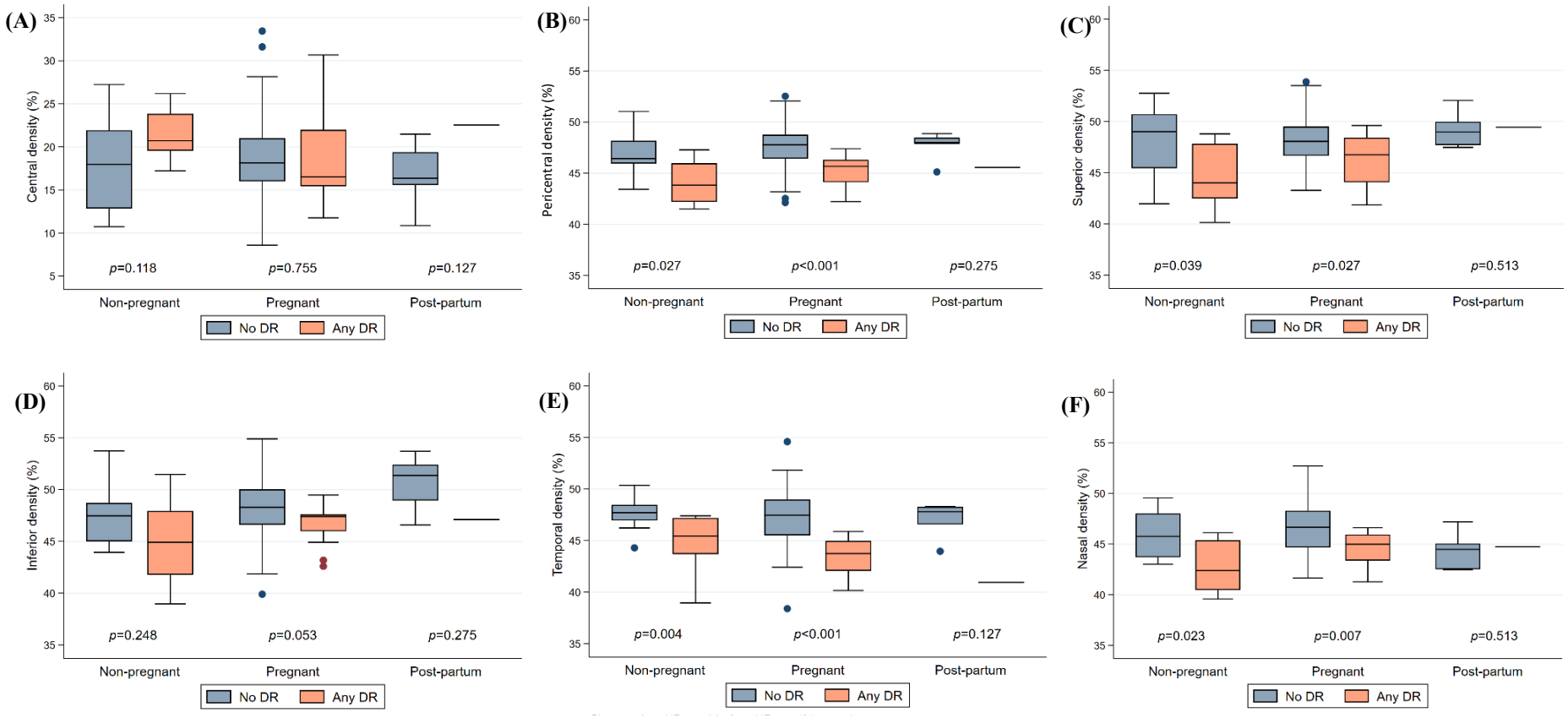


Figure 6-10. Boxplots of the vessel density (%) across non-pregnant, pregnant, and postpartum groups, by DR status

P-values relate to the Wilcoxon rank-sum test for difference between eyes with no DR compared to eyes with any DR within each group. **A**, central VD; **B**, pericentral VD; **C**, superior VD; **D**, inferior VD; **E**, temporal VD; **F**, nasal VD. Abbreviations: DR, diabetic retinopathy; VD, vessel density.

Table 6-3. Mean (95% CI) of the vessel density (%) at the first exam with the most complete OCTA data, by pregnancy status

	Overall (n = 117 eyes)	**Non-pregnant** (n = 21 eyes)	**Pregnant** (n = 88 eyes)	**Postpartum** (n = 8 eyes)	***p*1**[*]	***p*2**[*]	***p*3**[*]
Eyes without DR							
N eyes	94	12	75	7			
Central	18.33 (17.37 - 19.29)	17.94 (14.48 - 21.40)	18.53 (17.45 - 19.61)	16.90 (13.76 - 20.05)	0.730	0.276	0.615
Pericentral[†]	47.57 (47.14 - 48.00)	47.19 (45.28 - 49.11)	47.59 (47.11 - 48.08)	47.79 (46.65 - 48.92)	0.652	0.719	0.542
Superior	48.29 (47.78 - 48.81)	48.03 (45.86 - 50.21)	48.25 (47.69 - 48.82)	49.16 (47.74 - 50.59)	0.833	0.194	0.338
Inferior[‡]	48.44 (47.82 - 49.06)	47.61 (45.05 - 50.16)	48.34 (47.66 - 49.02)	50.51 (48.26 - 52.77)	0.540	0.059	0.063
Temporal	47.36 (46.88 - 47.83)	47.68 (46.69 - 48.68)	47.33 (46.76 - 47.90)	47.10 (45.68 - 48.53)	0.518	0.737	0.448
Nasal[§]	46.31 (45.83 - 46.79)	45.99 (44.53 - 47.46)	***46.55 (46.01 - 47.08)***	***44.37 (42.88 - 45.86)***	0.452	***0.010***	0.091
Eyes with any DR							
N eyes	23	9	13	1			
Central	19.99 (17.80 - 22.18)	21.49 (19.10 - 23.88)	18.75 (15.09 - 22.41)	22.53	0.181	0.385[¶]	0.602[¶]
Pericentral[‖]	44.84 (44.04 - 45.64)	44.10 (42.23 - 45.96)	45.24 (44.35 - 46.13)	45.56	0.227	0.710[¶]	0.439[¶]
Superior	45.71 (44.48 - 46.94)	44.73 (42.38 - 47.08)	46.10 (44.55 - 47.66)	49.44	0.288	0.172[¶]	0.117[¶]
Inferior[‖]	46.12 (44.77 - 47.48)	44.96 (41.42 - 48.50)	46.76 (45.50 - 48.03)	47.11	0.290	0.710[¶]	0.439[¶]
Temporal	43.82 (42.74 - 44.90)	44.67 (42.45 - 46.89)	43.45 (42.18 - 44.73)	40.96	0.299	0.385[¶]	0.223[¶]
Nasal	43.89 (42.93 - 44.85)	42.72 (40.71 - 44.72)	44.63 (43.63 - 45.64)	44.74	0.074	0.710[¶]	0.602[¶]

[*] *p*-values relate to the difference between the two groups examined using t-test or [¶]Wilcoxon rank-sum test, as appropriate. *p*1, statistical significance between the non-pregnant and pregnant groups; *p*2, statistical significance between the pregnant and postpartum groups; *p*3, statistical significance between the non-pregnant and postpartum groups.

[†] Contributed data: 9 eyes in the non-pregnant group, 72 eyes in the pregnant group, and 7 eyes in the postpartum group without DR.

[‡] Contributed data: 9 eyes in the non-pregnant group, 73 eyes in the pregnant group, and 7 eyes in the postpartum group without DR.

[§] Contributed data: 12 eyes in the non-pregnant group, 74 eyes in the pregnant group, and 7 eyes in the postpartum group without DR.

[‖] Contributed data: 8 eyes in the non-pregnant group, 13 eyes in the pregnant group, and 1 eye in the postpartum group with any DR.

Abbreviations: DR, diabetic retinopathy; CI, confidence interval; OCTA, optical coherence tomography angiography.

6.3.2. Foveal Avascular Zone Area

A total of 124 eyes (from 63 women) were included for the FAZ area analysis. One woman with PDR in both eyes was excluded from the FAZ area analysis due to neovascularisation that crossed the FAZ area. This vascular remodelling occurred during the follow-up period and altered the FAZ area in a manner which rendered the FAZ areas of these eyes incomparable with the eyes of the other participants where the FAZ was defined by perfused physiological capillaries. **Figure 6-11** and **Table 6-4** demonstrate the comparison of the FAZ area at the first eye-visit with the most complete OCTA data across the pregnancy status groups and in eyes without and with any DR at that exam. When comparing the FAZ area between eyes without DR and with any DR, no statistically significant difference was observed in any pregnancy status group. Additionally, no significant difference was found between the three groups in eyes without nor with any DR.

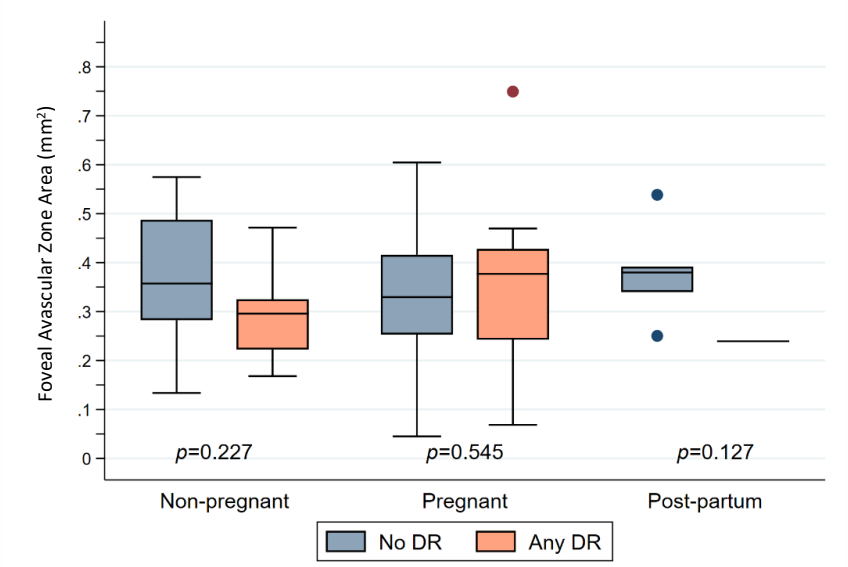


Figure 6-11. Boxplots of the FAZ area (mm^2) in non-pregnant, pregnant, and postpartum groups

P-values relate to the Wilcoxon rank-sum test for difference between eyes with no DR vs with any DR within each group. Abbreviations: DR, diabetic retinopathy; FAZ foveal avascular zone.

Table 6-4. Mean (95% CI) of the foveal avascular zone area (mm^2) at the first exam with the most complete OCTA data, by pregnancy status

	Overall (n= 124 eyes)	**Non-pregnant** (n= 22 eyes)	**Pregnant** (n=94 eyes)	**Postpartum** (n= 8 eyes)	***p*1***	***p*2***	***p*3***
Eyes without DR							
N eyes	102	12	83	7			
FAZ area	0.336 (0.312 - 0.360)	0.363 (0.276 - 0.451)	0.328 (0.302 - 0.355)	0.376 (0.297 - 0.456)	0.421	0.208	0.799
Eyes with any DR							
N eyes	22	9	12	1			
FAZ area	0.326 (0.261 - 0.391)	0.297 (0.221 - 0.373)	0.355 (0.241 - 0.468)	0.239	0.359	0.423†	0.602†

* *p*-values relate to the difference between the two groups examined using t-test or †Wilcoxon rank-sum test, as appropriate. *p*1, statistical significance between the non-pregnant and pregnant groups; *p*2, statistical significance between the pregnant and postpartum groups; *p*3, statistical significance between the non-pregnant and postpartum groups.

Abbreviations: CI, confidence interval; DR, diabetic retinopathy; FAZ, foveal avascular zone.

6.3.3. Relationships between OCTA Parameters and DR Change over time

The relationships between the FAZ area and the central and parafoveal VD were assessed. A total of 116 eye-visits from 60 women and 109 eye-visits from 56 women were included for each analysis, respectively. As expected, there was a strong and significant inverse correlation between the FAZ area and central VD (rho = -0.931, $p < 0.0001$; **Figure 6-12 A**) but no correlation was found between the FAZ area and parafoveal VD (rho = 0.097, $p = 0.316$; **Figure 6-12 B**).

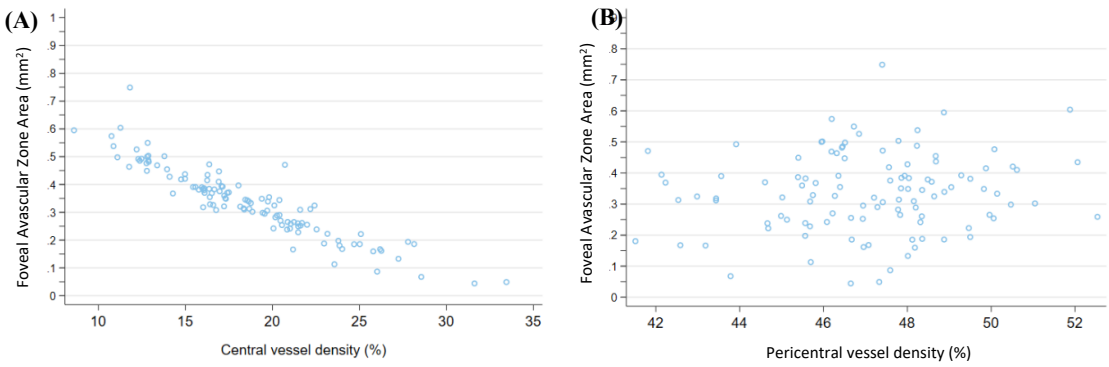


Figure 6-12. Relationships between OCTA parameters

The mean FAZ area (mm^2) and (**A**) the mean central VD (n= 116 eye-visits; Spearman rho = -0.931, $p < 0.0001$); and (**B**) the mean pericentral VD (n= 109 eye-visits, Spearman rho = 0.097, $p = 0.3160$). Abbreviations: FAZ, foveal avascular zone; VD, vessel density; OCTA, optical coherence tomography angiography.

Figure 6-13 to Figure 6-15 present the trajectory plots of individual eyes that exhibited change in DR and DMO status during the study period. There were only eight eyes (from

six women) with observed DR changes at OCTA eye-visits. Specifically, one woman had one eye progress from mild NPDR to PDR in the third trimester which then improved to moderate NPDR at the postpartum visit (**plot C**). Another eye progressed from mild to moderate NPDR in the third trimester and was stable at the postpartum visit (**plot D**). Moreover, one eye progressed from no DR to mild NPDR (**plot H**), one eye with mild NPDR at baseline was found to have new DMO at the postpartum visit (**plot G**), three eyes from two women had one-step improvement from mild NPDR to no DR (**plot B, E, F**), and one eye had resolved DMO (**plot A**).

It can be seen in the figures that there were inconsistent patterns regarding the relationships between individual OCTA parameters and the DR longitudinal changes. Likewise, no obvious patterns were discernible in the change of OCTA parameters over different pregnancy statuses and stages in those eyes with no change (**Figure 6-16**). Unfortunately, due to the overall size of the study, the small number of eyes exhibiting changes in DR status over time, and high overall variability in OCTA parameters, sufficient power could not be achieved to adequately address aim 2.3 statistically.

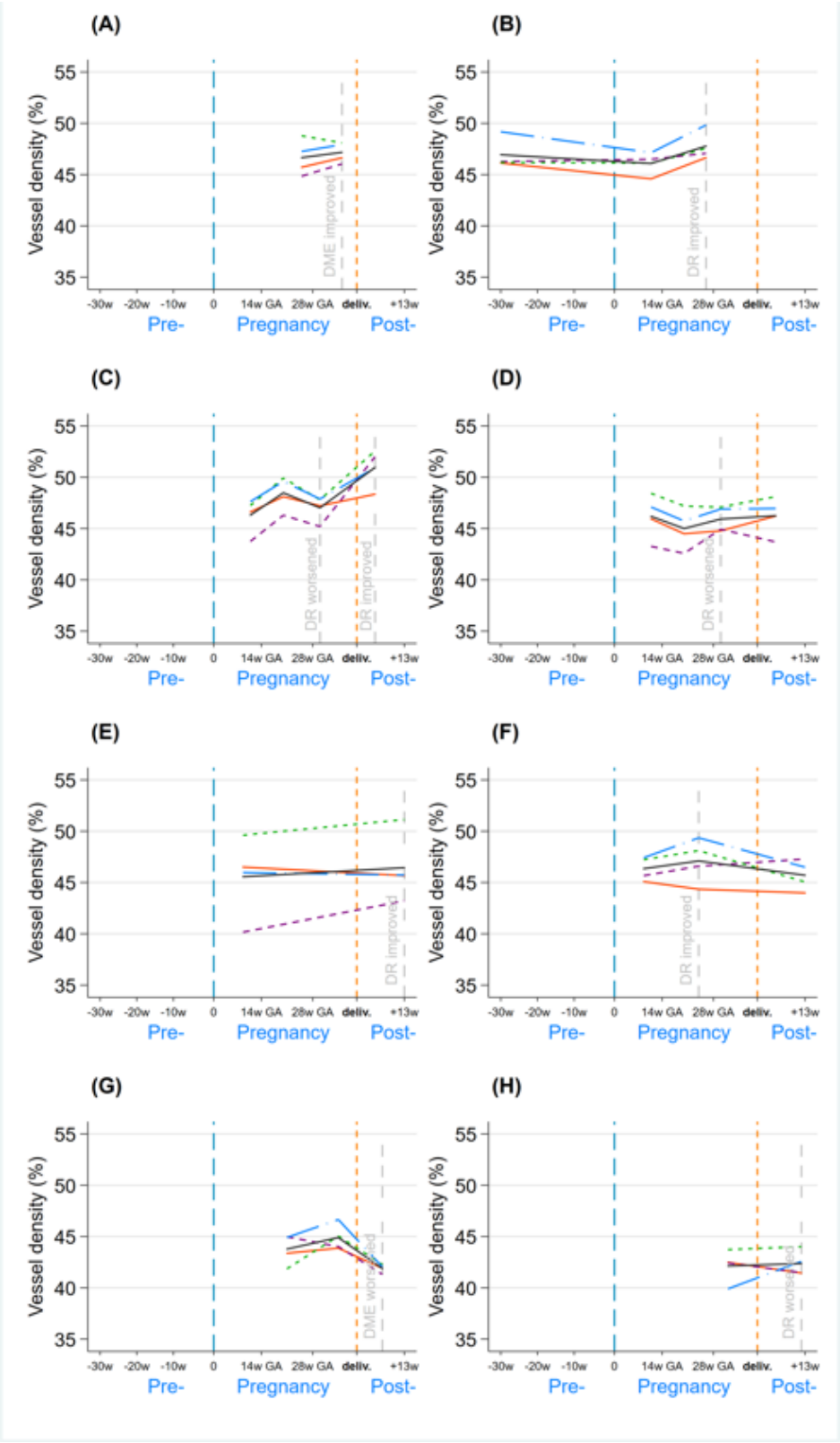


Figure 6-13. Vessel Densities over time in eyes with change* in DR or DMO status (*either progressed, improved, or both)

The eight plots (**A-H**) denote an individual eye with change. *Red line* shows nasal VD; *purple dash* shows temporal VD; *green dash* shows superior VD; *blue line* shows inferior VD; *grey line* shows pericentral VD. Abbreviations: deliv., delivery; DMO, diabetic macular oedema; DR, diabetic retinopathy; GA, gestational age; VD, vessel density.

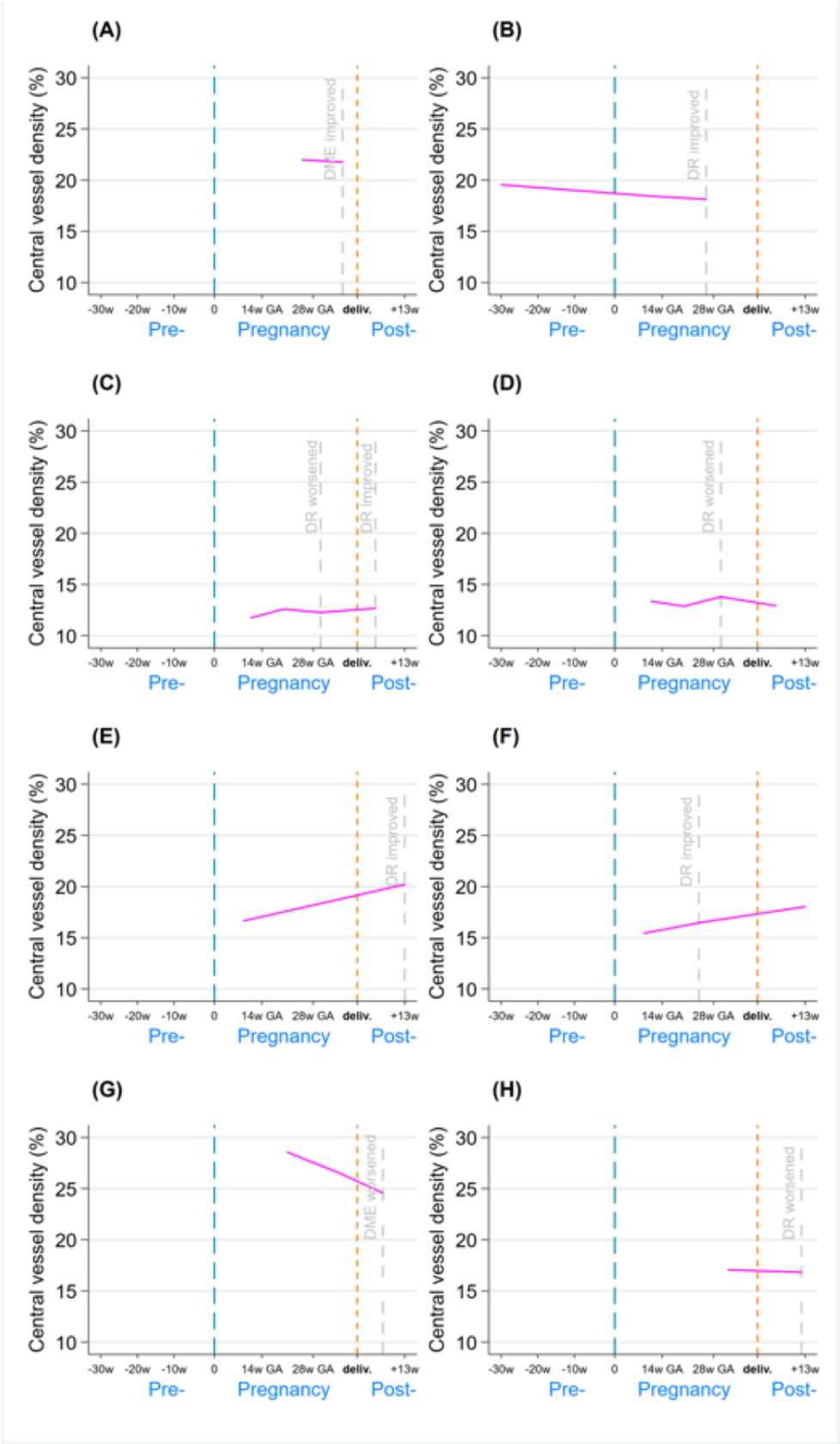


Figure 6-14. Central VD over time in eyes with change* in DR or DMO status (*either progressed, improved, or both)

The eight plots (**A-H**) denote an individual eye with change. Abbreviations: deliv., delivery; DMO, diabetic macular oedema; DR, diabetic retinopathy; GA, gestational age.

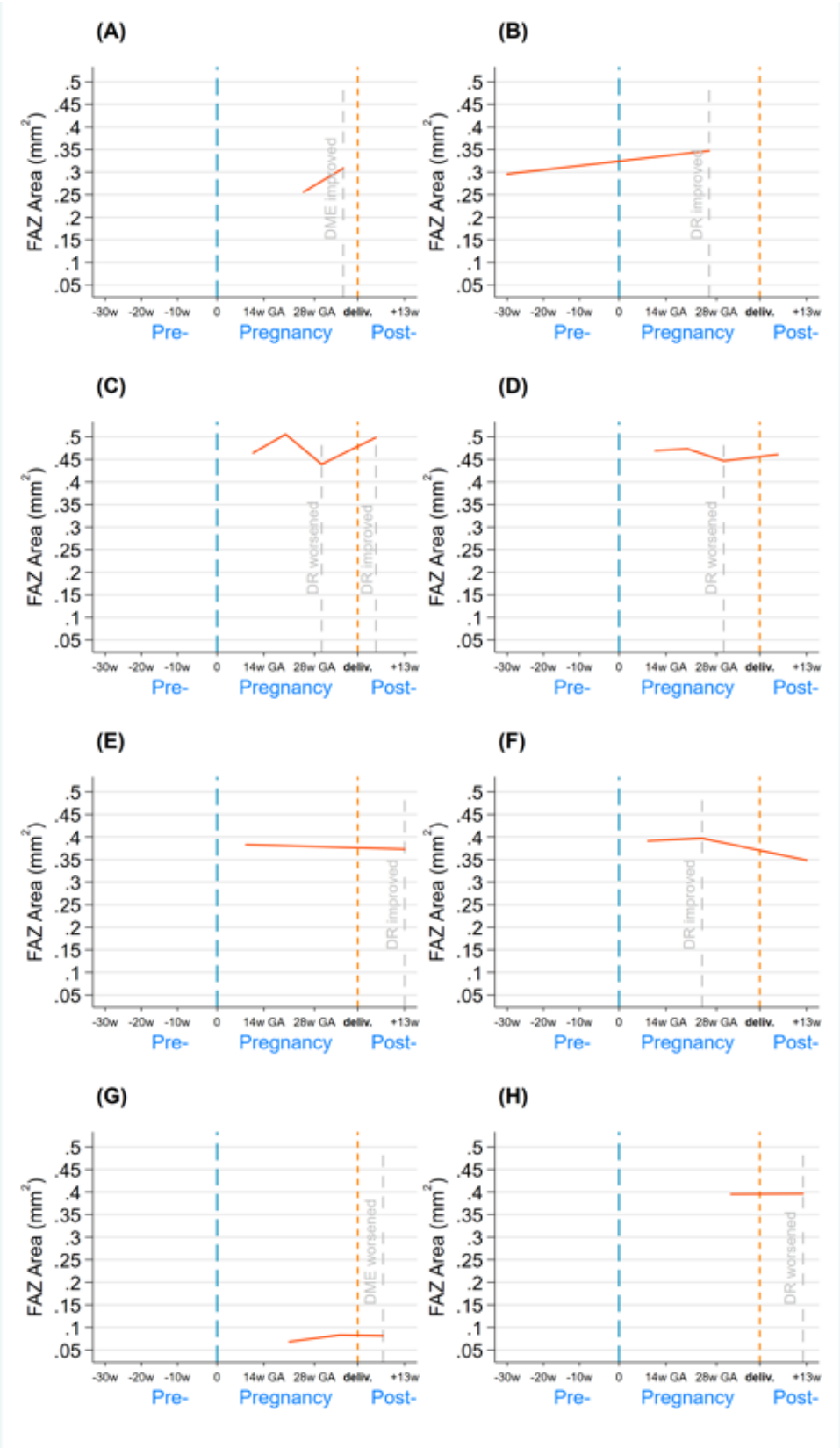


Figure 6-15. FAZ area over time in eyes with change* in DR or DMO status (*either progressed, improved, or both)

The eight plots (**A-H**) denote an individual eye with change. Abbreviations: deliv., delivery; DMO, diabetic macular oedema; DR, diabetic retinopathy; FAZ, foveal avascular zone; GA, gestational age.

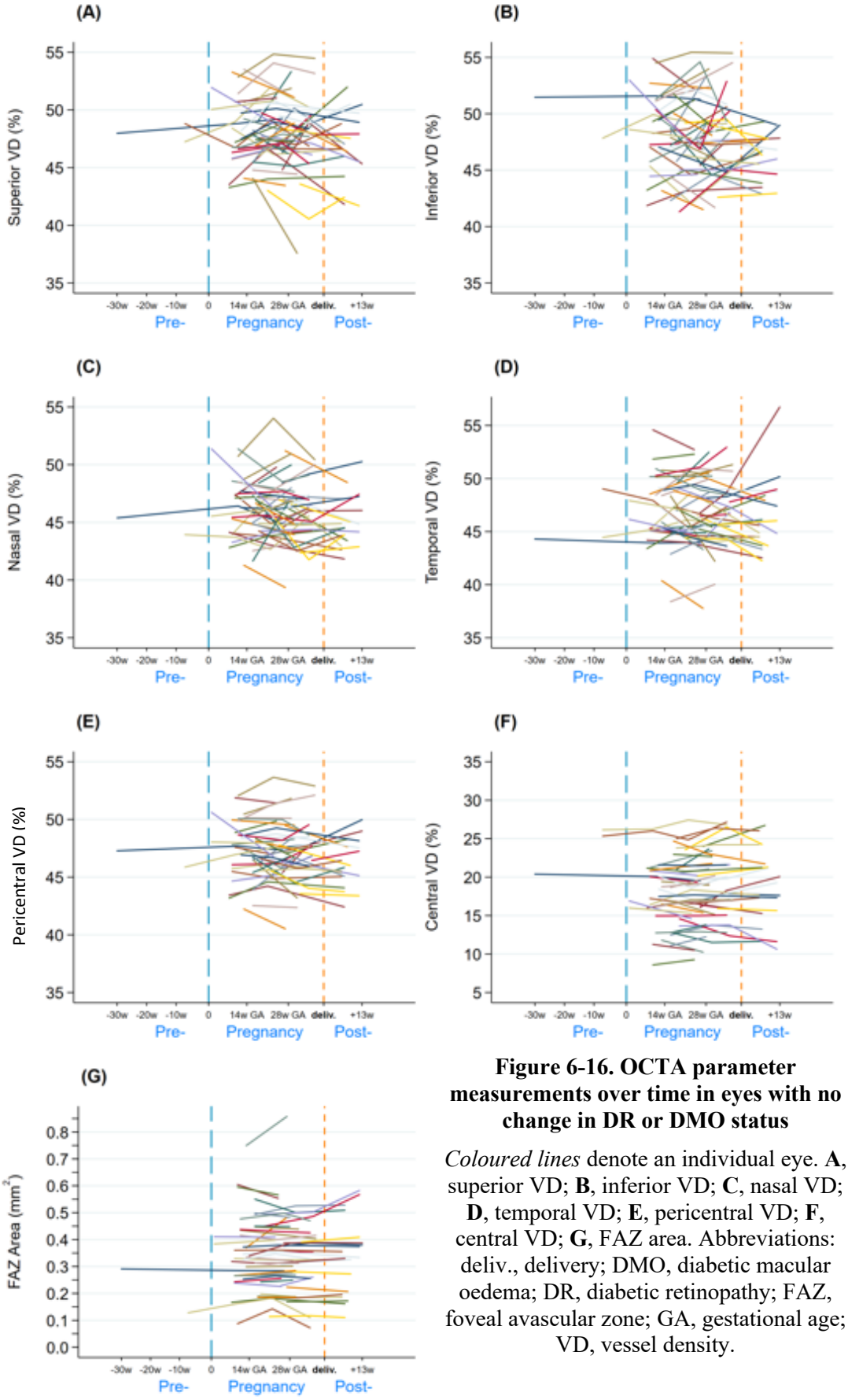


Figure 6-16. OCTA parameter measurements over time in eyes with no change in DR or DMO status

Coloured lines denote an individual eye. **A**, superior VD; **B**, inferior VD; **C**, nasal VD; **D**, temporal VD; **E**, pericentral VD; **F**, central VD; **G**, FAZ area. Abbreviations: deliv., delivery; DMO, diabetic macular oedema; DR, diabetic retinopathy; FAZ, foveal avascular zone; GA, gestational age; VD, vessel density.

6.4. Discussion

The use of OCTA has been widely studied in the non-pregnant population, both in the diabetic and non-diabetic demographics. However, very limited information was available for the diabetic pregnant group. This study assessed the retinal vasculature in the superficial capillary plexus (SCP) of diabetic women in three different pregnancy statuses using OCTA imaging. Vessel densities and FAZ area were evaluated and compared in eyes with and without DR across pregnancy status groups. We found that pericentral VD was significantly lower in eyes with DR than those without DR, irrespective of pregnancy status, except for the postpartum group. A similar trend was observed for the VD of the individual subfields defined by the ETDRS macular grid (superior, temporal, nasal, and inferior). Interestingly, the VD of the nasal subfield in eyes with no DR in the pregnant group was significantly higher than those in the postpartum group. Although not statistically significant, the pericentral VD in pregnant women was higher than in non-pregnant women. This held true for each of the constituent pericentral subfields with the exception of the temporal subfield where the VD was lower in the pregnant group than the non-pregnant group. This finding was especially marked in eyes with DR.

These findings contribute to the understanding of the impact that the combination of pregnancy and diabetes has on the retinal circulation. The retinal circulation usually auto-regulates, and this allows the retina to maintain fairly constant blood flow despite changes in systemic blood pressure and varying metabolic demands.[261] Chen *et al.* performed pioneering work assessing the effects of pregnancy and diabetes on retinal blood flow (RBF). Using laser doppler velocimetry measurements of major retinal venules combined with photographic determination of vascular diameters, they found a trend towards slightly higher RBF in non-diabetic pregnancies, and statistically significant increases in RBF in diabetic pregnant women. Interestingly, significant increases in retinal venular particle velocity and RBF were largely restricted to subjects who demonstrated progression of their DR during pregnancy.[17] This provided early evidence that diabetes was responsible for a reduction in the capacity for the retina to auto-regulate in pregnancy. More recent studies by Loukovaara *et al.* that studied retinal capillary blood flow using blue-field entoptoscopy[18] and retinal flowmetry[122] support previous suspicions. The authors observed a significantly higher RBF in diabetic pregnant women than in healthy

pregnant women in the first and third trimesters, and at 3 months postpartum. In one of these studies, a much higher RBF was recorded in eyes with moderate-severe DR than those with no or very mild DR.

Multiple changes associated with pregnancy have been hypothesised to alter retinal perfusion. Cardiovascular changes in pregnancy, such as increased heart rate, increased plasma volume, increased cardiac contractility, and decreased peripheral vascular resistance, facilitate the hyperdynamic circulation required to support the increased metabolic demands for foetal development.[116,262] Likewise, hormonal adaptations during pregnancy affect the ocular vasculature: an elevation in oestrogen level, in particular, causes retinal capillary dilatation and decreased vascular resistance.[263,264] Together, these cardiovascular and hormonal changes cause an increase in the RBF.

We found a trend towards increased pericentral VD in all of the ETDRS subfields except for the temporal. This held true for both eyes without DR and those with DR. The DRI Triton instrument uses a proprietary algorithm that determines the proportion of the pixels in the scan area that show a flow signal.[265] Consequently, an increase in VD may result from either an increase in the diameter or the length of vessels detected in the area of interest. Vascular density can also be affected by signal strength and image quality.[266]

It is most likely that the increases in VD reported here are explained by increased vascular diameter, and that this increased vascular diameter allows the retina to increase its blood flow while minimising increases in flow velocity which would in turn cause increased shearing forces on the luminal endothelial cells. The possibility that vascular length density as determined by OCTA may alter in pregnancy has been investigated by Chanwimol *et al*.[177] These investigators excluded any alteration in vascular length density in the ten women they studied. Furthermore, recruitment of retinal capillaries in other haemodynamic states has not been documented on OCTA at the time of writing. However, it is feasible that vessels exhibiting very low flow may not usually be detected by OCTA, especially if the vessels are scanned during diastole, and that these low flow vessels may become more evident in hyperdynamic states.

The trends that we identified concord with the findings of other investigators. A recent study by Yildirim *et al.* compared the retinal OCTA findings of healthy pregnant and non-pregnant women. They found that pregnant women had a consistently greater parafoveal

VD in the SCP that was statistically significant in the deep capillary plexus (DCP).[267] The term "parafoveal" in this study is similar to our "pericentral" region. These authors suggested that the increase of VD was an echo of the increased RBF during pregnancy. Kiziltunc *et al.* observed the same trend in pregnant women in all three trimesters.[178] In contrast, Chanwimol *et al.* found a reduction in perfusion density of the SCP, although this coexisted with an increase in perfusion density of the DCP.[177] While this finding seems to contradict the other published papers, no definition of perfusion density appears in the paper, and it is unclear whether this measure is directly comparable with VD. An interesting feature of the work of Chanwimol and colleagues is that a seemingly paradoxical increase in DCP perfusion density was observed. Hydrostatic pressure and anatomical differences were invoked to explain the differing effects of pregnancy on each plexus. It was hypothesized that the respiratory alterations of pregnancy may explain the reduced perfusion density seen in the SCP.

It is of interest that the temporal subfield behaved differently to the other three pericentral subfields: where the other subfields showed trends towards increased VD during pregnancy, the temporal subfield demonstrated a trend in the other direction in both eyes with DR and without. The temporal region of the macula is most susceptible to pre-proliferative changes of DR.[268] It is possible that these findings point towards a failure of normal auto-regulatory processes in the temporal subfield which contribute to its heightened vulnerability to DR.

The ability to draw statistical inferences between OCTA parameters during pregnancy and the postpartum from the current study is limited by the number of eyes included in the postpartum group.

Several studies of non-pregnant people with diabetes have indicated that DR is associated with a decrease in the VD of the capillary network and an enlargement of the FAZ area.[168,170,259] The reduction in VD and increase in FAZ area represent capillary non-perfusion, which is a biomarker of DR, and also involved in the pathogenesis of PDR. The current study observed a similar trend towards an inverse correlation between VD and DR. Interestingly, no association between the FAZ area and DR was observed in pregnant women. It is possible that pregnancy protects against non-perfusion of the capillaries defining the margins of the FAZ. Alternatively, and more likely, our small sample size and the relatively mild DR seen in most participants in our study may have

limited our ability to detect an association.

To the best of our knowledge, only two OCTA studies have been conducted in the diabetic pregnant population and only one of them observed DR changes. Sugimoto *et al.* compared the FAZ area of non-pregnant healthy women with pregnant women with GDM and pre-existing diabetes without DR.[179] No significant differences were found in the FAZ area of either the SCP or DCP between the three groups. The advantage of our study compared to Sugimoto *et al.*'s was that we were able to compare between diabetic non-pregnant and pregnant women, between eyes with and without DR, and also look for interactions between pregnancy and DR. In our cohort, the FAZ area in the pregnant group without DR was not significantly different to those in the non-pregnant group. Although different groups were being compared, findings from both studies may suggest that the FAZ area in the eyes of women with diabetes but without DR is not affected by pregnancy.

In addition to FAZ area, we studied pericentral VD. Our results suggest that the various pericentral subfields respond differently to the pregnant state, and that there is an interaction between the pregnant state and DR status. The nasal, superior and inferior subfields showed trends towards an increased VD in pregnancy, and eyes with DR exhibited greater numerical differences than those without. In contrast, the temporal subfield demonstrated reduced VD in pregnancy in eyes with DR. As suggested earlier, VD increases in this study were likely to be largely a manifestation of increased vascular diameter. One interpretation of these findings is that increased vessel diameter is an autoregulatory mechanism which works to minimise the exposure of the vessels to increased blood velocity. The lack of increased VD in the temporal region in eyes without DR may be an indication that this region, which is known to be particularly vulnerable to DR,[268] demonstrates a reduced capacity for retinal vascular autoregulation. Moreover, there was a trend towards reduced VD in the temporal subfield in eyes with DR. As mentioned before, the principal reasons for a reduction in VD are progressive capillary non-perfusion, narrowing of vessel calibre, and worsened image quality.[265,266] Thus, the consistent reduction in VD seen in the temporal subfield in eyes with DR may be a result of altered autoregulation or of progressive non-perfusion.

It is well understood that elevated RBF, such as during pregnancy, may introduce shear stress to the retinal capillaries.[17,269] Elevated flow is thought to be particularly hazardous

when the capillaries are exposed to an increased velocity of flow, which can occur when autoregulatory mechanisms fail, and is exacerbated by the increased pressure differentials seen in systemic hypertension. The work of Chen *et al.* demonstrated, at the level of the first order venules, that the combination of pregnancy and diabetes leads to retinal vascular auto-regulatory failure, especially in eyes that subsequently demonstrate progressive DR.[17] Our work suggests that auto-regulatory failure can also be observed at the capillary level in pregnant women with DR. This helps to explain why pregnant women with diabetes are at an increased risk of DR progression compared to the non-pregnant population.

Akushichi and colleagues presented a case-report of a pregnant woman with T2DM who experienced DR progression after delivery.[270] Fundal examination showed mild NPDR in early pregnancy and this was associated with regions of capillary non-perfusion. The level of DR remained essentially stable during pregnancy. However, after delivery, OCTA non-perfusion increased and their DR progressed. Using OCTA, Akushichi *et al.* could determine capillary-level changes in the retina, which in this case were most likely induced by a hypertensive state. This case-report emphasised the potential role of OCTA in monitoring diabetic changes in the retinal vasculature in the pregnant population in order to predict progression of pre-existing DR. Unfortunately, our study was not sufficiently powered to detect an association between progression of retinal non-perfusion and increasing severity of DR.

This study has some limitations. First, as has been mentioned, the overall size of this OCTA study is relatively small, and many patients did not have OCTA images in each trimester and postpartum. Consequently, we could not compare OCTA parameters in different trimesters and, due to the small number of participants who completed OCTA studies postpartum, our ability to draw statistical inferences regarding this time point is limited. Additionally, it should be noted that the non-pregnant group in this cohort was small due to the nature of patient recruitment in the main study; therefore, the interpretation of our results should be made carefully. Second, a relatively small number of eyes experienced DR status changes over the course of our study which renders our study underpowered to determine the predictive value of our OCTA parameters in predicting DR progression in this study population. Third, due to the obstacles hitherto described concerning the limitations in the DRI Triton software functionality, we were

unable to determine numerical parameters such as VD for the DCP. Prior studies have shown that pregnancy-related and DR-related changes are more evident in the DCP than SCP.[172,173,267] Despite these limitations, to the best of our knowledge, this is the first study to evaluate OCTA parameters in pregnant diabetic women and assess their relationships with DR status.

In summary, it has been suggested that OCTA has a potential role in monitoring progression of diabetes-related retinal non-perfusion in pregnancy. Our results suggest that OCTA may have a further role in detecting retinal vascular autoregulatory failure in pregnancy. Further work should assess whether retinal non-perfusion and alterations in the diameters of small vessels, as assessed by OCTA, are able to predict progression of DR. These may become important biomarkers for DR progression once high-quality OCTA becomes more generally available.

CHAPTER 7: ADHERENCE AND BARRIERS TO ATTEND RECOMMENDED EYE SCREENING GUIDELINES DURING PREGNANCY (AIM 3)

7.1. Overview

Diabetic retinopathy (DR) screening programs aim to detect DR in its early stages and, more importantly, identify sight-threatening DR at a treatable stage. With the risk of more rapid progression during pregnancy, more frequent eye examinations are needed to save sight in this population of women. Currently, there are two sets of guidelines in Australia that recommend regular eye screening examination during pregnancy. The Australian National Health and Medical Research Council (NHMRC) recommends pregnant women with pre-existing diabetes have their eyes checked during their first trimester and be followed closely throughout pregnancy based on their clinician's judgement.[48] In comparison, the Australasian Diabetes in Pregnancy Society (ADIPS) recommends three-monthly eye screening examination, especially for pregnant women with risk factors.[203]

As explained in **Chapter 2**, optimal eye care for pregnant women with pre-existing diabetes has not been achieved for multiple reasons. One of these reasons is patient attendance - the key measure for the evaluation of a screening program. Even though eye screening examinations in pregnancy have been promoted for a decade in Australia, there has been no report on the attendance rate of the Australian pregnant population, nor the barriers to attending these examinations. Knowledge of specific barriers to attendance could inform the design of measures to overcome these issues, with the implementation of these measures tested in future studies and programs.

This chapter presents the methods and results relating to the final aim of the study, which focuses on determining the adherence rate and barriers to adherence to the recommended eye screening guidelines during pregnancy in women with pre-existing diabetes. Specifically:

Aim 3.1: To determine the adherence rate to recommended eye screening guidelines in pregnancy in the survey respondent population.

Aim 3.2: To determine factors that relate to the adherence to recommended eye screening guidelines in pregnancy using the Compliance with Annual Diabetic Eye Exams Survey (CADEES).

Aim 3.3: To qualitatively determine the barriers to attendance at the recommended eye screening guidelines within our survey respondent population.

7.2. Methods

7.2.1. Study design

This portion of the study was a cross-sectional survey, which aimed to collect survey data on the enablers of and barriers to attending the guideline-recommended eye screening examination within this study's cohort of participants. This survey study commenced on 10 October 2018 (after ethics amendment approval [**Appendix A3**]) and continued until 30 September 2019.

7.2.2. Participants

All participants in the cohort study were asked to complete a questionnaire. In addition, patients who declined to participate in the cohort study were asked to solely participate in this survey study. These patients could then choose between only completing the survey or completing the survey and also sharing their demographic and clinical data (collected from their medical record) for the study. A separate patient information and consent form (PICF) was used for this portion of research (**Appendix A8**). The details of overall study participation have been discussed in **Chapter 4** (**section 4.11**).

7.2.3. Survey data collection

Survey instrument

The Compliance with Annual Diabetic Eye Exams Survey (CADEES)[221] was used to collect information regarding each participant's adherence to the recommended eye screening guidelines. The original CADEES consists of 14 clinical and demographic questions, 43 questions with 5-point Likert scale answers, one yes/no question and one open-ended question that was constructed to measure patient's health beliefs on DR and the routine eye screening examinations (available at https://

www.deverseye.org/CADEES/CADEES.pdf). This tool was based upon the Health Belief Model, a framework that has been proven to be useful to assess patient compliance to the preventive health recommendations.[271] The CADEES was intentionally built to cover six constructs of the Health Belief Model[272]:

a) Severity (expected severity of the impact of the disease)

b) Susceptibility (perceived susceptibility to the disease or health problem)

c) Benefits (regarding the benefits or efficacy of the recommended health behaviour)

d) Barriers (regarding the obstacles to executing the behaviour)

e) Cues to action (any belief [perception of symptoms, peer influence, or health campaigns] that trigger the conduct of the health behaviour), and

f) Self-efficacy (motivation or willingness to be concerned about health issues)

Modification of the CADEES to represent the pregnant population

CADEES was created and validated for use in adults with diabetes (either type 1 [T1DM] or type 2 diabetes [T2DM]). To ensure compatibility with our current study population, some modifications were made to suit the eye screening recommendations for pregnant women with pre-existing diabetes. Some questions in the demographic/clinical information were adjusted so that important clinical data of participants who agreed to only participate in the survey could be collected and a comparative analysis conducted. The main component of the CADEES, which consists of 43 questions with Likert scale responses and one yes/no question, remained unchanged. For our qualitative study, data was collected from the open-ended question (question 45). The wording of the question was altered slightly from the CADEES original phrasing of *"We are interested in why some people do not have yearly eye exams…"* to *"We are interested in why some people do not have routine eye exams during pregnancy…*".

The modified CADEES questionnaire was then tested on 15 participants to evaluate the suitability and feasibility for the survey to be completed within 10-15 minutes – the approximate time between a participant's appointments at the hospital. At the completion of testing, one additional question was added to assess each participant's perspective on

the level of importance of different health appointments during pregnancy. The final modified questionnaire utilised in this study can be found in **Appendix A9**.

Offline and online survey

Our survey was predominantly administered during a patient's clinic visit (offline). A paper questionnaire was provided by the study coordinator (FW) to all participants for completion during their pregnancy visit. The completed survey data was then entered into our study database (REDCap); with the hardcopy stored in a secure storage locker.

If, due to any reason, participants were unable to complete the survey in the clinic, a secure online survey link was sent to the participant's email. The online survey was created using REDCap, which provides online survey tools for data collection. Participants received unique survey links, and all responses were stored automatically to the participant's individual record in the REDCap database. For participants who had completed their pregnancy prior to the start date of this survey study, an invitation to complete the survey was sent via email or text message (based on the preferred method of communication indicated at the time of consent). The script of this invitation can be found in **Appendix A10**.

Reminders for participants - online survey

For participants who received the online survey invitation, two reminders to complete the survey were sent via email or text message if a response had not been received. The first reminder was sent within two weeks after the invitation was sent, with the second reminder posted a week before the closing date of the study (30 August 2019) if their survey remained incomplete. The script of the reminders can be found in **Appendix A10**.

7.2.4. Determining participant's adherence

As previously explained in the methodology chapter (**Chapter 4**), eye screening examinations in this study cohort were scheduled once in each pregnancy trimester (adapted from the ADIPS guidelines). For this component of the study, two guideline adherence outcomes were assessed and defined as: 1) Adhered to the NHMRC guidelines if participants had at least one eye examination in the first trimester (defined as the period from conception to 13 weeks of gestation); 2) Adhered to the study protocol if they had

an eye examination once in each trimester or on a 3-monthly schedule. For example, if a participant had no eye examination at the third trimester due to early birth or health restriction (such as being hospitalised) but had their last eye-check less than three months before delivery, this participant would be considered to have adhered to the defined study protocol.

7.2.5. Statistical analysis

Calculating the adherence rate

Statistical analyses were carried out using Stata IC 15.1 for Windows (College Station, TX, USA). Adherence rates were determined only among women who participated in the survey study (respondents). Adherence rates to NHMRC guidelines and study protocol were calculated as proportions with Agresti-Coull 95% confidence intervals (CIs) and converted to percentages to simplify interpretation. Descriptive analysis was used to present the baseline characteristics of the respondents. The normality of the demographic data distribution was tested for the continuous variable using the Skewness and kurtosis test for normality, the Shapiro-Wilk test and the Shapiro-Francia test to reach consensus before presenting the summary statistics as a mean (with 95% CI), or median (with interquartile range [IQR]), as appropriate. Demographic characteristics were compared between adherent and non-adherent groups using Fisher's exact test or Kruskal Wallis test. Differences were considered to be statistically significant at a two-sided p-value of <0.05.

Assessing the barriers to attend the recommended eye screening examinations during pregnancy

A. Principal component analysis

In the development of the CADEES tool, Sheppler and colleagues performed principal component analysis (PCA) to assess the construct validity (the degree of which survey items relate to each other in groups as predicted by the creator) and determined whether the outcomes were consistent with the desired constructs (in this case, either as perceived severity, susceptibility, benefits, barriers, cues to action, or self-efficacy construct). PCA is a proven method to simplify the dimensionality of multivariate data into a limited number of new variables (called "principal components") that consist of uncorrelated

variables.[221] The goal is to present the maximum amount of variance in the data with the least number of principal components so that data can be better visualised graphically.[273]

For this study, preliminary PCA was conducted on the scaled and centred survey results. Question 34 ("My insurance covers most of the cost of an eye exam") was removed because its responses did not have an ordinal interpretation in comparison to the others and was not as applicable to our cohort as insurance status does not determine the out-of-pocket costs of eye examinations in Australia. The first principal component (PC1) explained a substantial proportion of the variation in the survey (eigenvalue 6.1, explaining 16% of the variation in the survey). Subsequent components had much less explanatory power, with PC2 to PC4 having eigenvalues between 2.3 and 3.0, with remaining components all showing eigenvalues below 2.0 (**Figure 7-1**). The first four components accounted for 36% of the variation in collected survey responses. Although these components covered higher variance compared to the creator's findings (with 3 components which accounted for 32% of the variance), they did not cover enough variation (<60% of variance)[274]; thus suggesting that the principal components may not be beneficial as a summary of the overall survey.

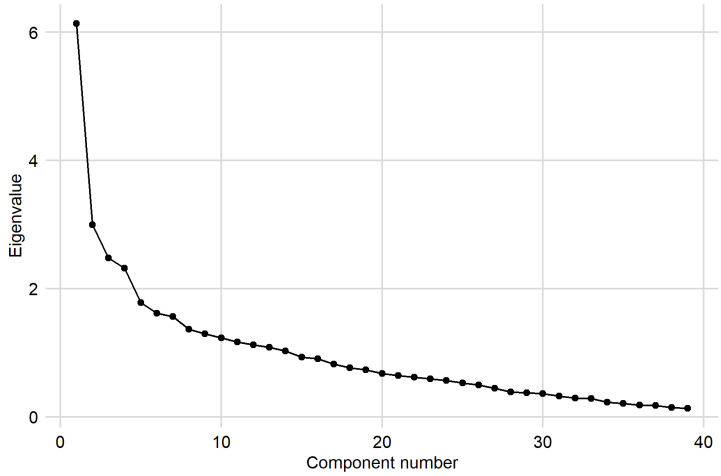


Figure 7-1. Scree plot of the principal component analysis

After conducting the second PCA using varimax rotation, the factor loadings for the first four principal components also showed little resemblance to the Health Belief Model constructs defined by Sheppler *et al.* (**Supplementary table S7-1**). As a result, in this current study, the survey was analysed on the basis of individual questions rather than principal components or constructs.

B. Individual CADEES item analysis

Each of the Likert-scale survey items was dichotomised for analysis by combining neutral responses with "disagree" responses to compare against combined "agree" responses. Each survey item was then compared across adherent and non-adherent groups based upon two recommended guidelines using the Wilcoxon rank-sum test to identify items that were associated with adherence. Logistic regression models were constructed to investigate associations between adherence to screening recommendations and responding with an agreement to a CADEES item, individually and after adjusting for type of diabetes, or by comparing ethnicity groupings or another demographic variable of interest. Covariates for the multivariate logistic model were identified as interesting by the demographic analysis (p-value <0.05 between adherent and non-adherent groups) or were likely confounders. Ethnicity, type of diabetes, and self-reported DR were included separately in logistic models; type of diabetes and self-reported DR were also included together in a separate model. Differences were considered to be statistically significant at a two-sided p-value of <0.05.

Qualitative analysis

The CADEES has not previously been used in this unique patient population, which has specific challenges not faced by the non-pregnant diabetic community. To better understand our study population's problems regarding routine eye screening examinations during pregnancy, qualitative data analysis was performed.

Qualitative data was collected by asking one open question (the last question on the CADEES: "*We are interested in why some people do not have routine eye exams during pregnancy. Can you think of any reasons we did not ask about in this survey"?*

First, respondent's answers were categorised into substantive (e.g., "No idea which eye doctor to go") and non-substantive (e.g., blank, "no", "not applicable", or "NIL"). Respondents' answers were entered into REDCap and then imported to NVivo for coding. Thematic analysis was conducted to allow flexibility in coding which would facilitate easy retrieval of information and the ability to provide rich and detailed data. Qualitative data analysis was conducted in 6 steps: familiarisation of data, generating initial codes, collating codes into particular themes, reviewing the themes, defining and naming the themes, and reporting the data.[275] A rater (FW) conducted the first five steps, with a

second-rater (Sandra Staffieri; SS) reviewing the grouping of themes. Disagreements between the raters were resolved by discussion until consensus was reached. Presented quotes are as written verbatim by the respondents.

7.3. Results

7.3.1. Adherence rate

One hundred and twenty-five (125) participants completed our survey. Approximately 51% of respondents had type 1 diabetes, the median age was 34 years (range 19 – 47 years), and the majority were either Caucasian (50.4%) or Asian (31.2%). Most respondents (82.4%) agreed to full study participation, and 4.8% of respondents consented to only the survey component of the study, with no shared clinical data. No statistically significant difference was observed between the three participation groups (full participation, survey including medical record data, and survey only) except for health insurance status (**Table 7-1**). Of the overall survey cohort of 125 respondents, 108 (86.4%) had at least one eye examination at some stage during their pregnancy and 109 (87.2%) understood that they needed more frequent eye examinations during pregnancy than the general diabetic population.

The demographic characteristics of respondents were compared between those who did and did not adhere to NHMRC recommendations (**Table 7-2**) and the study protocol (**Table 7-3**). Among those who completed the survey, 44.8% (95% CI 36.36 – 53.54) adhered with the NHMRC guidelines whilst only 26.4% (95% CI 19.43 – 34.78) adhered with the study protocol. Respondents who adhered to both recommendations were more likely to have type 1 diabetes (p-values ≤ 0.041), and to have self-reported DR before pregnancy (p-values ≤ 0.047). Respondents who agreed to participate in the full study were more likely to adhere with the NHMRC guidelines compared to those who did not ($p < 0.001$), but this trend was not found between the non-adherent vs adherent groups based on the study protocol. Worryingly, 84.8% (95% CI 75.9 - 90.8) of respondents who did not adhere to the study protocol acknowledged that more frequent eye exams were needed during pregnancy.

Table 7-1. Respondent's demographics by study participation groups

Demographic characteristics	**Overall Survey Cohort** (n = 125)	Study Participation Group			***p*-value**[*]
		Full study participation (n = 103)	**Survey & shared medical data** (n = 16)	**Survey only** (n = 6)	
Age [years], median (IQR)	34 (30 - 36)	34 (30 - 36)	35 (33 - 37)	30.5 (28 - 35)	0.349
Type of diabetes, n (%)					0.538
T1DM	64 (51.2)	55 (53)	7 (44)	2 (33)	
T2DM	61 (48.8)	48 (47)	9 (56)	4 (67)	
T1DM:					0.261
Duration [years], median (IQR)	17 (8 - 23)	17 (8 - 23)	23 (8 - 27)	6.4 (0.8 - 12)[†]	
T2DM:					0.672
Duration [years], median (IQR)	3 (1 - 5.4)	3.5 (0.95 - 5.7)	3 (2.5 - 5)	0.9 (0.45 - 7.5)	
N children, n (%)					0.421
none	53 (42.4)	41 (40)	9 (56)	3 (50)	
1	44 (35.2)	40 (39)	3 (19)	1 (17)	
2 or more	28 (22.4)	22 (21)	4 (25)	2 (33)	
Attendance at pre-pregnancy care [yes], n (%)	64 (51.2)	55 (53)	6 (38)	3 (50)	0.501
Ethnicity, n (%)					0.842
Asian, Indian	39 (31.2)	34 (33)	3 (19)	2 (33)	
Caucasian	63 (50.4)	50 (49)	10 (62)	3 (50)	
other	23 (18.4)	19 (18)	3 (19)	1 (17)	
Education, n (%)					0.558
Primary school	3 (2.4)	2 (2)	1 (6)	0	
Secondary school	18 (14.4)	14 (14)	3 (19)	1 (17)	
Trade certificate	17 (13.6)	15 (15)	2 (13)	0	
Diploma	15 (12.0)	15 (15)	0	0	
University	72 (57.6)	57 (55)	10 (62)	5 (83)	
Relationship, n (%)					0.524
Single	3 (2.4)	3 (3)	0	0	
Married	97 (77.6)	81 (79)	12 (75)	4 (67)	
Separated	2 (1.6)	1 (1)	1 (6)	0	
Domestic partner	23 (18.4)	18 (17)	3 (19)	2 (33)	
Lives with partner/spouse, n (%)	120 (96.0)	99 (96)	15 (94)	6 (100)	0.627
Has health insurance [yes], n (%)	70 (56.5)	***57 (56)***	***12 (75)***	***1 (17)***	***0.044***
Annual family income[‡], n (%)					0.254
<AU$ 15,000	1 (1.1)	0	0	1 (50)	
AU$ 15,000–24,999	8 (8.9)	8 (10)	0	0	

AU$ 25,000–34,999	1 (1.1)	1 (1)	0	0	
AU$ 35,000–49,999	10 (11.1)	10 (13)	0	0	
AU$ 50,000–74,999	12 (13.3)	11 (14)	1 (10)	0	
AU$ 75,000–99,999	19 (21.1)	16 (21)	3 (30)	0	
>=AU$ 100,000	39 (43.3)	32 (41)	6 (60)	1 (50)	
History of DR diagnosis (self-reported), n (%)					0.518
None	95 (76)	77 (74.8)	12 (75)	6 (100)	
DR	30 (24)	26 (25.2)	4 (25)	0	

* *p*-value was estimated using Fisher's exact test or Kruskal Wallis test as appropriate.
† Only two respondents.
‡ Contributed data: 78 women in the full study group, 10 women in the survey & shared group, 2 women in the survey only group.
Abbreviations: DR, diabetic retinopathy; IQR, interquartile range; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 7-2. Respondent demographics by adherent and non-adherent groups based on the NHMRC guidelines

Demographic Variables	Non-adherent	Adherent	*p*-value*
N	69	56 (**44.8%**)	
Age [years], median (IQR)	35 (30 - 37)	33 (30 - 35.5)	0.308
Participation type, n (%)			***<0.001***
Full study	***49 (71)***	***54 (96)***	
Survey + records	***15 (22)***	***1 (2)***	
Survey only	***5 (7)***	***1 (2)***	
Type of diabetes, n (%)			***0.041***
T1DM	***30 (43.5)***	***34 (61)***	
T2DM	***39 (56.5)***	***22 (39)***	
T1DM:			0.316
Duration [years], median (IQR)	16.5 (7.3 - 23)	18.4 (11.5 - 23)	
T2DM:			0.465
Duration [years], median (IQR)	3 (0.4 - 66)	3.5 (2 - 5.4)	
N children, n (%)			0.101
none	31 (45)	22 (39)	
1	19 (27.5)	25 (45)	
2 or more	19 (27.5)	9 (16)	
Attendance at pre-pregnancy care [yes], n (%)	34 (49)	30 (54)	0.383
Ethnicity, n (%)			0.245
Asian, Indian	24 (35)	15 (27)	
Caucasian	30 (43)	33 (59)	
other	15 (22)	8 (14)	
Education, n (%)			0.533
Primary	2 (3)	1 (2)	
Secondary	13 (19)	5 (9)	
Trade certificate	8 (12)	9 (16)	
Diploma	7 (10)	8 (14)	
University	39 (56)	33 (59)	
Lives with partner/spouse, n (%)	65 (94)	55 (98)	0.254
Has health insurance, n (%)	38 (55)	32 (58)	0.435
Annual family income†, n (%)			0.617
< AU$ 15,000	1 (2)	0	
AU$ 15,000 – 24,999	2 (4)	6 (13)	
AU$ 25,000 – 34,999	1 (2)	0	
AU$ 35,000 – 49,999	6 (13)	4 (9)	
AU$ 50,000 – 74,999	7 (16)	5 (11)	
AU$ 75,000 – 99,999	9 (20)	10 (22)	
>= AU$100,000	19 (42)	20 (44)	
History of DR diagnosis (self-reported), n (%)			***0.005***
None	***59 (85.5)***	***36 (64)***	
DR present	***10 (14.5)***	***20 (36)***	

* *p*-value was estimated using Fisher's exact or Kruskal Wallis test as appropriate.

† Contributed data: 45 women in the non-adherent group, 45 women in the adherent group.

Abbreviations: DR, diabetic retinopathy; IQR, interquartile range; NHMRC, National Health and Medical Research Council; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

Table 7-3. Respondent demographics by adherent and non-adherent groups based on the study protocol

Demographic Variables	Non-adherent	Adherent	*p*-value*
N	92	33 (**26.4%**)	
Age [years], median (IQR)	34 (31 - 37)	33 (29 - 35)	0.183
Participation type, n (%)			0.137
Full study	72 (78)	31 (94)	
Survey + records	14 (15)	2 (6)	
Survey only	6 (7)	0	
Type of diabetes, n (%)			***0.030***
T1DM	***42 (46)***	***22 (67)***	
T2DM	***50 (54)***	***11 (33)***	
T1DM:			0.191
Duration [years], median (IQR)	14.5 (8 - 23)	19.5 (13.5 - 25)	
T2DM:			0.807
Duration [years], median (IQR)	3 (0.7 - 6)	3 (2 - 4)	
N children, n (%)			0.063
none	35 (38)	18 (55)	
1	32 (35)	12 (36)	
2 or more	25 (27)	3 (9)	
Attendance at pre-pregnancy care [yes], n (%)	46 (50)	18 (56)	0.404
Ethnicity, n (%)			0.416
Asian, Indian	31 (34)	8 (24)	
Caucasian	43 (47)	20 (61)	
other	18 (20)	5 (15)	
Education, n (%)			0.422
Primary	3 (4)	0	
Secondary	15 (16)	3 (9)	
Trade certificate	14 (15)	3 (9)	
Diploma	12 (13)	3 (9)	
University	48 (52)	24 (73)	
Lives with partner/spouse, n (%)	87 (95)	33 (100)	0.210
Has health insurance, n (%)	49 (54)	21 (64)	0.222
Annual family income†, n (%)			0.925
<AU$ 15,000	1 (2)	0	
AU$ 15,000 – 24,999	6 (10)	2 (7)	
AU$ 25,000 – 34,999	1 (2)	0	
AU$ 35,000 – 49,999	8 (13)	2 (7)	
AU$ 50,000 – 74,999	8 (13)	4 (14)	
AU$ 75,000 – 99,999	11 (18)	8 (28)	
>=AU$100,000	26 (43)	13 (45)	
History of DR diagnosis (self-reported), n (%)			***0.047***
None	***74 (80)***	***21 (64)***	
DR present	***18 (20)***	***12 (36)***	

* *p*-value was estimated using Fisher's exact or Kruskal Wallis test as appropriate.

† Contributed data: 61 women in the non-adherent group, 29 women in the adherent group.

Abbreviations: DR, diabetic retinopathy; IQR, interquartile range; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

7.3.2. Factors associated with adherence

7.3.2.1 Individual CADEES item analysis

Women who adhered to NHMRC guidelines responded differently to those who did not adhere in four out of 43 CADEES items (**Figure 7-2**). Guideline-adhering respondents agreed more strongly that they were happy with the care provided by the eye service ($p = 0.008$) and wanted to have regular eye exams ($p = 0.026$). Moreover, the group who did not adhere agreed more often that they had many eye doctors in their area ($p = 0.045$) and that getting a regular eye exam was not their priority during pregnancy ($p = 0.024$), when compared to the adherent group.

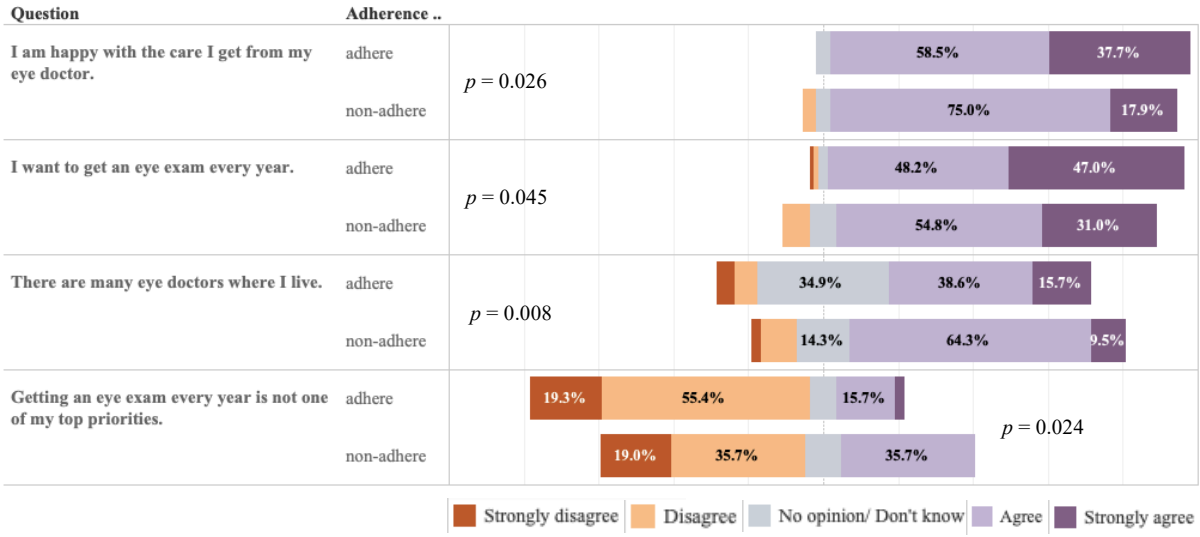


Figure 7-2. The individual CADEES items between adherent and non-adherent groups, by NHMRC guidelines

Gantt per cent represents per cent of total sizing for each group in each question. *P*-value relates to the difference between two groups examined using Wilcoxon rank-sum test. Abbreviations: CADEES, Compliance with Annual Eye Exams Survey; NHMRC, National Health and Medical Research Council.

By comparison, women who adhered to the study protocol responded differently to non-adhering respondents in seven out of 43 CADEES items (**Figure 7-3**). Respondents with good adherence agreed more strongly that diabetes could damage the blood vessels in the eye ($p = 0.042$), that having regular eye exams help prevent vision loss ($p = 0.019$) and would benefit them ($p = 0.039$), that screening exams could find other eye problems in addition to DR ($p = 0.020$), and they wanted to attend regular eye exams ($p = 0.006$). Furthermore, the non-adherent group agreed more often that they could (adequately) control their blood glucose ($p = 0.042$)

and that getting regular eye exams was not their top priority during pregnancy ($p = 0.006$) in comparison to the adherent group.

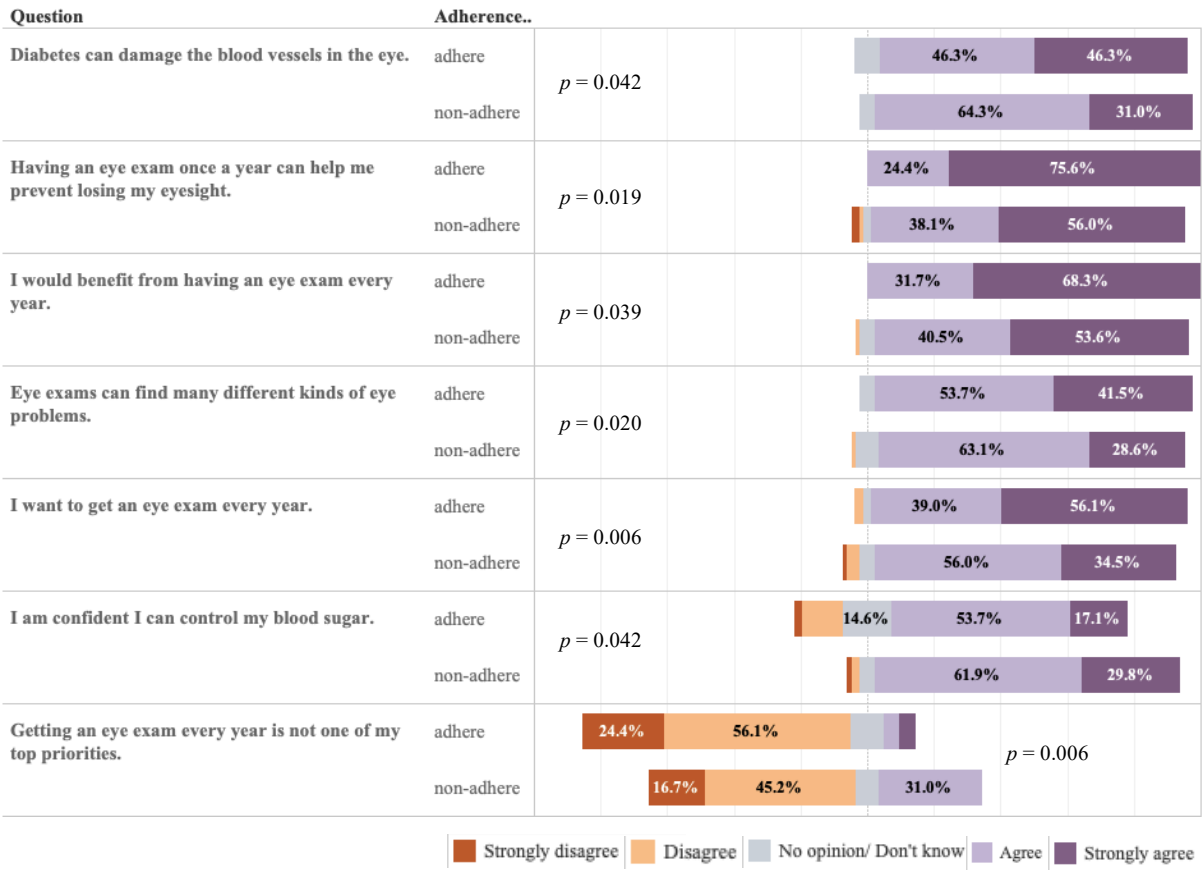


Figure 7-3. The individual CADEES items between adherent and non-adherent groups, by the study protocol

Gantt per cent represents per cent of total sizing for each group in each question. *P*-value relates to the difference between two groups examined using Wilcoxon rank-sum test. Abbreviations: CADEES, Compliance with Annual Eye Exams Survey.

Table 7-4 presents the results of the logistic regression analysis to determine predictive factors for adherence to NHMRC guidelines. Logistic regression demonstrated that adherence to NHMRC recommendations was less likely in respondents who agreed (in any strength) with the statement: "*There are many eye doctors where I live*" compared to those who disagreed or gave a neutral response (unadjusted odds ratio [OR] 0.33; 95% CI 0.16 - 0.69). This result persisted even after adjusting for covariates (p-values ≤ 0.03). In contrast, adherence to NHMRC guidelines was more likely in respondents who agreed with the statement: *"My family members or friends help me make doctor appointments"* compared to those who responded neutral or disagree, after adjusting for covariates (p-values ≤ 0.049).

Table 7-5 shows the odds ratio for potential factors that may predict adherence to the study protocol. The likelihood of adherence with the study protocol was reduced in respondents who agreed (in any strength) with the statement "*I am confident I can control my blood sugar"* (OR 0.25; 95% CI 0.09 - 0.69) or *"Getting an eye exam every year is not one of my top priorities"* (OR 0.15; 95% CI 0.33 - 0.66) compared to those who disagreed or were neutral, even after adjusting for covariates (*p*-values ≤0.007 and ≤0.027, respectively). Further analysis on the prioritisation of eye examinations will be analysed further in **section 7.3.4**.

Table 7-4. Association of CADEES items with adherence to NHMRC guidelines (agreed in any strength compared to those who answered disagree or neutral)

Compliance with Annual Diabetic Eye Exams Survey Item	**Odds of adherence, given that participant agreed with the item statement**							
	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
There are many eye doctors where I live (Q27)	***0.33 (0.16 - 0.69)***	***0.003***	***0.31 (0.14 - 0.66)***	***0.002***	***0.31 (0.14 - 0.67)***	***0.003***	***0.30 (0.14 - 0.66)***	***0.003***
My family members or friends help me make doctor appointments (Q28)	1.70 (0.77 - 3.73)	0.186	***2.38 (1.00 - 5.63)***	***0.049***	***2.73 (1.08 - 6.91)***	***0.033***	***2.81 (1.17- 6.74)***	***0.021***

Model 1: logistic regression, unadjusted; Model 2: adjusted for DM type; Model 3: adjusted for ethnicity groupings; Model 4: adjusted for DM type and self-reported DR status. The adjusted odds ratio for self-reported DR status is presented in **Supplementary table S7-2**.
Abbreviations: CI, confidence interval; DM, diabetes mellitus; DR, diabetic retinopathy; OR, odds ratio.

Table 7-5. Association of CADEES items with adherence to the study protocol (agreed in any strength compared to those who answered disagree or neutral)

Compliance with Annual Diabetic Eye Exams Survey Item	**Odds of adherence, given that participant agreed with the item statement**							
	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
I am confident I can control my blood sugar (Q30)	***0.25 (0.09 - 0.69)***	***0.007***	***0.24 (0.08 - 0.67)***	***0.007***	***0.23 (0.08 - 0.65)***	***0.006***	***0.23 (0.08 - 0.65)***	***0.006***
Getting an eye exam every year is not one of my top priorities (Q40)	***0.15 (0.33 - 0.66)***	***0.012***	***0.17 (0.04 - 0.78)***	***0.023***	***0.16 (0.03 - 0.72)***	***0.017***	***0.18 (0.04 - 0.82)***	***0.027***

Model 1: logistic regression, unadjusted; Model 2: adjusted for DM type; Model 3: adjusted for ethnicity groupings; Model 4: adjusted for DM type and self-reported DR status. The adjusted odds ratio for self-reported DR status is presented in **Supplementary table S7-2**.
Abbreviations: CI, confidence interval; DM, diabetes mellitus; DR, diabetic retinopathy; OR, odds ratio.

7.3.2.2 Qualitative analysis of barriers to attendance at the recommended eye screening guidelines

From the open-ended question: "*We are interested in why some people do not have routine eye exams during pregnancy. Can you think of any reasons we did not ask about in this survey?*", substantive answers were obtained from 60 (48%) respondents. This response rate was higher than in Sheppler and colleagues' original paper (38%).[221] Of the 60 women who responded to this open question, 57% had type 1 diabetes (95% CI 44% – 70%), the median age was 34 (IQR 32 – 36) years, 52% (95% CI 39% – 64%) were Caucasian, and 20% (95% CI 10% – 30%) had self-reported DR before pregnancy.

Following inductive thematic analysis, five overarching themes were established: a) **Conflicting commitments**; b) **Knowledge**; c) **Negative experiences and feelings**; d) **Accessibility**; and e) **Perception of health**. Reasons to not attend eye examinations were presented according to frequency (n) of the data coded to each of these themes, with an example of respondent's statements that represent each idea.

a) Conflicting commitments

The most cited reason that prevented respondents from attending regular eye exams during pregnancy was conflicting commitments, including being too busy (n = 9); having multiple appointments (n = 6); dealing with comorbidities (n = 6); caring for young children (n = 5); and work (n = 3). Three respondents suggested that non-attendance to eye screening might be due to forgetting to book or to attend an appointment.

> *"**Being T1 diabetic means so many more appointments. It's easy for someone to feel overwhelmed/too busy/can't be bothered with other appointments not specifically relating to the baby.**"* 33 years old, T1DM, first pregnancy.

> *"**Finding the time with young children to have an eye exam.**"* 32 years old, T1DM, student, second pregnancy.

> *"**Getting time off work.**"* 35 years old, T1DM, social worker, first pregnancy.

b) Knowledge

Several respondents provided reasons for non-attendance that related to knowledge. These included: lack of concern regarding their eye health or diabetes (n = 10); being unaware of its importance (n = 7); lack of knowledge of DR (n = 4); and not being advised to do so by their doctors (n = 3).

> "***Maybe people doesn't [sic] have proper education regarding importancy[sic] about this exam***." 33 years old, T2DM, medical practice manager, second pregnancy.

> "***Maybe some people are unaware of the importance of regular eye checks and the impacts on eye health if they are not checked****."* 33 years old, T1DM, teacher, first pregnancy.

c) Negative experience and feelings

Some respondents quoted a negative experience that prevented them from attending the eye exams. These included: Fear, stress, and anxiety (n = 8); eye dilatation (n = 6); duration of exams (n = 4); discomfort (n = 2); and misrepresentation of clinic staff (n = 1).

> *"****I went to one exam which took 90 mins and [the eye dilatation] left me stranded without good sight on a bright day. There was talk of spots in my eyes - which terrified me and nothing was properly said to me [by the examiner]… [I] don't appreciate the time taken for this [eye exams]. I don't need this stress.****"* 30 years old, T1DM, second pregnancy.

> ***"…[I] felt the whole team there [the optometrist clinic] more inclined to sell you glasses. As soon as you saw the doctor, a salesperson came in & talk thru/ brought you to the glasses section. They didn't seem quite happy when you don't buy anything & asked for a copy of the report."*** 36 years old, T2DM, housewife, fourth pregnancy.

d) Accessibility

Accessibility to eye exams also contributed to non-attendance. Accessibility related to cost was the most cited reason (n = 8), followed by not understanding the new health system after migration to Australia (n = 5), access to eye clinics (n = 4), travel and transportation issues (n = 2), and language barriers (n = 1) also contributed.

> *"**Money constraint.**"* 36 years old, T2DM, student, second pregnancy.
>
> ***"[I have] only been in Australia 2 years and didn't have frequent hospital visits to be referred... not know how to book through unless referred by doctor."*** 26 years old, T1DM, retail manager, first pregnancy.
>
> *"**No Idea which eye doctor to go.**"* 33 years old, T2DM, housewife, third pregnancy.

e) Perception of health

The belief that the eyes are healthy if there was no problem noted with their vision (n = 8) and believing that they had reasonable diabetes control (n = 1) were identified as being barriers to attending recommended eye screening exams. Additionally, denial of their health condition also was cited (n = 2).

> *"**If there is no pain or change in sight then no need to make change [to eye screening schedule].**"* 32 years old, T1DM, student, third pregnancy.
>
> *"**I have excellent diabetic control.**"* 30 years old, T1DM, second pregnancy.
>
> *"**People are scared that they might disclose their eye condition and don't want to know of any problems.**"* 31 years old, T1DM, housewife, third pregnancy.

7.3.3. Health appointment priorities during pregnancy

To further explore the health priorities of this cohort, respondents were asked to rank the various health appointments they needed to attend during pregnancy from 1 (most

important) to 7 (least important). Overall, obstetric (median rank 1.5 [IQR 1-2]) and endocrinology (median rank 2 [IQR 1-3]) appointments were cited as the most important appointments to attend, followed by the diabetes educator (median rank 3 [IQR 3-5]). Eye exams were ranked as the fourth priority (median rank 4 [IQR 4-5]) similar to the general practitioner (GP) (median rank 4 [IQR 3-6]). A dietician appointment was ranked as the second last priority (median rank 5 [IQR 4-6]), followed by a podiatry appointment (median rank 7 [IQR 6-7]) as the lowest priority (**Figure 7-4**).

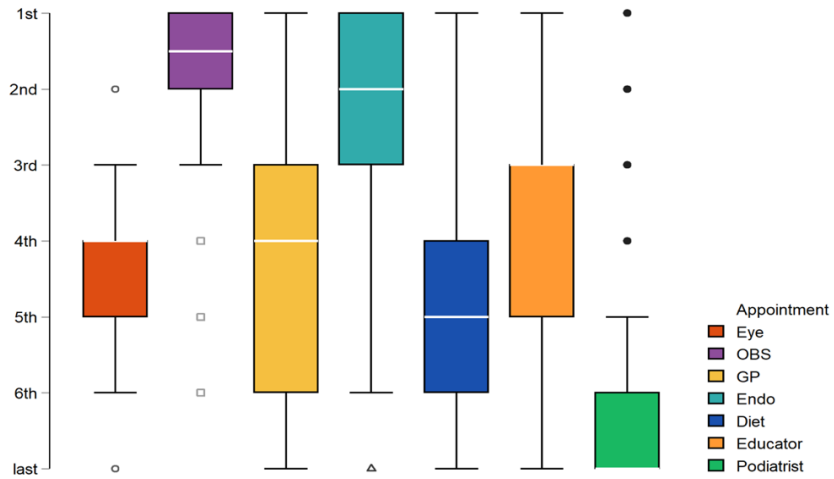


Figure 7-4. The rank of health appointment priorities during pregnancy

Abbreviations: Diet, dietician; Endo, endocrinologist; GP, general practitioner; OBS, obstetrician.

Looking further into these priority rankings across the type of diabetes (**Figure 7-5**), respondents with T1DM ranked their endocrinologist appointment as slightly more important (median rank 2 [IQR 1-2] vs 2 [IQR 2-4]; $p = 0.001$) and ranked GP (median rank 5 [IQR 4-6] vs 4.5 [IQR 1-6.5]; $p = 0.004$) and dietician (median rank 6 [IQR 5.5-6] vs 5 [IQR 4.5-6]; $p = 0.039$) appointments lower than respondents with T2DM. Respondents with T1DM ranked their eye appointment slightly higher than the T2DM group, but this was not statistically different (4 [IQR 4-5] vs 5 [IQR 4-6]; $p = 0.935$). When comparing these rankings across ethnic groups (Caucasian vs Asian vs 'other'), no difference was found in the importance rankings by respondents' ethnicity, except for responses relating to endocrinology and dietician appointments (**Figure 7-6**). Caucasian women ranked endocrinologist appointments slightly higher and dietician appointment

lower than women of Asian and 'other' ethnicity (p-values ≤ 0.006 – **Supplementary table S7-3**).

Furthermore, a comparison of priority rankings between the adherent and non-adherent respondents (**Figure 7-7**) showed that those who adhered to the NHMRC guidelines and the study protocol ranked attendance at eye appointments higher than the non-adherent group (p-values ≤ 0.024). Additionally, respondents who adhered to the study protocol ranked their endocrinologist appointment slightly higher (p = 0.002) and the GP slightly lower (p = 0.019) than those who did not adhere (**Supplementary table S7-4**).

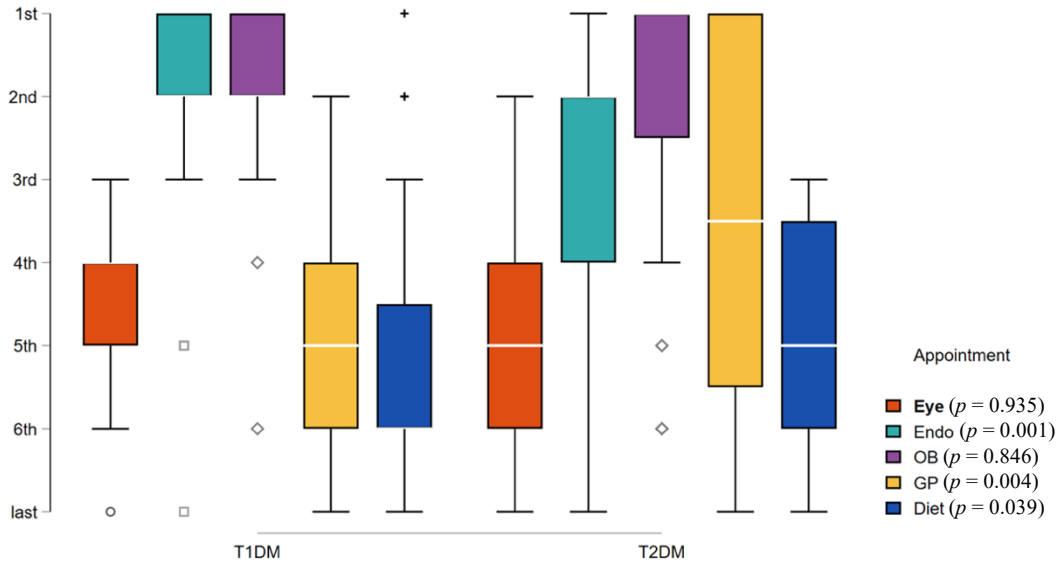


Figure 7-5. Health appointments rank between type 1 diabetes (T1DM) and type 2 diabetes (T2DM) groups

Abbreviations: Diet, dietician; Endo, endocrinologist; GP, general practitioner; OB, obstetrician.

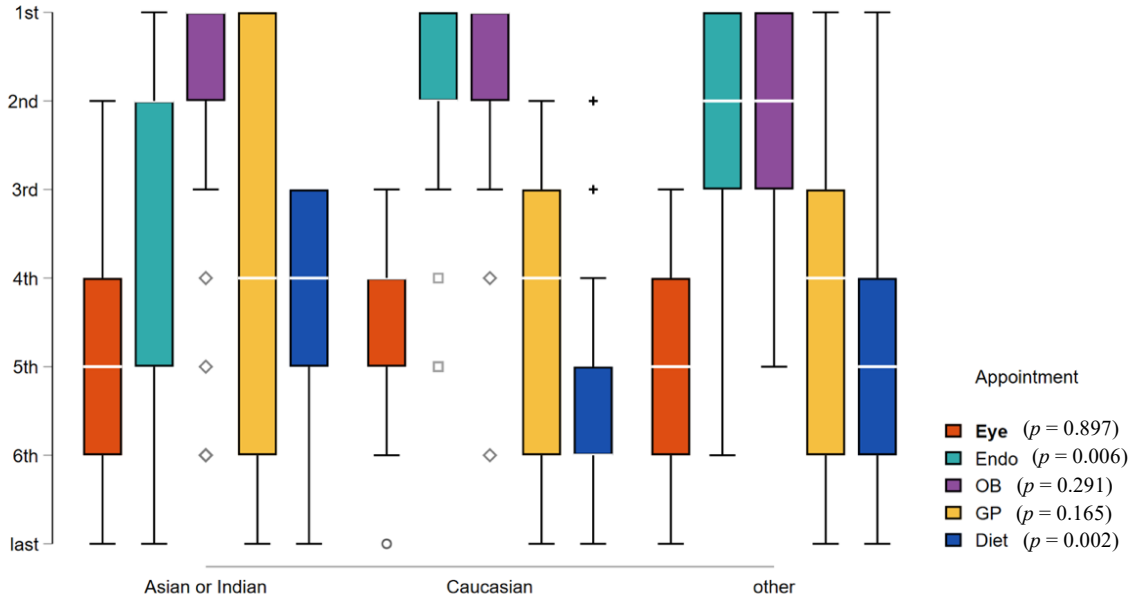


Figure 7-6. Health appointments rank between three ethnicity groupings

Abbreviations: Diet, dietician; Endo, endocrinologist; GP, general practitioner; OB, obstetrician.

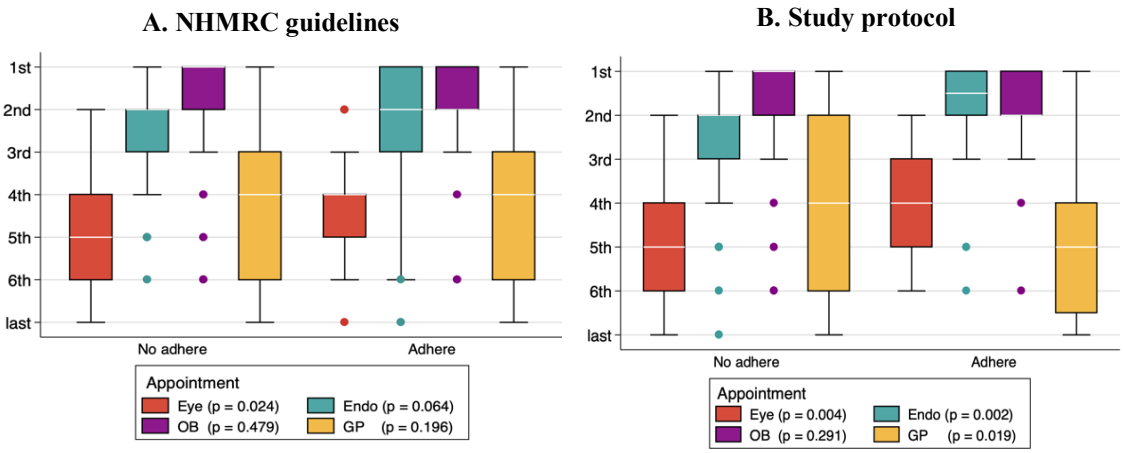


Figure 7-7. Health appointments rank between adherent and non-adherent groups

Abbreviations: Endo, endocrinologist; GP, general practitioner; NHMRC, National Health and Medical Research Council; OB, obstetrician.

7.4. Discussion

This is the first Australian study and one of the few studies globally that assessed the adherence rates to the recommended eye screening guidelines in pregnant women with pre-existing diabetes. Despite the risk of DR during pregnancy, only about 45% of this

study population had an eye examination during their first trimester, as recommended by the NHMRC DR screening guidelines. Even fewer (26.4%) adhered to the ADIPS guidelines, of which this study protocol was based upon, that recommends more frequent examinations. Having T1DM and having been diagnosed with DR prior to falling pregnant were associated with better adherence.

The reported adherence rates of this current study appeared significantly lower than the Atlantic Diabetes in Pregnancy (Atlantic DIP) study.[150] This multicentre study in Ireland reported that 70.7% of their pregnant women with either T1DM or T2DM had at least one retinal evaluation and 60.3% of all had adequate retinal examinations. The latter rate was reported to improve to 74.1% after the establishment of integrated diabetes antenatal clinics to improve care delivery, which included the development of local clinical guidelines and educational resources for professionals and patients.[150,206,276] However, this study applied different DR screening recommendations compared to our study; therefore, a direct comparison might not be appropriate. Their local guidelines defined an adequate retinal evaluation during pregnancy as having at least two examinations in different trimesters; and if DR was present, more frequent assessments were advised. Both our study population and the Atlantic DIP population were relatively similar, except for the proportion of Caucasian women (Atlantic DIP vs current study: 90.6% vs 50.4%) and the attendance rate to pre-pregnancy care (42.02% vs 51.2%).

Interestingly, if we used the same adherence definition as per the Atlantic DIP study (i.e., at least one eye examination during pregnancy), the adherence rate in our study population would be higher (86.4%) but the rate for adequate DR screening during pregnancy would be lower (two or more eye examinations during pregnancy, 54.4%). These differences might be due to several reasons. First, the higher rate of having at least one exam in our study might be affected by the higher rate of attendance to pre-pregnancy care amongst our participants, as attendance at pre-pregnancy care appointments was associated with higher adherence to scheduled eye examinations in the Atlantic DIP study.[150] This was likely a result of the incorporation of counselling regarding the risk of DR and the importance of DR screening during pregnancy at pre-pregnancy care visits.[48,190,203,277] Therefore, women who attended pre-pregnancy care were more aware and more likely to attend eye appointments compared to those who did not. Additionally, the fact that the majority of our study population who were exposed to this part of the

clinical study were actively involved in the whole study protocol indicates that our study population might be more knowledgeable about diabetes and the risk of DR compared to the Atlantic DIP study, which was a retrospective study. As shown in our findings, women who were fully involved in the study were more adherent than women with less involvement in the study. A previous study also reported this correlation.[278]

Secondly, the lower rate of adequate eye examinations in our study might reflect the different local eye screening recommendations between both studies. The Australian NHMRC guidelines recommends that women have at least one eye examination during pregnancy, and further examinations are determined by the clinician's judgement, based on the woman's clinical condition (i.e., DR status), for which there are no formal guidelines that are specific to pregnancy as to how frequent these examinations ought to be. Follow-up visits were thus also only advised for those who had pre-existing DR. This was reflected in our study respondents where those with pre-existing DR were indeed more likely to have follow-up examinations compared to those who had no DR.

It is interesting to note that our study population had relatively a high attendance rate to eye examinations during pregnancy, but only a few women attended appointments during their first trimester (n = 58, 44.6%, see **Chapter 5**, **Table 5-2**). A similar problem was reported by Hampshire *et al.* where many of their pregnant women did not attend eye screening until the second or third trimester, despite being advised to do so at their first antenatal visit.[204] These findings emphasise the need to improve the eye screening uptake for pregnant women with pre-existing diabetes in their first trimester.

Furthermore, this study also sought to explore respondents' reasons for not attending diabetic eye screening examinations during pregnancy. Barriers to attendance at diabetic eye screening programs in the non-pregnant population have been extensively investigated.[36,199,279,280] However, very few studies have reported barriers for pregnant women, and our study offers additional insight in this area. We found that negative experiences, lack of knowledge, and perception of having good health were factors that prevented our study participants from attending diabetic eye screening examinations. These findings were similar to what has been observed in the non-pregnant population.[36] However, more importantly, we observed that conflicting priorities were the most significant barrier for attending eye examinations during pregnancy. This was due to the fact that these women were required to attend multiple health appointments during

pregnancy (up to five appointments per visit, ranging from every four weeks in the 1st trimester increasing to every week in the 3rd trimester[193]). They found this to be very time consuming in addition to daily blood glucose monitoring, work, and family responsibilities. Pregnancy itself, indeed, was an independent barrier to attending diabetic eye screening.[205] It was obvious that during pregnancy, the most important priority for patients was their future baby; hence, obstetric and endocrinology appointments become more important than maintaining their eye health.

In the context of this current study, diabetes-specific clinics with an integrated multidisciplinary antenatal care incorporating obstetricians, endocrinologists, diabetes educators, and dieticians were offered at both of our hospital sites. Unfortunately, this did not include eye care. As a result, our patients had to be referred individually to an eye clinic (either to an optometrist or an ophthalmologist) that was located separately to the maternity hospital. Since these women ranked eye health as a low priority during pregnancy, the low attendance for eye screening examinations may be attributable to this inconvenience in accessing an eye care services. Similar issues with access to eye care services were also suggested by Hampshire *et al.* where they hypothesised that the distance between their photographic review clinic and antenatal clinics might contribute to the low attendance rate.[204] Distances between the diabetes clinic and eye clinic was also identified as an issue in the general diabetic population.[36] Another interesting observation in our study was that the presence of multiple eye care providers in a woman's neighbourhood was associated with non-adherence, rather than greater adherence. Although this seems counter-intuitive, several reasons could potentially explain this finding. After analysing our data qualitatively and reflecting on a recent systematic review of diabetic eye screening barriers in the general diabetes population,[36] we hypothesise that despite many eye care providers being available within these women's range, there was:

1) A lack of information of where to go (i.e., which eye care providers could provide diabetic eye screening examinations),

2) a long waiting period to get the eye appointment (public services), or

3) concern about out-of-pocket cost (private services).

Further study is needed to confirm these hypotheses.

On the other hand, this study also found several factors that enabled pregnant women to adhere to the recommended eye examinations. Knowledge of the benefits of eye screening examinations and support from relatives (e.g., having someone to drive them after being dilated during the eye examination) motivated women to attend eye appointments. These findings were aligned with the results of previous studies.[36,279,280] We also observed that endocrinologists and GPs may play a role in improving women's adherence to eye examinations in this study population. We hypothesise that it would be useful if specialists that frequently meet with these women could advise and ensure that their pregnant patients receive diabetic eye screening as recommended. Promotion of diabetic eye screening programs by other health professionals was reported to improve patient attendance to this program in the Australian non-pregnant population.[200] A close communication between health professionals and eye care providers who care for pregnant women with diabetes could also increase adherence.[204] An effort to involve other health professionals in primary health care to implement integrated eye care in the Australian health system has been initiated and has been proven to improve the DR screening rate for the non-pregnant Indigenous population.[281] Unfortunately, this movement has not yet targeted antenatal care services, the primary health care for pregnant women with diabetes.

Overall, this is the first study that has explored potential barriers and enablers to attend the recommended diabetic eye screening guidelines in pregnancy. This study provides clear evidence that there are gaps in the current health system regarding DR management for pregnant women with pre-existing diabetes in Australia that might affect the adherence rate to attend eye screening examinations. This study also identified some barriers and enablers that can be targeted for improvement in future guidelines. However, there were some limitations in this study. First, the survey questionnaire that was used was not specifically developed for the pregnant population, and we tried to compensate for this limitation by performing a qualitative analysis on respondents' answers to an open question and thus could reflect on the actual barriers that prevented them from attending eye screening examinations. Second, with the implementation of the online survey, there was no assurance that those women who completed the survey through the online survey link did so by themselves, therefore potentially leading to a misinterpretation of the survey questions that they could not clarify with the researcher directly. In saying this, only seven out of 125 of our respondents completed the survey online. Lastly, due to the

nature of our main study as a clinical trial, our respondents, especially those with full participation, received multiple benefits, such as a free service, flexible appointment times, and travel assistance to attend the eye clinic, which may have influenced their behaviour and responses to the survey questions. Therefore, our findings might overestimate adherence rates.

In summary, more than half of pregnant women with pre-existing diabetes in Metropolitan Melbourne did not attend recommended eye screening examinations during pregnancy and about 70% did not receive examinations at the recommended frequency. Proactive efforts are required to educate these women about the risk of DR worsening during pregnancy and the importance of routine eye screening examinations in pregnancy. More importantly, there is an urgent need to integrate eye screening examinations into antenatal care programs to prevent vision loss in this growing demographic in Australia. “One-stop-shop” care has been suggested by previous studies as the potential solution to improve attendance to eye screening examinations, by ensuring more convenient access for pregnant women. Moreover, by providing integrated eye care, there is an opportunity to also improve the patient screening uptake in the first trimester of pregnancy as recommended by the NHMRC.

CHAPTER 8: UTILISING CURRENT EVIDENCE TO OPTIMISE THE MANAGEMENT OF DIABETIC RETINOPATHY IN PREGNANT WOMEN WITH PRE-EXISTING DIABETES IN AUSTRALIA

8.1. Overview

In **Chapter 3**, results from our meta-analysis show the trends in diabetic retinopathy (DR) prevalence and its progression rate during pregnancy from the available literature globally; gaps in the literature, especially the lack of contemporary Australian data, were demonstrated. The following chapters presented three different, yet interconnected, investigations into several core areas relating to DR management. The first, reported the prevalence of DR, sight-threatening DR (STDR), and its progression rate during pregnancy and the early postpartum period in metropolitan Melbourne (**Chapter 5**). Next, the use of optical coherence tomography angiography (OCTA) was assessed for evaluating retinal vascular changes in diabetic patients in the non-pregnant, pregnant and postpartum state (**Chapter 6**). Finally, the rates of and barriers to adherence to the recommended eye screening guidelines during pregnancy in women with pre-existing diabetes were determined (Chapter 7).

In this chapter, the key findings from these investigations are synthesised and applied to a broader context in an attempt to explore the overall burden of DR in pregnancy in the Australian population and to discover potential solutions that can inform the future development of updated guidelines for DR management in pregnancy in Australia.

8.2. Key Findings

8.2.1. The prevalence of DR and its progression rate in Australian pregnant women with pre-existing diabetes (Aim 1)

This prospective longitudinal study is the first since 1980 that studied the effect of pregnancy on DR in the Australian pregnant population with pre-existing diabetes. We found that the prevalence of any DR and STDR per eye during pregnancy and in the early postpartum was 20.8% and 6.6% respectively, whilst the prevalence per woman was

21.5% and 9.4%, respectively. Our prevalence of any DR is similar to that in the non-pregnant diabetic population. The National Eye Health Survey (NEHS) in Australia reported that 28.5% of their non-Indigenous participants had DR and 4.5% had STDR.[239] Although their prevalence of STDR is slightly lower, this difference could be due to variations in the definition of STDR rather than an actual difference in the rate. In our study, STDR was defined as the presence of proliferative DR (PDR) or diabetic macular oedema (DMO) whereas in the NEHS study, it was defined as the presence of severe non-proliferative DR (NPDR), PDR, or clinically significant macular oedema (CSMO). Since our definition included all types of DMO, it is most likely that our higher STDR prevalence is due to the inclusion of women with less severe DMO who would not have been counted as STDR in the NEHS. A meta-analysis by Yau *et al.* that used a similar STDR definition estimated a comparable STDR prevalence to ours (10.2%).[33] Considering that participants in these studies were older than our population by around 20-30 years, a similar DR rate in the pregnant population would conceivably cause an even greater societal burden in terms of vision loss and work productivity.

With regard to DR progression, 1 in 10 eyes (9.7%) in our cohort progressed between early to late pregnancy (a period of around 6 months), of which almost half developed STDR. Sight-threatening progression was found to be more commonly due to the development of DMO than PDR, an under-investigated condition in previous studies. This risk of progression to DMO may still occur even after delivery, emphasising the need for retinal evaluation in the postpartum period which includes DMO assessment. That being said, impaired vision from DMO was rarely found.

Our progression rate is lower than the majority of historical studies with cohorts that had poor diabetes control[13,112,114,138] but is similar to the more contemporary studies with cohorts that had relatively well-controlled diabetes.[147,150] Two important points can be deduced from these findings. Firstly, diabetes control is one of the key predictors of DR progression risk during pregnancy as has been reported in previous studies.[148,149] In Australia, it has been advised that optimised diabetes control should be achieved before women fall pregnant (if possible). Therefore, the majority of our patients had reasonable glycaemic control in early pregnancy which is in line with the reported data from another study of Australian pregnant women with pre-existing diabetes.[282] As a result, a lower DR progression rate was observed in our study. Secondly, looking into the timeline of

these studies, it is highly likely that there has been an improvement in DR or diabetes management, in general, over time. As discussed in **Chapter 3**, a global trend towards a lower DR progression rate was observed after the St. Vincent Declaration in 1989, which established a new standard of care for pregnant women with diabetes (see **section 2.5** in **Chapter 2**), which confirms our findings.

It is believed that pregnancy can accelerate DR development or progression.[9,123] However, almost no studies have made a side-by-side comparison between pregnant and non-pregnant cohorts to justify this statement. There are few well-known studies that have reported the DR progression rate in the general diabetic population.[74,283,284] Among these studies, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) is the only one to study a younger aged cohort comparable to our study population.[283] The WESDR demonstrated that within their group of women with type 1 diabetes (T1DM), the rate of new DR development was 62.5% within a 4-year period, which roughly equates to 7.8% over a 6-month period - similar to the rate seen in our T1DM group. However, in pre-existing DR, the rate of progression in our study (4 out of 24 eyes [16.7%] or 3 out of 12 women [25%]; data was not presented) is much higher than that in the WESDR (roughly 5.4% over 6 months). It is important to note that both studies had a slightly different approach for determining DR progression and that the interpolation to a 6-month rate from the WESDR 4-year rate is imprecise. Therefore, this comparison should be interpreted with caution. Unfortunately, there are no studies on the DR progression rate of young adults with type 2 diabetes (T2DM) with a similar methodology available for comparison. Nevertheless, our data appears to support previous opinions that more rapid progression can occur in pregnancy, especially for those who have DR before the onset of pregnancy. Therefore, special attention should be given to monitoring DR during the perinatal period in those known to already have DR.

8.2.2. Characteristics of women who are most at risk of DR progression during pregnancy (Aim 1)

Within our study population, pregnant women with T1DM were more likely to have DR or STDR compared to those with T2DM. Additionally, a higher HbA1c in early pregnancy and a longer duration of diabetes were also associated with the prevalence of DR and STDR in pregnancy, respectively. These findings are in line with those reported for the non-pregnant population.[33,285] If we refer to past reports on pregnant cohorts, these

factors were also associated with an increased risk of DR progression during pregnancy. In contrast to these findings, in our study, we did not find this correlation. From logistic regression, pre-existing DR and an elevated systolic blood pressure (SBP) in early pregnancy were the only factors that significantly increased the risk of DR progression. Our results support evidence from the most recent study in this field, the Atlantic Diabetes in Pregnancy (Atlantic DIP) study.[150] Even though the same risk factors were correlated with the increased risk of sight-threatening progression in our study, it should be noted that the group with sight-threatening progression in our cohort was not sufficiently represented due to the limited number of cases; thus, the elucidation of these results should be made cautiously.

Interestingly, although the prevalence of DR was significantly greater in T1DM women, the risk of progression during pregnancy was not significantly different between both types of diabetes. A similar relationship was also shown in our meta-analysis (**Chapter 3**) and has been observed in more current studies.[147,150] Despite this equivalent risk of progression, the management of women with T2DM appears relatively less intense than for those with T1DM, possibly due to the perception that T2DM does not result in sight-threatening disease to the same extent as T1DM, especially at a young age. This misconception is caused by the scarcity of data on DR during pregnancy in T2DM women as has been highlighted in a recent review paper.[9] Even worse, young adults with T2DM have been found to be vulnerable to low DR screening uptake due to unique clinical and psychosocial barriers compared to people with T1DM.[286] A similar trend was observed in pregnant women with T2DM[256] and our study cohort (as presented in **Chapter 7**). With more than half of diabetic pregnant women in Australia having T2DM, our findings stress the importance of ensuring this growing population receives regular eye examinations during pregnancy.

8.2.3. Assessment of retinal vascular changes in pregnancy using optical coherence tomography angiography (Aim 2)

Recently, a new retinal imaging modality, optical coherence tomography angiography (OCTA), has been introduced and its ability to evaluate retinal vasculature has been described as being equal to that of fundus fluorescence angiography (the current gold standard for assessing retinal nonperfusion) without needing an intravenous dye injection.[161,287] From our OCTA study (**Chapter 6**), it appeared that the presence of DR

could be reflected by a decrease in the pericentral vessel density (VD) value, which is in concordance with the findings from previous studies in non-pregnant populations.[168,170] Moreover, we also found that pregnancy influenced VD measurements, most likely through its effect on vascular diameter[17]; therefore, future studies of OCTA in pregnancy should consider the diameter of vessels as well as the overall length of vessels in each area of interest. No significant differences were observed in the foveal avascular zone (FAZ) area between the non-pregnant and pregnant groups.

Our results also suggest that the temporal subfield responds differently to the pregnant state than the other subfields, and that there is a possible interaction between DR status and pregnancy that may explain the pathophysiology of DR worsening in pregnancy. A trend towards higher VD in pregnancy was shown in the nasal, superior and inferior subfields, and eyes with DR exhibited greater magnitude of difference than those without. In contrast, the temporal subfield demonstrated lower VD during pregnancy and those eyes with DR had substantially lower VD compared to eyes without DR. As explained earlier, the higher VDs in the pregnant group were most likely a manifestation of increased vascular diameter. One interpretation of these findings is that increased vessel diameter is an autoregulatory mechanism which works to minimise vessel exposure to increased blood velocity, such as may occur during pregnancy or in systemic hypertension, thus potentially reducing the extent of endothelial capillary injury. The lower VD in the temporal region in eyes without DR may be an indication that this region, which is known to be particularly vulnerable to DR,[268] demonstrates a retinal vascular auto-regulatory failure. Meanwhile, the trend towards lower VD in the temporal subfield in eyes with DR may be a result of this altered autoregulation or of progressive non-perfusion or a combination of both.

These results give an indication that auto-regulatory failure may be evident at the capillary level in pregnant women with DR. This may explain why pregnant women with diabetes are at an increased risk of DR progression compared to the non-pregnant population,[18] and may provide a mechanism to explain our finding from Aim 1 (**Chapter 5**) that elevated SBP is the chief risk factor for progressive DR in pregnancy.

8.2.4. The current Australian guidelines on DR screening in pregnancy, the adherence rate and barriers to attendance (Aim 3)

Regular diabetic eye screening examinations provide an opportunity to detect DR in its early stages and identify individuals who are most at risk of developing STDR so that sight-saving treatment can be initiated before the onset of irreversible vision loss. The Australian National Health and Medical Research Council (NHMRC) guidelines recommend to "*Conduct comprehensive eye examinations on pregnant women with diabetes during the 1st trimester and follow women with DR throughout their pregnancy*".[48] In addition to this guideline, there is another guideline from the Australasian Diabetes in Pregnancy Society (ADIPS) which states that "*Formal eye review should be at least 3 monthly if baseline retinopathy is present, if there is a rapid improvement in glycaemic control, or if there has been a long duration of pre-existing diabetes*"[203] It is obvious that there is a lack of consistency between these recommendations and it appears that this leads to confusion amongst clinicians.

The outcomes pertaining to **Chapter 7** demonstrate the adherence rate to these eye screening examinations in our survey cohort, the crucial key measure for the evaluation of screening recommendations. Worryingly, more than half of our survey cohort did not attend an eye examination in the first trimester, and about 70% did not attend eye exams as frequently as that recommended by the ADIPS. Nonetheless, we also found that pregnant women with T1DM and those who had pre-existing DR were associated with better adherence. This is somewhat reassuring, given our findings from Aim 1 (Chapter 5) which showed that these women were the ones who were more likely to have DR or STDR in pregnancy and were most at risk of DR progression during pregnancy, respectively.

Thus far, only the Atlantic DIP study[150] has reported the adherence rate to the advised diabetic eye examination schedule for the pregnant population. Despite similarities in cohort characteristics, the adherence rate of our participants was lower than that reported by the Atlantic DIP study. These findings highlight the need to address barriers to eye screening adherence given the significant risk of DR progression in this unique population.

Since non-adherence to eye examination guidelines places women at risk of missing the

opportunity for timely treatment of STDR, the exploration of the barriers to attending the recommended number of eye screening exams during pregnancy is of major importance. This topic has undergone limited exploration in the past. Comparison of our results with those of previous studies that assessed the barriers to attending diabetic eye screening examinations in the non-pregnant population[36] demonstrates that pregnant women have complex issues that prevented them attending frequent eye exams as frequently as recommended. It has been shown in this study that other than negative experiences, lack of knowledge, and a perception of having reasonable diabetes control, conflicting priorities were the most significant barrier that was encountered by our survey cohort. The requirement to attend multiple health appointments during pregnancy on top of daily glucose monitoring, work, and family responsibilities have hugely impacted not only the ability, but also the motivation, to attend eye screening examinations during pregnancy.

None of the previous studies explored these barriers in the pregnant population, so in this Aim 3 (**Chapter 7**), an important contribution has been made by providing clear evidence of the gaps in the current health system regarding diabetic eye screening examinations for pregnant women with pre-existing diabetes in Australia that can be addressed to improve adherence. Moreover, the potential role of health professionals, such as endocrinologists and general practitioners, in promoting routine eye screening examinations in pregnancy has been highlighted. The involvement of other health professionals in primary health care to implement integrated eye care in the Australian health system has been proven to improve the DR screening uptake in the non-pregnant Indigenous population.[281] Unfortunately, this approach has not yet targeted antenatal care services, the primary health service for pregnant women with diabetes. In order to improve the adherence rate amongst diabetic pregnant women, more accessible and convenient eye services are required.

8.3. Strengths of This Study

8.3.1. Highly collaborative, multi-disciplinary, cross-specialty research team

One of the major strengths of this study is the extensive collaboration between health professionals from multiple different sub-specialties who contributed their unique expertise in the development of this research plan and also in the conduct of the study. Our study took into account every relevant medical perspective from different specialties.

Our collaborative team included ophthalmologists, optometrists, obstetricians, and endocrinologists. The involvement of endocrinologists and obstetricians, specifically, have contributed to the patients' trust and interest in our study. The study coordinator (FW) also received extensive support from diabetes educators and hospital staff who gave further insights into "being a pregnant woman with diabetes" since these health professionals communicate regularly with this group of patients. Their input helped the development of this study's Aim 3.

8.3.2. Robust study design

In regard to the study protocol, during this study, we established a referral pathway, which was previously lacking, as well as a patient booking and reminder system that has helped both clinicians and patients in getting eye screening examinations scheduled and attended. Firstly, we developed and implemented a clear referral pathway from Royal Women's Hospital (RWH) for both DR screening examinations by Melbourne Eyecare Clinic and treatment of any sight-threatening disease that was detected at the Royal Melbourne Hospital (RMH). Secondly, we developed a referral pathway from Mercy Hospital for Women (MHW) to the Repatriation Hospital for DR screening examinations and treatment. A similar retinal screening program has been implemented in the UK for the diabetic pregnant population.[204]

Moreover, this study is superior to previous studies because we also estimated the prevalence and incidence rate of DMO during pregnancy, a crucial condition in DR that has been understudied in pregnant women, aside from the prevalence of DR and STDR. Additionally, all earlier studies in this area diagnosed DMO based on fundus photographs[13,110,113] whilst our study used optical coherence tomography (OCT), the current standard of care that is more sensitive for diagnosing DMO. Surprisingly, we found that sight-threatening progression that occurred in pregnancy was more commonly due to the development of DMO than PDR. Although similar observations were reported by several studies,[13,110,150,245] none highlighted the importance of monitoring the occurrence of DMO during pregnancy.

8.3.3. Statistical analysis and data presentation

In comparison to past studies, this current study has a number of strengths in its statistical analysis and data presentation. Firstly, most previous studies primarily aimed to

determine progression rate rather than prevalence; thus, their DR prevalence was only an estimation from the baseline or booking visit (which was either before or in early pregnancy) rather than during the entire pregnancy. Furthermore, a proportion of women with less than two eye exams during pregnancy (the required number to assess DR progression) were excluded. Consequently, women with no DR or with T2DM who were more likely to have only one exam were probably underrepresented in their estimations. This current study presented the prevalence of DR for the entire study period which includes during pregnancy and up to 3-months after delivery, potentially providing a more accurate representation of the overall burden of DR within this specific population. More importantly, although some women were excluded in the progression analysis due to insufficient eye data, we included these women in the prevalence calculation; therefore, our results are less likely to be affected by sample selection bias.

Secondly, we employed regression analysis to determine the risk factors that were associated with the risk of DR progression and calculated the Mantel-Haenszel stratified risk ratios to adjust for variables of interest, an approach that was rarely seen in earlier studies on this topic. We found that pre-existing DR and a higher SBP in early pregnancy significantly increased the risk of DR progression even after adjusting for type of diabetes, duration of diabetes, and the presence of any DR in early pregnancy (for the SBP variable).

Lastly, since our cohort consisted of women with T1DM and T2DM, it cannot be denied that the type of diabetes would confound the assessment of diabetes duration as a risk factor for DR progression. In fact, in our data, duration of diabetes was clearly different between both diabetes types (**Figure 8-1**). Therefore, in this study, associations with duration of diabetes were also analysed based on the median duration of each diabetes type. With this approach, the interaction between the type and duration of diabetes could be adjusted for to elucidate relationships. We found that T1DM was associated with the presence of DR and STDR, but a longer duration of diabetes was only related to the presence of STDR.

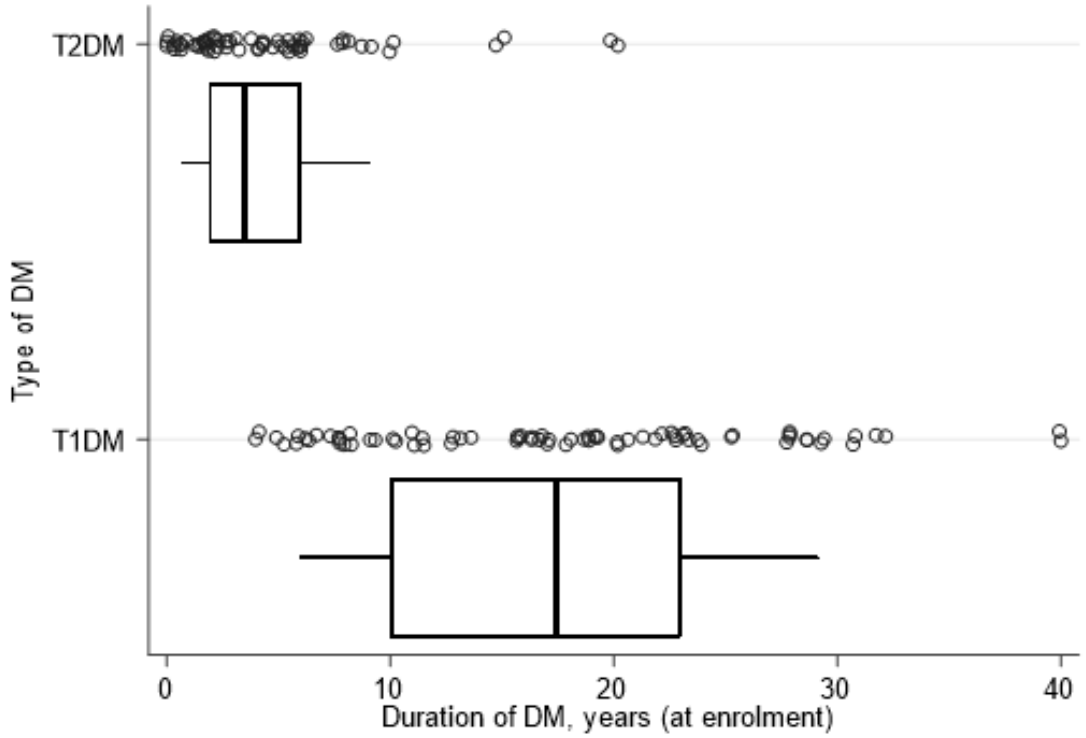


Figure 8-1. Relationships between the type and duration of diabetes in this study cohort

Figures included eyes with sufficient data for progression analysis only. Abbreviations: DM, diabetes mellitus; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

8.3.4. Utilisation of novel imaging modalities in a unique patient population

To the best of our knowledge, this study is the pioneer study to evaluate OCTA findings in diabetic pregnant women and correlate them with DR status. To date, only two OCTA studies have been conducted in the diabetic pregnant population. The first is a prospective, cross-sectional study by Sugimoto *et al.* which compared the size of the FAZ area between healthy non-pregnant women, pregnant women with gestational diabetes and pre-existing diabetes without DR and found no significant difference in the FAZ area between these three groups.[179] Meanwhile, the second paper is a case-report by Akushichi and colleagues that observed a pregnant woman with T2DM during the perinatal period who experienced significant DR progression after delivery.[270] Using OCTA, the authors could identify capillary-level changes in the retina of this woman over time.

Our current study explored the retinal vascular changes that may be caused by pregnancy and DR. As mentioned above, our results suggest that these changes could be identified in our OCTA data. Combining our findings with the key literature in this topic,[17,18] we

found the possible explanation for how pregnancy may worsen DR, the pathogenesis for which has been under debate. The findings from our OCTA investigation support the concept that the hyperdynamic state during pregnancy may play a role in DR progression.

8.3.5. Identification of significant barriers to adherence to the recommended eye screening guidelines

To our knowledge, our survey study from Aim 3 is the first to report the adherence rates and potential barriers to adherence to the Australian recommended eye screening guidelines in pregnancy. Many studies have investigated the barriers to attendance at diabetic eye screening programs in the non-pregnant population.[36,199,279,280] However, none were conducted to specifically explore the barriers in the pregnant population. This current study offers additional insights into this topic by conducting both quantitative and qualitative research. Our findings demonstrate clear gaps in the current eye health system regarding DR management for Australian pregnant women with pre-existing diabetes which then affect the adherence rate to eye screening recommendations. We identified significant barriers that can be addressed to improve future guidelines.

8.4. Limitations of This Study

8.4.1. Challenges in patient recruitment, high attrition rate and incomplete postpartum follow-up due to COVID-19

Significant barriers were encountered during patient recruitment at the start of the study which was then followed by a high attrition rate. The prevalence of DR in pregnancy in the Atlantic Diabetes in Pregnancy study[150] and the reported odds ratio of DR progression during pregnancy by the DCCT study[105] were used to calculate the minimum sample size and it was determined that at least 120 women should be examined to achieve statistical power. Originally, we planned to only recruit patients from the RWH and perform eye examinations at Melbourne Eyecare Clinic. However, due to the low participation rate in the first year of recruitment, additional study sites were arranged to include the MHW as another recruitment site and the Repatriation Hospital as the corresponding eye clinic for MHW's patients. Furthermore, the recruitment process was also improved. Active involvement of the diabetes antenatal clinic's physicians played an important role in

increasing the participation rate. They endorsed our study to patients when discussing the need for eye-checks during pregnancy and introduced the study coordinator (FW) to patients in the clinic. This approach successfully developed rapport and gained the patients' trust compared to the previous recruitment method where patients were directly approached in the waiting room. Other than that, travel assistance to the eye clinic (a ride share service from the RWH to Melbourne Eyecare Clinic or parking fee reimbursement for each visit to the Repatriation Hospital) was provided. We also introduced options for patients to either participate fully in the study or to have eye examinations at their preferred local clinic and then share their medical and eye data with our study (shared care participants), as described in detail in **Chapter 4**. These methods increased the participation rate from 25% in the first year to 80% in the last year of recruitment.

Despite these improvements, a higher-than-expected attrition rate of study participants was encountered (approximately 45% vs the initial estimation of 10%) due to the multiple barriers that have been presented in **Chapter 7**. Only around 88% of our participants had at least one eye exam during pregnancy, and just under half had at least two eye examinations available for assessing DR change. Although sufficient statistical power was still achieved to detect the prevalence of DR, the certainty surrounding the estimates of DR progression rate was affected. To mitigate this, our rates were calculated as rates per eye rather than rates per woman to improve precision. Nevertheless, our main reported rates (the prevalence of DR and rate of any progression per eye) were quite similar to those per woman (as presented in **Chapter 5**). Additionally, due to the small number of sight-threatening progression cases, it was a challenge to perform multivariate logistic regression to determine any associations with the risk factors of interest. Therefore, we only presented the crude risk ratio for the risk factors related to sight-threatening progression.

A similar issue with attrition was met in the postpartum follow-up and was also significantly impacted by Government-mandated restrictions in response to the COVID-19 pandemic throughout 2020. Only 31 women attended follow-up exams after delivery and only nine of them had DR progression during pregnancy. Consequently, we could only descriptively present these cases.

8.4.2. Variations in data collection methodology

Due to the limited study period and the long follow-up time, we included pregnant women at any stage of their pregnancy to recruit as many women as possible. Consequently, there was variation in the timing of the baseline visit amongst our participants. Approximately 45% of our participants had a baseline eye-visit in the first trimester whilst the remaining participants had baseline visits later on in their pregnancy. Moreover, due to challenges that were encountered by our participants in their pregnancy (for instance, failure to attend a scheduled eye exam due to an unexpected, prolonged visits at the maternity hospital for additional BP monitoring), not all participants could follow the eye examination schedule (which was 3-monthly). As a result, the interval between eye-visits varied and participants did not necessarily have one eye exam in each trimester. This limitation particularly affected the OCTA study where data was collected only from Melbourne Eyecare Clinic, with a consequent further limitation of sample size, and contributed to the inability to address Aim 2.3: assessing predictors of DR progression using OCTA parameters.

Limitations in the clinical data collection methodology were also present. As mentioned previously, we introduced an option for women to be shared care participants. In this group of women, eye examinations were performed at their local clinics (either by optometrists or ophthalmologists) and with the patient's consent, we then collected their eye data from these clinics. Unfortunately, not all clinics took fundus photography in evaluating their patient's DR status. Consequently, the DR status of this portion of women was determined from the clinical DR grading rather than our independent grader. There were 72 out of 542 (13.3%) available eye-visits that had no fundus photography. This risk of bias was unfortunately unavoidable.

Additionally, pathology tests, which include HbA1c data, were ordered by their physicians as per routine care and were collected from patients' records for this study (tests were not independently organised by the study coordinator). Therefore, there was variation in the availability of HbA1c data and, unfortunately, the number of women with sufficient HbA1c data (defined as having HbA1c data in pre-pregnancy, early, and late pregnancy) was lower than we expected. The lack of available data in the pre-pregnancy period was mainly due to low attendance at pre-pregnancy care clinics (only around 50% of participants attended pre-pregnancy care, as shown in Chapter 7). Moreover, during the conduct of this study, a new program that subsidised the use of continuous glucose

monitoring (CGM) for women with T1DM who were pregnant or planned to become pregnant was introduced, which resulted in more women with T1DM switching to CGM. Although HbA1c values have been used to assess patients' glycaemic control and predict the development of diabetes-related complications, it only measures the mean blood glucose level over 2-3 months and cannot capture glycaemic variability over this period, which may contribute to adverse microvascular outcomes.[288] Meanwhile, the new technology, CGM, provides more information on patient's' glycaemic levels over time and its parameters (such as time in range [TIR], time above range, and average glucose levels) are reported to be associated with both HbA1c levels,[289-291] and the incidence of diabetes complications (including DR[292,293]). Due to these reasons, there has been a transition in how physicians assess patient's diabetes control. This was particularly the case in one of the two study hospitals, where patients' glycaemic control was then mainly assessed from CGM parameters instead of HbA1c values. For women from this hospital whose CGM reports provided estimated HbA1c values, these HbA1c data was recorded (n= 3, 50%). Unfortunately, not all CGM devices had this feature and as a result, HbA1c data was not available for some women. Although there have been studies that tried to translate TIR values to HbA1c levels, no agreement has been reached.[291]

8.4.3. Nature of the main study as a clinical trial

Before the conduct of this study, no formal screening program existed for pregnant women with pre-existing diabetes despite the geographical proximity between the maternity hospitals and the eye clinics. Even after the establishment of a referral pathway that was developed early in this study, logistical challenges halted participation of our patients. Therefore, we developed a protocol that accommodated our participants to make the eye examinations more convenient, such as a free service, flexible appointment times, and travel assistance to attend the eye clinic. Due to these reasons, there is a possibility that our results are not truly or wholly reflective of the actual condition in the population. For example, participation in this clinical trial may have affected their behaviour and responses to the survey questions in our Aim 3. Our findings, hence, might overestimate adherence rates to the recommended eye screening guidelines.

8.5. Future Directions and Recommendations

8.5.1. Future Directions

We have demonstrated that pregnancy increased the risk of DR progression in Australian pregnant women with pre-existing diabetes and that sight-threatening progression was also observed in the early postpartum. It has been reported that the risk of DR progression persists until a year after delivery.[105] These findings seemingly contradict the information that has been given to patients which states that DR is expected to regress after delivery.[294,295] Future studies that observe DR in the postpartum period will be beneficial to better understand the extent of problems after delivery, in particular to determine the risk of progression and whether a "wait and see" approach is appropriate when potentially sight threatening DR is encountered, as opposed to commencing immediate treatment prior to delivery. Such evidence from the postpartum period will be also crucial to inform clinicians and patients about the importance of continuing to monitor DR after delivery.

Moreover, with the increasing use of CGM, especially in pregnant women with pre-existing diabetes in Australia, further studies that explore the potential associations between various CGM parameters and their effect on DR in pregnancy will be valuable and may suggest new parameters that can be used to predict DR progression.

Learning from our findings regarding the barriers to attending diabetic eye screening examinations in this growing population, further studies that assess a new model of care that integrates eye care into the antenatal care clinic will investigate whether an integrated care model can improve patient adherence. The antenatal care clinic is the clinic which these patients are most likely to attend. We also encourage future investigators to conduct similar research in rural areas for comparison. Further studies that include or exclusively study Indigenous Australians will be of interest, particularly due to the fact that Indigenous people have more severe diabetes and poorer pregnancy outcomes than non-Indigenous people,[249,296] and also have limited access to eye health care.[297] It is possible for this particular study to be conducted in the near future, especially in light of the NEHS - a nationwide population-based study which included Indigenous participants - that has established strong community engagement amongst the Indigenous community and has the potential to be re-conducted. Research that assesses the DR progression risk in Indigenous pregnant women with diabetes will be beneficial since these women are most

at risk.

Lastly, further studies are required to examine the predictive value of retinal non-perfusion and changes in the vascular diameter, as assessed by OCTA, and to explore the OCTA parameters in the deep capillary plexus (DCP). Prior studies have shown that pregnancy-related and DR-related changes are more evident in the DCP than superficial capillary plexus.[172,173,267] These may become important biomarkers for DR progression once high-quality OCTA becomes more widely available.

8.5.2. Implications for practice and recommendations

This PhD study has provided updated data pertaining to the burden of DR in pregnancy and evidence of insufficient uptake of eye health care services amongst pregnant women with pre-existing diabetes who have a higher risk of developing DR progression compared to similarly aged non-pregnant diabetic women. As discussed in previous chapters, there is inconsistency between guidelines regarding frequency of DR screening examinations in pregnancy across the globe, even within Australia. Inconsistencies in the literature and lack of local data have made it difficult to generate suitable local guidelines for the Australian diabetic pregnant population. More importantly, current guidelines' recommendations for screening of pregnant women with diabetes fail to distinguish between T1DM and T2DM. The lack of uptake of eye screening examinations amongst T2DM patients may reflect a perceived "minimal risk" on behalf of the patient and health care provider with more focus being placed on those patients with T1DM, a misconception that needs to be addressed sooner rather than later.

The current NHMRC guidelines recommend a less-specific eye screening exam schedule for pregnant women with pre-existing diabetes which was adopted from the American Diabetes Association (ADA) guidelines.[298] The NHMRC evidence level for this recommendation is IV (based on case-series or expert consensus), which is the lowest of the evidence levels. Surprisingly, the ADA guidelines were updated in 2019 and now state that "*Dilated eye examinations should occur ideally before pregnancy or in the first trimester, and then patients should be monitored every trimester and for 1-year postpartum as indicated by the degree of retinopathy and as recommended by the eye care provider*".[190] Despite this, there has been no update to the NHMRC guidelines since it was published in 2008. In comparison, the ADIPS guidelines, upon which this study

protocol was based upon, was published in 2005 and had the recommendation for diabetic eye screening exams in pregnancy with a level of evidence equivalent to level II (based on at least one well-designed RCT). Despite this higher level of evidence, the ADIPS guidelines have just recently been updated in 2020 and recommend that retinal screening should be performed in the "… *first trimester (unless performed within 3 months prior to conception) and consider repeating in third trimester if no evidence of diabetic retinopathy on initial screen, or earlier if baseline retinopathy is detected as directed by ophthalmologist*".[189] Unfortunately, ADIPS guidelines are generally known only to obstetricians and endocrinologists, who specialise in pregnancy with diabetes, and not to eye care providers. This shows that there is an urgent need to update our national guidelines, especially since this PhD study has provided the most current local evidence that can be used to develop better Australian DR guidelines for this unique and growing group of women.

Based upon our findings and reflecting on the most current ADIPS guidelines, we recommend that eye screening examinations for pregnant women with pre-existing diabetes should be scheduled as follow (**Figure 8-2**):

1. An eye exam in the first trimester or as soon as pregnancy is recognised is mandatory (unless performed within 3 months prior to conception).
2. If from this exam, no DR is observed then for women with T1DM, one additional exam during pregnancy is advised. However, for those with T2DM, no further exams are required during pregnancy.
3. If any DR is observed in the first exam, one exam in each trimester is recommended or more frequently as indicated by the clinicians, irrespective of the type of diabetes.
4. After delivery, an additional exam within 12 months is advised for both types of diabetes.

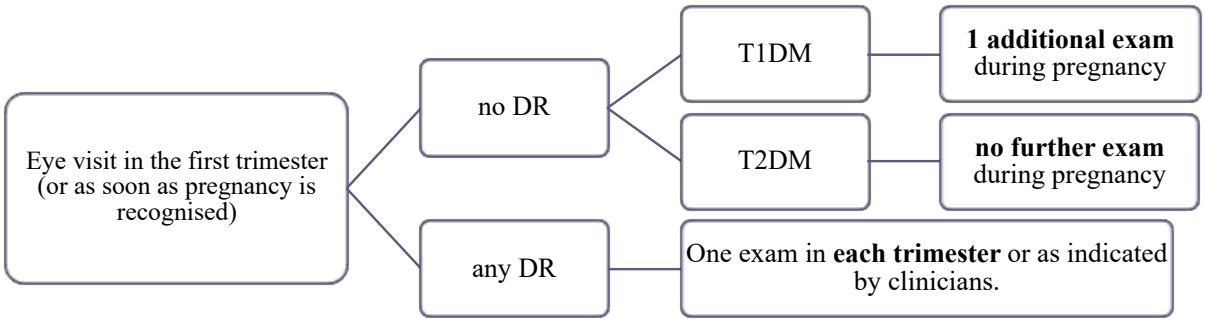


Figure 8-2. Recommended eye screening examinations for pregnant women with pre-existing diabetes

However, as has been noted, adherence to more frequent eye examinations would not be achieved without changes to the current model of care due to the barriers that are encountered by this cohort. This is compounded by the fact that the Australian public health system does not have a sustainable and effective DR screening strategy. Integrating eye screening examinations into antenatal care programs may become a potential solution since it has been suggested that a "one-stop-shop" health service may improve attendance to eye screening examinations, by ensuring more convenient access for pregnant women.[204] Moreover, by providing integrated eye care, there is an opportunity to also improve the patient screening uptake in the first trimester of pregnancy as recommended by the majority of available guidelines.

Our findings also have shown that glycaemic and blood pressure optimisation in early pregnancy or before conception is associated with a decreased risk of DR progression in pregnancy. Therefore, as has been suggested, pre-pregnancy care has an important role in ensuring diabetic women have reasonable diabetes and blood pressure control before they fall pregnant and educating them on the importance of routine eye screening exams to prevent sight-threatening disease. Although further studies are required to assess its broader applicability to clinical practice, OCTA shows promise in predicting DR progression in pregnant patients non-invasively in research settings.

8.6. Conclusions

This PhD study has succeeded in filling some notable gaps in the literature regarding DR in pregnant women with pre-existing diabetes. The first aim of this study has contributed contemporary evidence on the burden of DR and its progression during pregnancy and

has identified characteristics of women who are most at risk of progressive DR. Our second aim has illustrated a potential explanation of how pregnancy induces DR progression and has demonstrated the potential role of OCTA in evaluating DR in pregnancy. Lastly, the third aim of this study has provided data on the adherence rate to the current Australian DR management guidelines in pregnancy and has presented the significant barriers to adherence specifically in the pregnant diabetic population that can and should be considered in the development of future sustainable DR screening programs. Taken together, the overall findings from this PhD will be beneficial to the future development of up-to-date, evidence-based guidelines for the management of DR in pregnant women with pre-existing diabetes to prevent vision loss in this growing demographic in Australia.

REFERENCES

1. Australian Bureau of Statistics (ABS). National Health Survey: First Results, 2017-18 [Internet] ABS Cat. No. 4364.0.55.001. Canberra: ABS; 2018 [cited 2019 Sept 19]. Available from: https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.001~2017-18~Main%20Features~Diabetes%20mellitus~50.
2. International Diabetes Federation. IDF Diabetes Atlas. 9th edn. Brussels (Belgium); 2019. Available from: http://www.diabetesatlas.org.
3. Gabbe SG. Pregnancy in women with diabetes mellitus. The beginning. Clin Perinatol. 1993;20(3):507-15.
4. Dunne FP, Avalos G, Durkan M, Mitchell Y, Gallacher T, Keenan M, et al. ATLANTIC DIP: pregnancy outcome for women with pregestational diabetes along the Irish Atlantic seaboard. Diabetes Care. 2009;32(7):1205-6. doi: 10.2337/dc09-1118.
5. Alexopoulos AS, Blair R, Peters AL. Management of preexisting diabetes in pregnancy: a review. JAMA. 2019;321(18):1811-9. doi: 10.1001/jama.2019.4981.
6. Diabetes Care and Research in Europe: The Saint Vincent Declaration. Diabet Med. 1990;7:360. doi: 10.1111/j.1464-5491.1990.tb01405.x.
7. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S13-S27. doi: 10.2337/dc18-S002.
8. Australian Institute of Health and Welfare. Australia's mothers and babies 2015-in brief. Canberra (ACT): AIHW; 2015.
9. Morrison JL, Hodgson LA, Lim LL, Al-Qureshi S. Diabetic retinopathy in pregnancy: a review. Clin Exp Ophthalmol. 2016;44(4):321-34. doi: 10.1111/ceo.12760.
10. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. Diabetes Care. 2008;31(5):899-904. doi: 10.2337/dc07-2345.
11. Klein BE. Overview of epidemiologic studies of diabetic retinopathy. Ophthalmic Epidemiol. 2007;14(4):179-83. doi: 10.1080/09286580701396720.
12. Loukovaara S, Immonen IR, Loukovaara MJ, Koistinen R, Kaaja RJ. Glycodelin: a novel serum anti-inflammatory marker in type 1 diabetic retinopathy during pregnancy. Acta Ophthalmol Scand. 2007;85(1):46-9. doi: 10.1111/j.1600-0420.2006.00766.x.
13. Rasmussen KL, Laugesen CS, Ringholm L, Vestgaard M, Damm P, Mathiesen ER. Progression of diabetic retinopathy during pregnancy in women with type 2 diabetes. Diabetologia. 2010;53(6):1076-83. doi: 10.1007/s00125-010-1697-9.
14. Vijan S, Hofer TP, Hayward RA. Cost-utility analysis of screening intervals for diabetic retinopathy in patients with type 2 diabetes mellitus. JAMA. 2000;283(7):889-96. doi: 10.1001/jama.283.7.889.
15. DCCT/ EDIC Research Group. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med. 2017;376(16):1507-16. doi: 10.1056/NEJMoa1612836.
16. Jenkins AJ, Joglekar MV, Hardikar AA, Keech AC, O'Neal DN, Januszewski AS. Biomarkers in diabetic retinopathy. Rev Diabet Stud. 2015;12(1-2):159-95. doi: 10.1900/RDS.2015.12.159.
17. Chen HC, Newsom RS, Patel V, Cassar J, Mather H, Kohner EM. Retinal blood flow changes during pregnancy in women with diabetes. Invest Ophthalmol Vis Sci. 1994;35(8):3199-208.

18. Loukovaara S, Kaaja R, Immonen I. Macular capillary blood flow velocity by blue-field entoptoscopy in diabetic and healthy women during pregnancy and the postpartum period. Graefes Arch Clin Exp Ophthalmol. 2002;240(12):977-82. doi: 10.1007/s00417-002-0590-8.
19. The National Diabetes Strategy Advisory Group. Australian National Diabetes Strategy 2016-2020 [E-book]. Canberra: Commonwealth of Australia; 2015. Available from: https://www.health.gov.au/resources/publications/australian-national-diabetes-strategy-2016-2020
20. Australian Institute of Health and Welfare. Improving national reporting on diabetes in pregnancy: technical report. Canberra (ACT): AIHW; 2019.
21. HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Int J Gynaecol Obstet. 2002;78(1):69-77. doi: 10.1016/s0020-7292(02)00092-9.
22. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991-2002. doi: 10.1056/NEJMoa0707943.
23. International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676-82. doi: 10.2337/dc09-1848.
24. Nankervis A, McIntyre H, Moses R, Ross G, Callaway L, Porter C, et al. ADIPS consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand. Australia: the Australasian Diabetes in Pregnancy Society; 2014.
25. Australian Institute of Health and Welfare. Incidence of gestational diabetes in Australia [Internet]. Canberra: AIHW; 2019 [updated 2019 Sep 4; cited 2020 Apr 4]. Available from: https://www.aihw.gov.au/reports/diabetes/incidence-of-gestational-diabetes-in-australia
26. Evers IM, de Valk HW, Visser GH. Risk of complications of pregnancy in women with type 1 diabetes: nationwide prospective study in the Netherlands. BMJ. 2004;328(7445):915. doi: 10.1136/bmj.38043.583160.EE.
27. Kitzmiller JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. Diabetes Care. 2008;31(5):1060-79. doi: 10.2337/dc08-9020.
28. Flaxel CJ, Adelman RA, Bailey ST, Fawzi A, Lim JI, Vemulakonda GA, et al. Diabetic retinopathy preferred practice pattern®. Ophthalmology. 2020;127(1):P66-P145. doi: 10.1016/j.ophtha.2019.09.025.
29. Shand AW, Bell JC, McElduff A, Morris J, Roberts CL. Outcomes of pregnancies in women with pre-gestational diabetes mellitus and gestational diabetes mellitus; a population-based study in New South Wales, Australia, 1998-2002. Diabet Med. 2008;25(6):708-15. doi: 10.1111/j.1464-5491.2008.02431.x.
30. McElduff A, Ross GP, Lagstrom JA, Champion B, Flack JR, Lau SM, et al. Pregestational diabetes and pregnancy: an Australian experience. Diabetes Care. 2005;28(5):1260-1. doi: 10.2337/diacare.28.5.1260.
31. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract. 2014;103(3):341-63. doi: 10.1016/j.diabres.2013.10.012.

32. Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. Surv Ophthalmol. 2012;57(4):347-70. doi: 10.1016/j.survophthal.2012.01.004.
33. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care. 2012;35(3):556-64. doi: 10.2337/dc11-1909.
34. Thomas RL, Dunstan FD, Luzio SD, Chowdhury SR, North RV, Hale SL, et al. Prevalence of diabetic retinopathy within a national diabetic retinopathy screening service. Br J Ophthalmol. 2015;99(1):64-8. doi: 10.1136/bjophthalmol-2013-304017. 35. Burgess PI, MacCormick IJC, Harding SP, Bastawrous A, Beare NAV, Garner P. Epidemiology of diabetic retinopathy and maculopathy in Africa: a systematic review. Diabet Med. 2013;30(4):399-412. doi: 10.1111/j.1464-5491.2012.03756.x.
36. Graham-Rowe E, Lorencatto F, Lawrenson JG, Burr JM, Grimshaw JM, Ivers NM, et al. Barriers to and enablers of diabetic retinopathy screening attendance: a systematic review of published and grey literature. Diabet Med. 2018;35(10):1308-19. doi: 10.1111/dme.13686.
37. Ola MS, Nawaz MI, Khan HA, Alhomida AS. Neurodegeneration and neuroprotection in diabetic retinopathy. Int J Mol Sci. 2013;14(2):2559-72. doi: 10.3390/ijms14022559.
38. Tang J, Kern TS. Inflammation in diabetic retinopathy. Prog Retin Eye Res. 2011;30(5):343-58. doi: 10.1016/j.preteyeres.2011.05.002.
39. Cai J, Boulton M. The pathogenesis of diabetic retinopathy: old concepts and new questions. Eye (Lond). 2002;16(3):242-60. doi: 10.1038/sj.eye.6700133.
40. American Academy of Ophthalmology. Retina and vitreous. Basic and clinical science course. San Francisco, CA: American Academy of Ophthalmology; 2011.
41. Hendrick AM, Gibson MV, Kulshreshtha A. Diabetic Retinopathy. Prim Care. 2015;42(3):451-64. doi: 10.1016/j.pop.2015.05.005.
42. Baumal CR, Duker JS. Current management of diabetic retinopathy. USA: Elsevier Inc.; 2018.
43. Zhang K, Ferreyra HA, Grob S, Bedell M, Zhang JJ. Diabetic retinopathy: genetics and etiologic mechanisms. In: Ryan SJ, Sadda SR, Hinton DR, Schachat AP, Sadda SR, Wilkinson CP, et al., editors. Retina. 5th ed. London: W.B. Saunders; 2013. p. 925-39.
44. Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, Fong DS, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology. 2007;114(3):525-36. doi: 10.1016/j.ophtha.2006.06.052.
45. Ou WC, Brown DM, Payne JF, Wykoff CC. Relationship between visual acuity and retinal thickness during anti-vascular endothelial growth factor therapy for retinal diseases. Am J Ophthalmol. 2017;180:8-17. doi: 10.1016/j.ajo.2017.05.014.
46. Sun JK, Radwan SH, Soliman AZ, Lammer J, Lin MM, Prager SG, et al. Neural retinal disorganization as a robust marker of visual acuity in current and resolved diabetic macular edema. Diabetes. 2015;64(7):2560-70. doi: 10.2337/db14-0782.
47. Joltikov KA, Sesi CA, de Castro VM, Davila JR, Anand R, Khan SM, et al. Disorganization of Retinal Inner Layers (DRIL) and neuroretinal dysfunction in early diabetic retinopathy. Invest Ophthalmol Vis Sci. 2018;59(13):5481-6. doi: 10.1167/iovs.18-24955.
48. Mitchell P, Australian Diabetes Society, National Health and Medical Research Council (Australia). Guidelines for the Management of Diabetic Retinopathy. Canberra: National Health and Medical Research Council; 2008.

49. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):786-806.
50. Moss SE, Meuer SM, Klein R, Hubbard LD, Brothers RJ, Klein BE. Are seven standard photographic fields necessary for classification of diabetic retinopathy? Invest Ophthalmol Vis Sci. 1989;30(5):823-8.
51. Hirano T, Imai A, Kasamatsu H, Kakihara S, Toriyama Y, Murata T. Assessment of diabetic retinopathy using two ultra-wide-field fundus imaging systems, the Clarus® and Optos™ systems. BMC Ophthalmol. 2018;18(1).
52. Olvera-Barrios A, Heeren TF, Balaskas K, Chambers R, Bolter L, Tufail A, Egan C, Anderson J. Comparison of true-colour wide-field confocal scanner imaging with standard fundus photography for diabetic retinopathy screening. Br J Ophthalmol. 2020 Nov;104(11):1579-84. doi: 10.1136/bjophthalmol-2019-315269.
53. Silva PS, Cavallerano JD, Haddad NM, Tolls D, Thakore K, Patel B, Sehizadeh M, Tolson AM, Sun JK, Aiello LP. Comparison of Nondiabetic Retinal Findings Identified With Nonmydriatic Fundus Photography vs Ultrawide Field Imaging in an Ocular Telehealth Program. JAMA Ophthalmol. 2016 Mar;134(3):330-4. doi: 10.1001/jamaophthalmol.2015.5605.
54. Silva PS, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. Ophthalmology. 2013 Dec;120(12):2587-95. doi: 10.1016/j.ophtha.2013.05.004.
55. Aiello LP, Odia I, Glassman AR, Melia M, Jampol LM, Bressler NM, Kiss S, Silva PS, Wykoff CC, Sun JK; Diabetic Retinopathy Clinical Research Network. Comparison of Early Treatment Diabetic Retinopathy Study Standard 7-Field Imaging With Ultrawide-Field Imaging for Determining Severity of Diabetic Retinopathy. JAMA Ophthalmol. 2019 Jan 1;137(1):65-73. doi: 10.1001/jamaophthalmol.2018.4982.
56. Kernt M, Hadi I, Pinter F, Seidensticker F, Hirneiss C, Haritoglou C, Kampik A, Ulbig MW, Neubauer AS. Assessment of diabetic retinopathy using nonmydriatic ultra-widefield scanning laser ophthalmoscopy (Optomap) compared with ETDRS 7-field stereo photography. Diabetes Care. 2012 Dec;35(12):2459-63. doi: 10.2337/dc12-0346.
57. Ashraf M, Shokrollahi S, Salongcay RP, Aiello LP, Silva PS. Diabetic retinopathy and ultrawide field imaging. Semin Ophthalmol. 2020 Jan 2;35(1):56-65. doi: 10.1080/08820538.2020.1729818.
58. Silva PS, Cavallerano JD, Haddad NM, Kwak H, Dyer KH, Omar AF, Shikari H, Aiello LM, Sun JK, Aiello LP. Peripheral Lesions Identified on Ultrawide Field Imaging Predict Increased Risk of Diabetic Retinopathy Progression over 4 Years. Ophthalmology. 2015 May;122(5):949-56. doi: 10.1016/j.ophtha.2015.01.008.
59. Early Treatment Diabetic Retinopathy Study Research Group. Classification of diabetic retinopathy from fluorescein angiograms. ETDRS Report Number 11. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98:807-22.
60. Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB, et al. Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. Ophthalmology. 1991;98(7):1139-42. doi: 10.1016/s0161-6420(91)32165-1.
61. Klein R, Klein BE, Magli YL, Brothers RJ, Meuer SM, Moss SE, et al. An alternative method of grading diabetic retinopathy. Ophthalmology. 1986;93(9):1183-7. doi: 10.1016/s0161-6420(86)33606-6.

62. Wilkinson CP, Ferris FL, 3rd, Klein RE, Lee PP, Agardh CD, Davis M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677-82. doi: 10.1016/S0161-6420(03)00475-5.
63. Fred Hollows Foundation New Zealand. Diabetes retinal screening, grading and management guidelines for use in Pasific Island Nations. Auckland; 2010.
64. Malaysia Ministry of Health. Clinical practice guidelines: screening of diabetic retinopathy. Putrajaya, Malaysia: Ministry of Health; 2011.
65. Haneda S, Yamashita H. [International clinical diabetic retinopathy disease severity scale]. Nihon Rinsho. 2010;68 Suppl 9:228-35. Japanese.
66. Lopez Galvez MI. Escala internacional de severidad de la retinopatía y del edema macular diabético [International severity scale of diabetic retinopathy and diabetic macular edema]. Arch Soc Esp Oftalmol. 2004;79(4):149-50. Spanish. doi: 10.4321/s0365-66912004000400001.
67. Ruia S, Saxena S, Gemmy Cheung CM, Gilhotra JS, Lai TY. Spectral domain optical coherence tomography features and classification systems for diabetic macular edema: a review. Asia Pac J Ophthalmol (Phila). 2016;5(5):360-7. doi: 10.1097/APO.0000000000000218.
68. Chalam KV, Bressler SB, Edwards AR, Berger BB, Bressler NM, Glassman AR, et al. Retinal thickness in people with diabetes and minimal or no diabetic retinopathy: Heidelberg Spectralis optical coherence tomography. Invest Ophthalmol Vis Sci. 2012;53(13):8154-61. doi: 10.1167/iovs.12-10290.
69. Panozzo G, Parolini B, Gusson E, Mercanti A, Pinackatt S, Bertoldo G, et al. Diabetic macular edema: an OCT-based classification. Semin Ophthalmol. 2004;19(1-2):13-20. doi: 10.1080/08820530490519934.
70. Diabetes Control Complications Trial Research Group, Nathan DM, Genuth S, Lachin J, Cleary P, Crofford O, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-86. doi: 10.1056/NEJM199309303291401.
71. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352(9131):837-53.
72. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XV. The long-term incidence of macular edema. Ophthalmology. 1995;102(1):7-16. doi: 10.1016/s0161-6420(95)31052-4.
73. The ACCORDION Eye Study Group and ACCORDION Study Group. Persistent effects of intensive glycemic control on retinopathy in type 2 diabetes in the Action To Control Cardiovascular Risk in Diabetes (ACCORD) follow-on study. Diabetes Care. 2016;39(7):1089-100. doi: 10.2337/dc16-0024.
74. The Diabetes Control Complications Trial Research Group. Early worsening of diabetic retinopathy in the Diabetes Control and Complications Trial. Arch Ophthalmol. 1998;116(7):874-86. doi: 10.1001/archopht.116.7.874.
75. Feldman-Billard S, Larger E, Massin P; Standards for screening and surveillance of ocular complications in people with diabetes SFD study group. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. Diabetes Metab. 2018;44(1):4-14. doi: 10.1016/j.diabet.2017.10.014.
76. Lim SW, van Wijngaarden P, Harper CA, Al-Qureshi SH. Early worsening of diabetic retinopathy due to intensive glycaemic control. Clin Exp Ophthalmol. 2019;47(2):265-73. doi: 10.1111/ceo.13393.

77. Suzuma I, Hata Y, Clermont A, Pokras F, Rook SL, Suzuma K, et al. Cyclic stretch and hypertension induce retinal expression of vascular endothelial growth factor and vascular endothelial growth factor receptor-2: potential mechanisms for exacerbation of diabetic retinopathy by hypertension. Diabetes. 2001;50(2):444-54. doi: 10.2337/diabetes.50.2.444.
78. Klein R, Klein BE. Blood pressure control and diabetic retinopathy. Br J Ophthalmol. 2002;86(4):365-7. doi: 10.1136/bjo.86.4.365.
79. Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM; UK Prospective Diabetes Study Group. Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. Arch Ophthalmol. 2004;122(11):1631-40. doi: 10.1001/archopht.122.11.1631.
80. Klein BE, Klein R, Moss SE, Palta M. A cohort study of the relationship of diabetic retinopathy to blood pressure. Arch Ophthalmol. 1995;113(5):601-6. doi: 10.1001/archopht.1995.01100050069033.
81. Klein R, Moss SE, Klein BE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. XI. The incidence of macular edema. Ophthalmology. 1989;96(10):1501-10. doi: 10.1016/s0161-6420(89)32699-6.
82. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008 Oct 9;359(15):1565-76. doi: 10.1056/NEJMoa0806359.
83. Klein BE, Moss SE, Klein R, Surawicz TS. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XIII. Relationship of serum cholesterol to retinopathy and hard exudate. Ophthalmology. 1991;98(8):1261-5. doi: 10.1016/s0161-6420(91)32145-6.
84. Chew EY, Klein ML, Ferris FL, 3rd, Remaley NA, Murphy RP, Chantry K, et al. Association of elevated serum lipid levels with retinal hard exudate in diabetic retinopathy. Early Treatment Diabetic Retinopathy Study (ETDRS) Report 22. Arch Ophthalmol. 1996;114(9):1079-84. doi: 10.1001/archopht.1996.01100140281004.
85. Miljanovic B, Glynn RJ, Nathan DM, Manson JE, Schaumberg DA. A prospective study of serum lipids and risk of diabetic macular edema in type 1 diabetes. Diabetes. 2004;53(11):2883-92. doi: 10.2337/diabetes.53.11.2883.
86. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, et al. Blood pressure, lipids, and obesity are associated with retinopathy: the hoorn study. Diabetes Care. 2002;25(8):1320-5. doi: 10.2337/diacare.25.8.1320.
87. Cai XL, Wang F, Ji LN. Risk factors of diabetic retinopathy in type 2 diabetic patients. Chin Med J (Engl). 2006;119(10):822-6.
88. Lyons TJ, Jenkins AJ, Zheng D, Lackland DT, McGee D, Garvey WT, et al. Diabetic retinopathy and serum lipoprotein subclasses in the DCCT/EDIC cohort. Invest Ophthalmol Vis Sci. 2004;45(3):910-8. doi: 10.1167/iovs.02-0648.
89. The ACCORD Study Group and ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med. 2010;363(3):233-44. doi: 10.1056/NEJMoa1001288.
90. Wright AD, Dodson PM. Medical management of diabetic retinopathy: fenofibrate and ACCORD Eye studies. Eye (Lond). 2011;25(7):843-9. doi: 10.1038/eye.2011.62.
91. Dirani M, Xie J, Fenwick E, Benarous R, Rees G, Wong TY, et al. Are obesity and anthropometry risk factors for diabetic retinopathy?: The diabetes management project. Invest Ophthalmol Vis Sci. 2011;52(7):4416-21. doi: 10.1167/iovs.11-7208.
92. Liu Y, Yang J, Tao L, Lv H, Jiang X, Zhang M, et al. Risk factors of diabetic retinopathy and sight-threatening diabetic retinopathy: a cross-sectional study of 13 473

patients with type 2 diabetes mellitus in mainland China. BMJ Open. 2017;7(9):e016280. doi: 10.1136/bmjopen-2017-016280.
93. Zhu W, Wu Y, Meng YF, Xing Q, Tao JJ, Lu J. Association of obesity and risk of diabetic retinopathy in diabetes patients: A meta-analysis of prospective cohort studies. Medicine (Baltimore). 2018;97(32):e11807. doi: 10.1097/MD.0000000000011807.
94. Sasongko MB, Widyaputri F, Sulistyoningrum DC, Wardhana FS, Widayanti TW, Supanji S, et al. Estimated resting metabolic rate and body composition measures are strongly associated with diabetic retinopathy in Indonesian adults with type 2 diabetes. Diabetes Care. 2018;41(11):2377-2384. doi: 10.2337/dc18-1074.
95. Lim LS, Tai ES, Mitchell P, Wang JJ, Tay WT, Lamoureux E, et al. C-reactive protein, body mass index, and diabetic retinopathy. Invest Ophthalmol Vis Sci. 2010;51(9):4458-63. doi: 10.1167/iovs.09-4939.
96. Man RE, Sabanayagam C, Chiang PP, Li LJ, Noonan JE, Wang JJ, et al. Differential association of generalized and abdominal obesity with diabetic retinopathy in Asian patients with type 2 diabetes. JAMA Ophthalmol. 2016;134(3):251-7. doi: 10.1001/jamaophthalmol.2015.5103.
97. Kostev K, Rathmann W. Diabetic retinopathy at diagnosis of type 2 diabetes in the UK: a database analysis. Diabetologia. 2013;56(1):109-11. doi: 10.1007/s00125-012-2742-7.
98. Zhou Y, Zhang Y, Shi K, Wang C. Body mass index and risk of diabetic retinopathy: A meta-analysis and systematic review. Medicine (Baltimore). 2017;96(22):e6754. doi: 10.1097/MD.0000000000006754.
99. Klein R, Klein BEK, Moss SE, Davis MD, Demets DL. The Wisconsin epidemiologic study of diabetic retinopathy: II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984;102(4):520-6. doi: 10.1001/archopht.1984.01040030398010.
100. Klein R, Klein BEK, Moss SE, Davis MD, Demets DL. The Wisconsin epidemiologic study of diabetic retinopathy: iii. prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol. 1984;102(4):527-32. doi: 10.1001/archopht.1984.01040030405011.
101. Florkowski CM, Scott RS, Coope PA, Graham PJ, Moir CL. Age at diagnosis, glycaemic control and the development of retinopathy in a population-based cohort of type 1 diabetic subjects in Canterbury, New Zealand. Diabetes Res Clin Pract. 2001;52(2):125-31. doi: 10.1016/s0168-8227(00)00248-5.
102. McKay R, McCarty CA, Taylor HR. Diabetic retinopathy in Victoria, Australia: the Visual Impairment Project. Br J Ophthalmol. 2000;84(8):865-70. doi: 10.1136/bjo.84.8.865.
103. Sasongko MB, Widyaputri F, Agni AN, Wardhana FS, Kotha S, Gupta P, et al. Prevalence of diabetic retinopathy and blindness in Indonesian adults with type 2 diabetes. Am J Ophthalmol. 2017;181:79-87. doi: 10.1016/j.ajo.2017.06.019.
104. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(12):e1221-e1234. doi: 10.1016/S2214-109X(17)30393-5.
105. The Diabetes Control Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes Care. 2000;23(8):1084-91. doi: 10.2337/diacare.23.8.1084.

106. Loukovaara S, Immonen I, Teramo KA, Kaaja R. Progression of retinopathy during pregnancy in type 1 diabetic women treated with insulin lispro. Diabetes Care. 2003;26(4):1193-8. doi: 10.2337/diacare.26.4.1193.
107. Kaaja R, Loukovaara S. Progression of retinopathy in type 1 diabetic women during pregnancy. Curr Diabetes Rev. 2007;3(2):85-93. doi: 10.2174/157339907780598252.
108. Beetham WP. Diabetic retinopathy in pregnancy. Trans Am Ophthalmol Soc. 1950:205-19.
109. Makwana T, Takkar B, Venkatesh P, Sharma JB, Gupta Y, Chawla R, et al. Prevalence, progression, and outcomes of diabetic retinopathy during pregnancy in Indian scenario. Indian J Ophthalmol. 2018;66(4):541-6. doi: 10.4103/ijo.IJO_1062_17.
110. Vestgaard M, Ringholm L, Laugesen CS, Rasmussen KL, Damm P, Mathiesen ER. Pregnancy-induced sight-threatening diabetic retinopathy in women with Type 1 diabetes. Diabet Med. 2010;27(4):431-5. doi: 10.1111/j.1464-5491.2010.02958.x.
111. Temple RC, Aldridge VA, Sampson MJ, Greenwood RH, Heyburn PJ, Glenn A. Impact of pregnancy on the progression of diabetic retinopathy in type 1 diabetes. Diabet Med. 2001;18(7):573-7. doi: 10.1046/j.1464-5491.2001.00535.x.
112. Axer-Siegel R, Hod M, Fink-Cohen S, Kramer M, Weinberger D, Schindel B, et al. Diabetic retinopathy during pregnancy. Ophthalmology. 1996;103(11):1815-9. doi: 10.1016/s0161-6420(96)30421-1.
113. Arun CS, Taylor R. Influence of pregnancy on long-term progression of retinopathy in patients with type 1 diabetes. Diabetologia. 2008;51(6):1041-5. doi: 10.1007/s00125-008-0994-z.
114. Horvat M, Maclean H, Goldberg L, Crock GW. Diabetic retinopathy in pregnancy: a 12-year prospective survey. Br J Ophthalmol. 1980;64(6):398-403. doi: 10.1136/bjo.64.6.398.
115. Sugiyama T, Saito M, Nishigori H, Nagase S, Yaegashi N, Sagawa N, et al. Comparison of pregnancy outcomes between women with gestational diabetes and overt diabetes first diagnosed in pregnancy: A retrospective multi-institutional study in Japan. Diabetes Res Clin Pract. 2014;103(1):20-5. doi: 10.1016/j.diabres.2013.10.020.
116. Wu G. Diabetic retinopathy : the essentials. Philadelphia: Wolters Kluwer/ Lippincott Williams & Wilkins Health; 2010.
117. Thornburg KL, Jacobson SL, Giraud GD, Morton MJ. Hemodynamic changes in pregnancy. Semin Perinatol. 2000;24(1):11-4. doi: 10.1016/s0146-0005(00)80047-6.
118. Bhatnagar A, Ghauri AJ, Hope-Ross M, Lip PL. Diabetic retinopathy in pregnancy. Curr Diabetes Rev. 2009;5(3):151-6. doi: 10.2174/157339909788920929.
119. Schocket LS, Grunwald JE, Tsang AF, DuPont J. The effect of pregnancy on retinal hemodynamics in diabetic versus nondiabetic mothers. Am J Ophthalmol. 1999;128(4):477-84. doi: 10.1016/s0002-9394(99)00234-2.
120. Larsen M, Colmorn LB, Bonnelycke M, Kaaja R, Immonen I, Sander B, et al. Retinal artery and vein diameters during pregnancy in diabetic women. Invest Ophthalmol Vis Sci. 2005;46(2):709-13. doi: 10.1167/iovs.04-0604.
121. Kohner EM. Diabetic retinopathy. BMJ. 1993;307(6913):1195-9. doi: 10.1136/bmj.307.6913.1195.
122. Loukovaara S, Harju M, Kaaja R, Immonen I. Retinal capillary blood flow in diabetic and nondiabetic women during pregnancy and postpartum period. Invest Ophthalmol Vis Sci. 2003;44(4):1486-91. doi: 10.1167/iovs.02-0293.
123. Pescosolido N, Campagna O, Barbato A. Diabetic retinopathy and pregnancy. Int Ophthalmol. 2014;34(4):989-97. doi: 10.1007/s10792-014-9906-z.

124. Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. Diabetes Care. 2007;30 Suppl 2:S112-9.
125. Larinkari J, Laatikainen L, Ranta T, Moronen P, Pesonen K, Laatikainen T. Metabolic control and serum hormone levels in relation to retinopathy in diabetic pregnancy. Diabetologia. 1982;22(5):327-32.
126. Bermea KC, Rodriguez-Garcia A, Tsin A, Barrera-Saldana HA. Somatolactogens and diabetic retinopathy. Growth Horm IGF Res. 2018;41:42-7.
127. Sone H, Okuda Y, Kawakami Y, Kondo S, Hanatani M, Matsuo K, et al. Progesterone induces vascular endothelial growth factor on retinal pigment epithelial cells in culture. Life Sci. 1996;59(1):21-5.
128. Galazios G, Papazoglou D, Tsikouras P, Kolios G. Vascular endothelial growth factor gene polymorphisms and pregnancy. J Matern Fetal Neonatal Med. 2009;22(5):371-8.
129. Almawi WY, Saldanha FL, Mahmood NA, Al-Zaman I, Sater MS, Mustafa FE. Relationship between VEGFA polymorphisms and serum VEGF protein levels and recurrent spontaneous miscarriage. Hum Reprod. 2013;28(10):2628-35.
130. Kianersi F, Ghanbari H, Naderi Beni Z, Naderi Beni A. Intravitreal vascular endothelial growth factor (VEGF) inhibitor injection in unrecognised early pregnancy. Invest New Drugs. 2016;34(5):650-3.
131. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. Nat Rev Cancer. 2003;3(6):401-10.
132. Mutter WP, Karumanchi SA. Molecular mechanisms of preeclampsia. Microvasc Res. 2008;75(1):1-8.
133. Lauszus FF, Klebe JG, Bek T, Flyvbjerg A. Increased serum IGF-I during pregnancy is associated with progression of diabetic retinopathy. Diabetes. 2003;52(3):852-6.
134. National Guideline Alliance (UK). Hypertension in pregnancy: diagnosis and management. London: National Institute for Health and Care Excellence (UK); 2019.
135. Lowe SA, Bowyer L, Lust K, McMahon LP, Morton MR, North RA, et al. The SOMANZ guidelines for the management of hypertensive disorders of pregnancy. 2014. Aust N Z J Obstet Gynaecol. 2015;55(1):11-6. doi: 10.1111/ajo.12253.
136. Kintiraki E, Papakatsika S, Kotronis G, Goulis DG, Kotsis V. Pregnancy-Induced hypertension. Hormones (Athens). 2015 Apr-Jun;14(2):211-23. doi: 10.14310/horm.2002.1582.
137. Rasdi AR, Nik-Ahmad-Zuky NL, Bakiah S, Shatriah I. Hypertensive retinopathy and visual outcome in hypertensive disorders in pregnancy. Med J Malaysia. 2011 Mar;66(1):42-7.
138. Rosenn B, Miodovnik M, Kranias G, Khoury J, Combs CA, Mimouni F, et al. Progression of diabetic retinopathy in pregnancy: association with hypertension in pregnancy. Am J Obstet Gynecol. 1992;166(4):1214-8.
139. Gordin D, Kaaja R, Forsblom C, Hiilesmaa V, Teramo K, Groop PH. Pre-eclampsia and pregnancy-induced hypertension are associated with severe diabetic retinopathy in type 1 diabetes later in life. Acta Diabetologica. 2013;50(5):781-7.
140. Wong TY, Mitchell P. The eye in hypertension. Lancet. 2007 Feb 3;369(9559):425-35. doi: 10.1016/S0140-6736(07)60198-6. Erratum in: Lancet. 2007 Jun 23;369(9579):2078. Wong, Tien [corrected to Wong, Tien Yin].
141. Bhargava M, Ikram MK, Wong TY. How does hypertension affect your eyes? J Hum Hypertens. 2012;26(2):71-83.

142. Abu Samra K. The eye and visual system in the preeclampsia/eclampsia syndrome: What to expect? Saudi J Ophthalmol. 2013 Jan;27(1):51-3. doi: 10.1016/j.sjopt.2012.04.003.
143. Errera MH, Kohly RP, da Cruz L. Pregnancy-associated retinal diseases and their management. Survey of Ophthalmology. 2013;58(2):127-42.
144. Cunningham FG, Fernandez CO, Hernandez C. Blindness associated with preeclampsia and eclampsia. Am J Obstet Gynecol. 1995 Apr;172(4 Pt 1):1291-8. doi: 10.1016/0002-9378(95)91495-1.
145. Reddy SC, Nalliah S, Rani S, George K, Who TS. Fundus changes in pregnancy induced hypertension. International Journal of Ophthalmology. 2012;5(6):694-7.
146. Shah A, Lune A, Magdum R, Deshpande H, Shah A, Bhavsar D. Retinal changes in pregnancy-induced hypertension. Med J Dr, D Y Patil Univ 2015;8(3):304-307.
147. Toda J, Kato S, Sanaka M, Kitano S. The effect of pregnancy on the progression of diabetic retinopathy. Jpn J Ophthalmol. 2016;60(6):454-8.
148. Chew EY, Mills JL, Metzger BE, Remaley NA, Jovanovic-Peterson L, Knopp RH, et al. Metabolic control and progression of retinopathy: The Diabetes in Early Pregnancy Study. Diabetes Care. 1995;18(5):631-7.
149. Klein BE, Moss SE, Klein R. Effect of pregnancy on progression of diabetic retinopathy. Diabetes Care. 1990;13(1):34-40.
150. Egan AM, McVicker L, Heerey A, Carmody L, Harney F, Dunne FP. Diabetic retinopathy in pregnancy: a population-based study of women with pregestational diabetes. J Diabetes Res. 2015;2015:310239. doi: 10.1155/2015/310239.
151. Lovestam-Adrian M, Agardh CD, Aberg A, Agardh E. Pre-eclampsia is a potent risk factor for deterioration of retinopathy during pregnancy in type 1 diabetic patients. Diabet Med. 1997;14(12):1059-65.
152. McElvy SS, Demarini S, Miodovnik M, Khoury JC, Rosenn B, Tsang RC. Fetal weight and progression of diabetic retinopathy. Obstet Gynecol. 2001 Apr;97(4):587-92. doi: 10.1016/s0029-7844(00)01202-3.
153. Sun Z, Tang F, Wong R, Lok J, Szeto SKH, Chan JCK, et al. OCT angiography metrics predict progression of diabetic retinopathy and development of diabetic macular edema: a prospective study. Ophthalmology. 2019;126(12):1675-84.
154. Agemy SA, Scripsema NK, Shah CM, Chui T, Garcia PM, Lee JG, et al. Retinal vascular perfusion density mapping using optical coherence tomography angiography in normals and diabetic retinopathy patients. Retina. 2015;35(11):2353-63.
155. Chow DR. Opticl coherence tomography angiography: understanding the basics. In: Chow DR, de Oliveira PRC, editors. OCT Angiography. New York: Thieme Publishers; 2018. p. 1-7.
156. Conrath J, Giorgi R, Raccah D, Ridings B. Foveal avascular zone in diabetic retinopathy: quantitative vs qualitative assessment. Eye (Lond). 2005;19(3):322-6.
157. Mac Enerney JK, Wong WP, Peyman GA. Evaluation of teratogenicity of fluorescein sodium. Am J Ophthalmol. 1977;84(6):847-50. doi: 10.1016/0002-9394(77)90508-6.
158. Halperin LS, Olk RJ, Soubrane G, Coscas G. Safety of fluorescein angiography during pregnancy. Am J Ophthalmol. 1990;109(5):563-6.
159. Spaide RF, Fujimoto JG, Waheed NK. Optical coherence tomography angiography. Retina. 2015;35(11):2161-2.
160. Novais E, Baumal C. The clinical utility of OCT Angiography: Retina specialists experienced in OCTA discuss the strengths—and the limitations—of this promising new technology [Internet]. Newtown Square (PA): Jobson Medical Information LLC; 2017 [cited 2020 Apr 5]. Available from:

https://www.reviewofophthalmology.com/article/the-clinical-utility-of-oct-angiography.
161. Matsunaga D, Yi J, Puliafito CA, Kashani AH. OCT angiography in healthy human subjects. Ophthalmic Surg Lasers Imaging Retina. 2014;45(6):510-5.
162. Dave PA, Dansingani KK, Jabeen A, Jabeen A, Hasnat Ali M, Vupparaboina KK, et al. Comparative evaluation of foveal avascular zone on two optical coherence tomography angiography devices. Optom Vis Sci. 2018;95(7):602-7.
163. de Carlo TE, Romano A, Waheed NK, Duker JS. A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous. 2015;1:5.
164. Ghasemi Falavarjani K, Al-Sheikh M, Akil H, Sadda SR. Image artefacts in swept-source optical coherence tomography angiography. Br J Ophthalmol. 2017;101(5):564-8.
165. Patel RC, Wang J, Hwang TS, Zhang M, Gao SS, Pennesi ME, et al. Plexus-specific detection of retinal vascular pathologic conditions with projection-resolved OCT Angiography. Ophthalmol Retina. 2018;2(8):816-26.
166. Ho J, Dans K, You Q, Nudleman EN, Freeman WR. Comparison of 3 mm x 3 mm Versus 6 mm x 6 mm optical coherence tomography angiography scan sizes in the evaluation of non–proliferative diabetic retinopathy. Retina. 2017;0:1-6.
167. Di G, Weihong Y, Xiao Z, Zhikun Y, Xuan Z, Yi Q, et al. A morphological study of the foveal avascular zone in patients with diabetes mellitus using optical coherence tomography angiography. Graefes Arch Clin Exp Ophthalmol. 2016;254(5):873-9.
168. Hwang TS, Jia Y, Gao SS, Bailey ST, Lauer AK, Flaxel CJ, et al. Optical coherence tomography angiography features of diabetic retinopathy. Retina. 2015;35(11):2371-6.
169. Hwang TS, Hagag AM, Wang J, Zhang M, Smith A, Wilson DJ, et al. Automated quantification of nonperfusion areas in 3 vascular plexuses with optical coherence tomography angiography in eyes of patients with diabetes. JAMA Ophthalmol. 2018;136(8):929-36.
170. Al-Sheikh M, Akil H, Pfau M, Sadda SR. Swept-source oct angiography imaging of the foveal avascular zone and macular capillary network density in diabetic retinopathy. Invest Ophthalmol Vis Sci. 2016;57(8):3907-13.
171. Hwang TS, Zhang M, Bhavsar K, Zhang X, Campbell JP, Lin P, et al. Visualization of 3 distinct retinal plexuses by projection-resolved optical coherence tomography angiography in diabetic retinopathy. JAMA Ophthalmol. 2016;134(12):1411-9.
172. Um T, Seo EJ, Kim YJ, Yoon YH. Optical coherence tomography angiography findings of type 1 diabetic patients with diabetic retinopathy, in comparison with type 2 patients. Graefes Arch Clin Exp Ophthalmol. 2020;258(2):281-8.
173. Rodrigues TM, Marques JP, Soares M, Simao S, Melo P, Martins A, et al. Macular OCT-angiography parameters to predict the clinical stage of nonproliferative diabetic retinopathy: an exploratory analysis. Eye (Lond). 2019;33(8):1240-7.
174. De Carlo TE, Chin AT, Bonini Filho MA, Adhi M, Branchini L, Salz DA, et al. Detection of microvascular changes in eyes of patients with diabetes but not clinical diabetic retinopathy using optical coherence tomography angiography. Retina. 2015;35(11):2364-70.
175. Fleissig E, Adhi M, Sigford DK, Barr CC. Foveal vasculature changes and nonperfusion in patients with diabetes types I and II with no evidence of diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2020;258(3):551-6.
176. Forte R, Haulani H, Jurgens I. Quantitative and qualitative analysis of the three capillary plexuses and choriocapillaris in patients with type 1 and type 2 diabetes mellitus

without clinical signs of diabetic retinopathy: a prospective pilot study. Retina. 2020;40(2):333-44.
177. Chanwimol K, Balasubramanian S, Nassisi M, Gaw SL, Janzen C, Sarraf D, et al. Retinal vascular changes during pregnancy detected with optical coherence tomography angiography. Invest Ophthalmol Vis Sci. 2019;60(7):2726-32.
178. Kiziltunc PB, Varli B, Buyuktepe TC, Atilla H. Ocular vascular changes during pregnancy: an optical coherence tomography angiography study. Graefes Arch Clin Exp Ophthalmol. 2020;258(2):395-401.
179. Sugimoto M, Wakamatsu Y, Miyata R, Matsubara H, Kondo M, Kamimoto Y, et al. Relationship between size of the foveal avascular zone and carbohydrate metabolic disorders during pregnancy. Biomed Res Int. 2019;2019:3261279.
180. Oguz H. Diabetic retinopathy in pregnancy: effects on the natural course. Semin Ophthalmol. 1999;14(4):249-57.
181. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. BMJ. 2006;333(7560):177.
182. Egan AM, Murphy HR, Dunne FP. The management of type 1 and type 2 diabetes in pregnancy. QJM. 2015;108(12):923-7.
183. Tajima K, Nagai S, Miyoshi H, Kondo T, Shimada S, Yanagisawa K, et al. A comparison of pregnancy outcomes in Japanese women with type 2 and type 1 diabetes mellitus at tertiary centers. Diabetol Int. 2011;2(2):86-93.
184. Ringholm L, Mathiesen ER, Kelstrup L, Damm P. Managing type 1 diabetes mellitus in pregnancy - From planning to breastfeeding. Nat Rev Endocrinol. 2012;8(11):659-67.
185. Xiang LJ, Wang Y, Lu GY, Huang Q. Association of the presence of microangiopathy with adverse pregnancy outcome in type 1 diabetes: A meta-analysis. Taiwan J Obstet Gynecol. 2018;57(5):659-64.
186. Price JH, Hadden DR, Archer DB, Harley JM. Diabetic retinopathy in pregnancy. BJOG. 1984;91(1):11-7.
187. Klein BE, Klein R, Meuer SM, Moss SE, Dalton DD. Does the severity of diabetic retinopathy predict pregnancy outcome? J Diabet Complications. 1988;2(4):179-84. doi: 10.1016/s0891-6632(88)80005-9.
188. Schaefer-Graf U, Napoli A, Nolan CJ, Diabetic Pregnancy Study Group. Diabetes in pregnancy: a new decade of challenges ahead. Diabetologia. 2018;61(5):1012-21.
189. Rudland VL, Price SAL, Hughes R, Barrett HL, Lagstrom J, Porter C, et al. ADIPS 2020 guideline for pre-existing diabetes and pregnancy. Aust N Z J Obstet Gynaecol. 2020;60(6):E18-E52. doi: 10.1111/ajo.13265.
190. American Diabetes Association. 14. Management of diabetes in pregnancy: standards of medical care in diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S165-S72.
191. Morrison M, Hendrieckx C, Nankervis A, Audehm R, Farrell K, Houvardas E, et al. Factors associated with attendance for pre-pregnancy care and reasons for non-attendance among women with diabetes. Diabetes Res Clin Pract. 2018;142:269-75.
192. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347-59.
193. National Collaborating Centre for Women's and Children's Health (UK). Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period. London: National Institute for Health and Care Excellence (UK);2015.

194. Cavan D, Makaroff L, da Rocha Fernandes J, Sylvanowicz M, Ackland P, Conlon J, et al. The Diabetic Retinopathy Barometer Study: Global perspectives on access to and experiences of diabetic retinopathy screening and treatment. Diabetes Res Clin Pract. 2017;129:16-24.
195. Schoenfeld ER, Greene JM, Wu SY, Leske MC. Patterns of adherence to diabetes vision care guidelines: baseline findings from the diabetic retinopathy awareness program. Ophthalmology. 2001;108(3):563-71.
196. American Diabetes Association. 10. Microvascular complications and foot care: standards of medical care in diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S105-S118. doi: 10.2337/dc18-S010.
197. Wong TY, Sun J, Kawasaki R, Ruamviboonsuk P, Gupta N, Lansingh VC, et al. Guidelines on diabetic eye care: The International Council of Ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology. 2018;125(10):1608-22.
198. Foreman J, Keel S, Xie J, Van Wijngaarden P, Taylor HR, Dirani M. Adherence to diabetic eye examination guidelines in Australia: the National Eye Health Survey. Med J Aust. 2017;206(9):402-6.
199. Fisher MD, Rajput Y, Gu T, Singer JR, Marshall AR, Ryu S, et al. Evaluating adherence to dilated eye examination recommendations among patients with diabetes, combined with patient and provider perspectives. Am Health Drug Benefits. 2016;9(7):385-93.
200. Tapp RJ, Zimmet PZ, Harper CA, de Courten MP, Balkau B, McCarty DJ, et al. Diabetes care in an Australian population: frequency of screening examinations for eye and foot complications of diabetes. Diabetes Care. 2004;27(3):688-93.
201. Aspelund T, Thornorisdottir O, Olafsdottir E, Gudmundsdottir A, Einarsdottir AB, Mehlsen J, et al. Individual risk assessment and information technology to optimise screening frequency for diabetic retinopathy. Diabetologia. 2011;54(10):2525-32.
202. Wang LZ, Cheung CY, Tapp RJ, Hamzah H, Tan G, Ting D, et al. Availability and variability in guidelines on diabetic retinopathy screening in Asian countries. Br J Ophthalmol. 2017;101(10):1352-60.
203. McElduff A, Cheung NW, McIntyre HD, Lagstrom JA, Oats JJ, Ross GP, et al. The Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy. Med J Aust. 2005;183(7):373-7.
204. Hampshire R, Wharton H, Leigh R, Wright A, Dodson P. Screening for diabetic retinopathy in pregnancy using photographic review clinics. Diabet Med. 2013;30(4):475-7.
205. Fathy C, Patel S, Sternberg P Jr, Kohanim S. Disparities in adherence to screening guidelines for diabetic retinopathy in the United States: A comprehensive review and guide for future directions. Semin Ophthalmol. 2016;31(4):364-77. doi: 10.3109/08820538.2016.1154170.
206. Dunne F. Outcomes for women with type 1 and type 2 diabetes; disease burden starting pregnancy and strategies to improve pregnancy outcomes. ADIPS 2019 Annual Scientific Meeting [Internet]. Sydney: Australasian Diabetes in Pregnancy Society; 2019 [cited 2019 Jul 20].
207. Hooper P, Boucher MC, Cruess A, Dawson KG, Delpero W, Greve M, et al. Excerpt from the Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy. Can J Ophthalmol. 2017;52 Suppl 1:S45-S74.

208. Grauslund J, Andersen N, Andresen J, Flesner P, Haamann P, Heegaard S, et al. Evidence-based Danish guidelines for screening of diabetic retinopathy. Acta Ophthalmol. 2018;96(8):763-9.
209. Wong MC, Sin CK, Lee JP. The reference framework for diabetes care in primary care settings. Hong Kong Med J. 2012;18(3):238-46.
210. IDF Clinical Guidelines Task Force. Global guideline on pregnancy and diabetes. Brussels: International Diabetes Federation; 2009.
211. Rajavi Z, Safi S, Javadi MA, Azarmina M, Moradian S, Entezari M, et al. Diabetic retinopathy clinical practice guidelines: customized for Iranian population. J Ophthalmic Vis Res. 2016;11(4):394-414.
212. Diabetes in pregnancy: Management of diabetes and its complications from preconception to the postnatal period. National Institute for Health and Care Excellence: Clinical Guidelines. London; 2015.
213. Diabetic retinal screening in pregnancy [Internet]. New Zealand: Ministry of Health; 2016 [cited 2019 Apr]. Available from: https://www.health.govt.nz/publication/diabetic-retinal-screening-grading-monitoring-and-referral-guidance.
214. Ghanchi F, Diabetic Retinopathy Guidelines Working Group. The Royal College of Ophthalmologists' clinical guidelines for diabetic retinopathy: a summary. Eye (Lond). 2013;27(2):285-7.
215. Scottish Intercollegiate Guidelines Network. Prevention of visual impairment. Management of diabetes – a national clinical guideline. Ediburgh, UK: Scottish Intercollegiate Guidelines Network; 2010.
216. Corcostegui B, Duran S, Gonzalez-Albarran MO, Hernandez C, Ruiz-Moreno JM, Salvador J, et al. Update on diagnosis and treatment of diabetic retinopathy: a consensus guideline of the working group of ocular health (Spanish Society of Diabetes and Spanish Vitreous and Retina Society). J Ophthalmol. 2017;2017:8234186.
217. Goh SY, Ang SB, Bee YM, Chen RY, Gardner D, Ho E, et al. Ministry of Health clinical practice guidelines: diabetes mellitus [Internet]. Singapore; 2014 [cited 2019 Apr]. Available from: http://www.smj.org.sg/sites/default/files/5506/5506cpg1.pdf.
218. Clinical practice guideline: management of diabetes mellitus [Internet]. Sri Lanka: Sri Lanka College of Obstetricians & Gynecologists [cited 2019 Apr]. Available from: http://www.slcog.lk/img/guidelines/Other%20national%20Gidelines/Physicians/Book%201/Management%20of%20Diabetes%20Mellitus.pdf.
219. Vision 2020 program of the IAPB for Latin America. Clinical practice guide for diabetic retinopathy for Latin America. Mexico; 2011.
220. van Wijngaarden P, Keel S, Scanlon PH. The case for extended screening intervals for people with diabetes and no or minimal retinopathy at baseline. JAMA Ophthalmol. 2019;137(4):449-450. doi: 10.1001/jamaophthalmol.2018.6901.
221. Sheppler CR, Lambert WE, Gardiner SK, Becker TM, Mansberger SL. Predicting adherence to diabetic eye examinations: development of the Compliance with Annual Diabetic Eye Exams Survey. Ophthalmology. 2014;121(6):1212-9.
222. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 2003;327(7414):557-60.
223. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane handbook for systematic reviews of interventions version 6.1 [Internet]. Cochrane; 2020 [updated 2020 Sep; cited 2020 Oct 14]. Available from: www.training.cochrane.org/handbook

224. Buchbinder A, Miodovnik M, McElvy S, Rosenn B, Kranias G, Khoury J, et al. Is insulin lispro associated with the development or progression of diabetic retinopathy during pregnancy? Am J Obstet Gynecol. 2000;183(5):1162-5.
225. Dibble CM, Kochenour NK, Worley RJ, Tyler FH, Swartz M. Effect of pregnancy on diabetic retinopathy. Obstet Gynecol. 1982;59(6):699-704.
226. Phelps RL, Sakol P, Metzger BE, Jampol LM, Freinkel N. Changes in diabetic retinopathy during pregnancy correlations with regulation of hyperglycemia. Arch Ophthal. 1986;104(12):1806-10.
227. Moloney JB, Drury MI. The effect of pregnancy on the natural course of diabetic retinopathy. Am J Ophthalmol. 1982;93(6):745-56. doi: 10.1016/0002-9394(82)90471-8.
228. Laatikainen L, Larinkari J, Teramo K, Raivio KO. Occurrence and prognostic significance of retinopathy in diabetic pregnancy. Metab Pediatr Ophthalmol. 1980;4(4):191-5.
229. Lapolla A, Cardone C, Negrin P, Midena E, Marini S, Gardellin C, et al. Pregnancy does not induce or worsen retinal and peripheral nerve dysfunction in insulin-dependent diabetic women. J Diabetes Complications. 1998;12(2):74-80. doi: 10.1016/s1056-8727(97)00002-0.
230. Rahman W, Rahman FZ, Yassin S, Al-Suleiman SA, Rahman J. Progression of retinopathy during pregnancy in type 1 diabetes mellitus. Clin Exp Ophthalmol. 2007;35(3):231-6.
231. Celia B, Richard H, Chineze O, Casey E, Elizabeth P, Macauley A. The St Vincent Declaration - 25 years on: review of maternal deaths reported to the confidential enquiry in the UK and the lessons learnt. Eur J Obstet Gynecol Reprod Biol. 2016;206:e139-e40.
232. Yoeli-Ullman R, Dori-Dayan N, Mazaki-Tovi S, Zemet R, Kedar N, Cohen O, et al. Towards implementation of the Saint Vincent Declaration: outcomes of women with pregestational diabetes. Isr Med Assoc J. 2020;22(3):137-41.
233. Goldenberg RL, McClure EM, Harrison MS, Miodovnik M. Diabetes during Pregnancy in Low- and Middle-Income Countries. Am J Perinatol. 2016 Nov;33(13):1227-1235. doi: 10.1055/s-0036-1584152.
234. Leung D, Dul M, Comer GW, Chaglasian M, Mehrabyan E, Fisher JL, et al. The development of a reference database with one-micron wavelength swept-source OCT DRI OCT Triton. Invest. Ophthalmol. Vis. Sci. 2018;59(9):1523.
235. Pazos M, Dyrda AA, Biarnés M, Gómez A, Martín C, Mora C, et al. Diagnostic accuracy of Spectralis SD OCT automated macular layers segmentation to discriminate normal from early glaucomatous eyes. Ophthalmology. 2017;124(8):1218-28. doi: 10.1016/j.ophtha.2017.03.044.
236. TOPCON 3D OCT series normative database. Japan: Topcon Medical Systems, Inc.; 2011.
237. Cirrus HD-OCT: How to read the Cirrus reports. USA: Carl Zeiss Meditec, Inc.; 2011.
238. Australian Bureau of Statistics (ABS). Community Profiles [Internet]. Canberra: Australian Bureau of Statistics; 2015 [cited 2018 Apr 24]. Available from: http://www.abs.gov.au/websitedbs/censushome.nsf/home/communityprofiles?opendocument& navpos=230.
239. Keel S, Xie J, Foreman J, van Wijngaarden P, Taylor HR, Dirani M. The prevalence of diabetic retinopathy in Australian adults with self-reported diabetes: The National Eye Health Survey. Ophthalmology. 2017;124(7):977-84.
240. World Health Organization. BMI classification. Global database on body mass index [Internet]. Available from: http://www.who.int/bmi/index. jsp

241. Mikolajczyk RT, Zhang J, Betran AP, Souza JP, Mori R, Gulmezoglu AM, et al. A global reference for fetal-weight and birthweight percentiles. Lancet. 2011;377(9780):1855-61.
242. Nielsen LR, Damm P, Mathiesen ER. Improved pregnancy outcome in type 1 diabetic women with microalbuminuria or diabetic nephropathy: effect of intensified antihypertensive therapy? Diabetes Care. 2009;32(1):38-44.
243. Massin P, Girach A, Erginay A, Gaudric A. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. Acta Ophthalmol Scand. 2006;84(4):466-74.
244. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthalmol. 2006;142(3):405-12.
245. Ohrt V. The influence of pregnancy on diabetic retinopathy with special regard to the reversible changes shown in 100 pregnancies. Acta Ophthalmol (Copenh). 1984;62(4):603-16.
246. Chan WC, Lim LT, Quinn MJ, Knox FA, McCance D, Best RM. Management and outcome of sight-threatening diabetic retinopathy in pregnancy. Eye. 2004;18(8):826-32.
247. Serup L. Influence of pregnancy on diabetic retinopathy. Acta Endocrinol Suppl (Copenh). 1986;277:122-4.
248. Lauszus F, Klebe JG, Bek T. Diabetic retinopathy in pregnancy during tight metabolic control. Acta Obstet Gynecol Scand. 2000;79(5):367-70.
249. Australian Institute of Health and Welfare. Diabetes in pregnancy 2014–2015. Canberra (ACT): AIHW; 2019.
250. Wahabi HA, Esmaeil SA, Fayed A, Al-Shaikh G, Alzeidan RA. Pre-existing diabetes mellitus and adverse pregnancy outcomes. BMC Res Notes. 2012;5:496.
251. Dunne FP, Avalos G, Durkan M, Mitchell Y, Gallacher T, Keenan M, et al. ATLANTIC DIP: pregnancy outcomes for women with type 1 and type 2 diabetes. Ir Med J. 2012;105(5 Suppl):6-9.
252. Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, et al. Diabetes and pregnancy: national trends over a 15 year period. Diabetologia. 2018;61(5):1081-8.
253. Australian Institute of Health Welfare. Diabetes in pregnancy: its impact on Australian women and their babies. Canberra (ACT): AIHW; 2010.
254. Cheung NW, McElduff A, Ross GP. Type 2 diabetes in pregnancy: a wolf in sheep's clothing. Aust N Z J Obstet Gynaecol. 2005;45(6):479-83.
255. Hillman N, Herranz L, Vaquero PM, Villarroel A, Fernandez A, Pallardo LF. Is pregnancy outcome worse in type 2 than in type 1 diabetic women? Diabetes Care. 2006;29(11):2557-8.
256. Weindling AM. The confidential enquiry into maternal and child health (CEMACH). Archives of Disease in Childhood. 2003;88(12):1034.
257. Shukla D, Rajendran A, Singh J, Ramasamy K, Perumalsamy N, Cunningham ET, Jr. Atypical manifestations of diabetic retinopathy. Curr Opin Ophthalmol. 2003;14(6):371-7.
258. Hirano T, Kitahara J, Toriyama Y, Kasamatsu H, Murata T, Sadda S. Quantifying vascular density and morphology using different swept-source optical coherence tomography angiographic scan patterns in diabetic retinopathy. Br J Ophthalmol. 2019;103(2):216-21.
259. Tang FY, Ng DS, Lam A, Luk F, Wong R, Chan C, et al. Determinants of quantitative optical coherence tomography angiography metrics in patients with diabetes. Sci Rep. 2017;7(1):2575.

260. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82.
261. Luo X, Shen YM, Jiang MN, Lou XF, Shen Y. Ocular blood flow autoregulation mechanisms and methods. J Ophthalmol. 2015;2015:864871. doi: 10.1155/2015/864871.
262. Mallika P, Tan A, S A, T A, Alwi SS, Intan G. Diabetic retinopathy and the effect of pregnancy. Malays Fam Physician. 2010;5(1):2-5.
263. Toker E, Yenice O, Akpinar I, Aribal E, Kazokoglu H. The influence of sex hormones on ocular blood flow in women. Acta Ophthalmol Scand. 2003;81(6):617-24.
264. Sato T, Sugawara J, Aizawa N, Iwama N, Takahashi F, Nakamura-Kurakata M, et al. Longitudinal changes of ocular blood flow using laser speckle flowgraphy during normal pregnancy. PLoS One. 2017;12(3):e0173127.
265. Shoji T, Yoshikawa Y, Kanno J, Ishii H, Ibuki H, Ozaki K, et al. Reproducibility of macular vessel density calculations via imaging with two different swept-source optical coherence tomography angiography systems. Transl Vis Sci Technol. 2018;7(6):31.
266. Yu JJ, Camino A, Liu L, Zhang X, Wang J, Gao SS, et al. Signal strength reduction effects in OCT angiography. Ophthalmol Retina. 2019;3(10):835-42.
267. Yildirim A, Kurt E, Altinisik M, Uyar Y. Evaluation of retinochoroidal tissues in third trimester pregnants: An optical coherence tomography angiography study. Eur J Ophthalmol. 2020. doi:10.1177/1120672120966566.
268. Dobree JH. Simple diabetic retinopathy. Evolution of the lesions and therapeutic considerations. Br J Ophthalmol. 1970;54(1):1-10.
269. Kohner EM, Patel V, Rassam SM. Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. Diabetes. 1995;44(6):603-7.
270. Akushichi M, Ishibazawa A, Ro-Mase T, Ishiko S, Yoshida A. A case of progressive diabetic retinopathy related to pregnancy followed on optical coherence tomography angiography. Ophthalmic Surg Lasers Imaging Retina. 2019 Jun 1;50(6):393-397. doi: 10.3928/23258160-20190605-09.
271. Abraham CS, Sheeran, P. The health belief model. In: Ayers S, Baum A, McManus C, Newman S, Wallston K, Weinman J, et al., editors. Cambridge Handbook of Psychology, Health and Medicine. 2nd ed. Cambridge: Cambridge University Press; 2007. p. 97-102.
272. Abraham CS, Sheeran, P. The health belief model. In: Conner M, Norman P, editors. Predicting and changing health behaviour: research and practice with social cognition models. 3rd ed. England: McGraw-Hill Education; 2015. p. 30 - 69.
273. Kassambara A. Practical guide to principal component methods in R. 1st ed: STHDA; 2017.
274. Peterson RA. A meta-analysis of variance accounted for and factor loadings in exploratory factor analysis. Market Lett. 2000;11(3):261 - 75.
275. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol. 2006;3(2):77-101.
276. Owens LA, Avalos G, Kirwan B, Carmody L, Dunne F. ATLANTIC DIP: closing the loop: a change in clinical practice can improve outcomes for women with pregestational diabetes. Diabetes Care. 2012;35(8):1669-71.
277. National Institute for Health and Care Excellence (NICE). Diabetes in pregnancy: management from preconception to the postnatal period. NICE Guideline NG3. NICE guideline [Internet]. 2015 [cited 2020 Jun 24]. Available from: nice.org.uk/guidance/ng3
278. van Onzenoort HA, Menger FE, Neef C, Verberk WJ, Kroon AA, de Leeuw PW, et al. Participation in a clinical trial enhances adherence and persistence to treatment: a retrospective cohort study. Hypertension. 2011;58(4):573-8.

279. Strutton R, Du Chemin A, Stratton IM, Forster AS. System-level and patient-level explanations for non-attendance at diabetic retinopathy screening in Sutton and Merton (London, UK): a qualitative analysis of a service evaluation. BMJ Open. 2016;6(5):e010952.
280. Hartnett ME, Key IJ, Loyacano NM, Horswell RL, Desalvo KB. Perceived barriers to diabetic eye care: qualitative study of patients and physicians. Arch Ophthalmol. 2005;123(3):387-91.
281. Taylor H, Anjou M. Annual update on the implementation of the roadmap to close the gap for vision [Internet]. Melbourne: Indigenous Eye Health, School of Population and Health, University of Melbourne; 2019 [cited 2020 Nov 20]. Available from: https://mspgh.unimelb.edu.au/centres-institutes/centre-for-health-equity/research-group/ieh/roadmap/annual-update
282. Abell SK, Boyle JA, de Courten B, Knight M, Ranasinha S, Regan J, et al. Contemporary type 1 diabetes pregnancy outcomes: impact of obesity and glycaemic control. Med J Aust. 2016;205(4):162-7.
283. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1989;107(2):237-43.
284. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. Diabetologia. 2001;44(2):156-63.
285. Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. Eye Vis (Lond). 2015;2:17.
286. Lake AJ, Rees G, Speight J. Clinical and psychosocial factors influencing retinal screening uptake among young adults with type 2 diabetes. Curr Diab Rep. 2018;18(7):41.
287. Salz DA, de Carlo TE, Adhi M, Moult E, Choi W, Baumal CR, et al. Select features of diabetic retinopathy on swept-source optical coherence tomographic angiography compared with fluorescein angiography and normal eyes. JAMA Ophthalmol. 2016;134(6):644-50.
288. Riddle MC, Gerstein HC, Cefalu WT. Maturation of CGM and Glycemic Measurements Beyond HbA1c-A Turning Point in Research and Clinical Decisions. Diabetes Care. 2017 Dec;40(12):1611-1613. doi: 10.2337/dci17-0049.
289. Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technol Ther. 2019 Feb;21(2):81-85. doi: 10.1089/dia.2018.0310.
290. Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, Rodbard D. The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c. J Diabetes Sci Technol. 2019 Jul;13(4):614-626. doi: 10.1177/1932296818822496.
291. Babaya N, Noso S, Hiromine Y, Taketomo Y, Niwano F, Yoshida S, Yasutake S, Kawabata Y, Ikegami H. Relationship of continuous glucose monitoring-related metrics with HbA1c and residual β-cell function in Japanese patients with type 1 diabetes. Sci Rep. 2021 Feb 17;11(1):4006. doi: 10.1038/s41598-021-83599-x.
292. Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. Acta Diabetol. 2013 Jun;50(3):437-42. doi: 10.1007/s00592-013-0459-9.

293. Lu J, Ma X, Zhou J, Zhang L, Mo Y, Ying L, Lu W, Zhu W, Bao Y, Vigersky RA, Jia W. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. Diabetes Care. 2018 Nov;41(11):2370-2376. doi: 10.2337/dc18-1131.
294. The National Diabetes Services Scheme. Having a healthy baby: a guide to planning and managing pregnancy for women with type 1 diabetes. In: NDSS, editor. 2015.
295. The National Diabetes Services Scheme. Having a healthy baby: a guide to planning and managing pregnancy for women with type 2 diabetes. In: NDSS, editor. 2015.
296. Williamson RL, McCarthy EA, Oats JJ, Churilov L, Lappas M, Shub A. Obstetric and perinatal outcomes for women with pre-existing diabetes in rural compared to metropolitan settings in Victoria, Australia. Aust N Z J Obstet Gynaecol. 2021. doi: 10.1111/ajo.13295.
297. Kelaher M, Ferdinand A, Taylor H. Access to eye health services among indigenous Australians: an area level analysis. BMC Ophthalmol. 2012;12:51. doi: 10.1186/1471-2415-12-51.
298. American Diabetes Association. Diabetic retinopathy. Diabetes Care. 2000;23 Suppl 1:S73-6.
299. Talks SJ, Manjunath V, Steel DH, Peto T, Taylor R. New vessels detected on wide-field imaging compared to two-field and seven-field imaging: implications for diabetic retinopathy screening image analysis. Br J Ophthalmol. 2015;99(12):1606-9.

SUPPLEMENTARY TABLES

Supplementary table S3-1. Quality score of eligible studies

Study	Eye exam timing		qual 1	qual 2	qual 3	qual 4	qual 5	qual 6	qual 7	qual 8	qual 9	qual 10	qual 11	qual 12	Quality score*	
	Early pregnancy	Late pregnancy													1†	2‡
T1DM only																
Arun, 2008	Trim 1 or 2	Trim 3	1	2	2	1	0	1	2	0	0	2	1	1	**10**	**14**
Axer-Siegel, 1996	around conception	during pregnancy	1	2	2	3	1	1	1	1	1	2	1	0	**12**	**16**
Buchbinder, 2000	Trim 1 or 2	early PP	1	2	2	1	0	0	2	1	1	0	0	1	**10**	**12**
Cassar, 1978	Trim 1 or 2		1	2	2	1	0	0	1	1					8	NA
Chew, 1995	Trim 1	early PP	1	2	2	3	0	1	2	1	1	2	1	1	**12**	**17**
Dibble, 1982	Trim 1	Trim 3	1	2	2	1	0	0	1	1	0	0	0	2	**10**	**12**
Gallen, 2008	unclear		1	2	0	0	0	0	0	0					3	NA
Horvat, 1980	Trim 1	during pregnancy	1	2	0	0	0	0	1	0	0	0	0	1	4	5
Irfan, 2004	Trim 1		1	2	0	0	0	0	0	1					4	NA
Jervell, 1979	around conception		1	2	0	0	0	0	0	0	0	0	0	0	NA	3
Jovanovic, 1984	Trim 1	Trim 3	1	2	2	1	0	0	0	1	1	0	0	2	NA	10
Kaaja, 1996	Trim 1		1	2	1	2	0	1	1	1					8	NA
Klein, 1990	Trim 1	Early PP	1	2	2	3	0	1	2	1	1	2	1	1	**12**	**17**
Laatikainen, 1980	Trim 1	Trim 3	1	2	2	1	0	1	1	1	1	0	1	2	**9**	**13**
Lapolla, 1998	Trim 1	Trim 3	1	2	2	1	0	0	2	1	1	2	0	2	**11**	**16**
Larinkari, 1982	Trim 1	Trim 3	1	2	2	1	0	1	0	1					8	NA
Lauszus, 2003	Trim 1	Trim 3	1	2	2	3	1	1	2	1	1	2	1	2	**13**	**19**
Loukovaara, 2003	Trim 1	Trim 3	1	2	2	3	0	1	2	1					**12**	NA
Maayah, 2001	around conception	during pregnancy	1	2	0	0	0	0	1	0	0	0	0	0	4	4
McElvy, 2001	Trim 1 or 2	Trim 3/early PP	1	2	2	1	0	1	2	1	1	0	1	1	**10**	**13**
Moloney, 1982	Trim 1	Trim 3	1	2	2	3	0	1	1	1					**11**	NA
Ohrt, 1984	Trim 1		1	2	0	0	0	0	0	0					2	NA

Study	Eye exam timing		qual 1	qual 2	qual 3	qual 4	qual 5	qual 6	qual 7	qual 8	qual 9	qual 10	qual 11	qual 12	Quality score*	
	Early pregnancy	Late pregnancy													1†	2‡
Phelps, 1986	Trim 1 or 2	Trim 3/early PP	1	2	2	2	0	1	2	1	1	0	1	1	**11**	**14**
Price, 1984	Trim 1	Trim 3	1	2	0	0	0	0	1	0					4	NA
Puza, 1996	Trim 1		1	2	0	0	0	0	1	0					6	NA
Rahman, 2007	Trim 1	Trim 3	1	2	0	0	0	1	2	1	0	2	1	2	7	**12**
Rosenn, 1992	Trim 1 or 2	Trim 3/early PP	1	2	2	1	0	1	1	1	1	0	1	1	**9**	**12**
Serup, 1986	Trim 1		1	2	0	0	0	0	0	0					4	NA
Temple, 2001	Trim 1	Trim 3	1	2	0	0	0	0	1	1	0	0	1	2	6	9
Vaarasmaki, 2002	Trim 1		1	2	0	0	0	1	1	1					6	NA
Vestgaard, 2010	Trim 1	Trim 3	1	2	2	3	0	0	2	1	1	0	1	2	**10**	**14**
T2DM only																
Rasmussen, 2010	Trim 1 or 2	Trim 3	1	2	2	3	0	1	2	1	1	2	1	2	**10**	**16**
Mixture of DM types																
Beetham, 1950	around conception	during pregnancy	1	2	0	0	0	0	1	1	0	0	0	0	2	2
Egan, 2015	Trim 1 or 2	during pregnancy	1	0	2	2	0	1	1	0	1	2	1	0	7	11
Hampshire, 2013	Trim 1	Trim 3	1	2	2	2	1	1	1	0	0	0	1	2	**10**	**13**
Makwana, 2018	Trim 1	Trim 3	1	1	2	1	0	0	2	0	0	2	0	1	8	11

- Good quality score: ≥9 for prevalence analysis and ≥12 for progression analysis

† Prevalence analysis

‡ Progression rate analysis

Abbreviations: NA, not applicable due to unavailable data; PP, postpartum; T1DM, type 1 diabetes; T2DM, type 2 diabetes; Trim, trimester.

Supplementary table S5-1. Comparison of characteristics between eye-visits with no photo/ ungradable photos and eye-visits with gradable photos

	Fundus photo unavailable or ungradable (N=75 eye-visits)	**Fundus photos gradable** (N=467 eye-visits)	***p*-value***
DR severity, n (%)			***<0.001***
None	***36 (51.4)***	***390 (83.5)***	
Mild NPDR	***20 (28.6)***	***56 (12.0)***	
Moderate NPDR	***2 (2.9)***	***12 (2.6)***	
Severe NPDR	***3 (4.3)***	***0***	
PDR	***9 (12.9)***	***9 (1.9)***	
DMO† [present], n (%)	***10 (15.9)***	***16 (3.7)***	***<0.001***

**p*-value relates to the difference between two groups examined using t-test, Wilcoxon rank-sum test or Fisher's exact test as appropriate to the distribution of each variable.
†Contributed data: 65 eye-visits without gradable photo and 452 eye-visits with gradable photo.
Abbreviations: DMO, diabetic macular oedema; DR, diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Supplementary table S5-2. Cardiac and other abnormalities observed among study participants' newborns and maternal complications

	N cases*
Cardiac abnormalities	
Ventricular septal defect	2
Heart valve defects	3
Hypertrophic cardiomyopathy	3
Left ventricular outflow tract obstruction	1
Aberrant subclavian right artery	1
Premature atrial ectopic's	1
Other abnormalities	
Birth trauma	4
Cystic kidney disease	1
Crossed fused renal ectopia	1
Thoracal-11 hemivertebra	1
Presumed congenital pneumonia	1
Meconium aspiration syndrome	1
Cyanotic episode	1
Apnoea of prematurity	1
Asymmetric (head-sparing) growth restriction	1
Maternal complications ("Other")	
Polyhydramnios	4
Oligohydramnios	1
Diabetic ketoacidosis	1
Urinary tract infection	1
Cardiac problems	3
Pyelonephritis postpartum	1
Cholestasis of pregnancy	1

* A mother or baby could have multiple problems per person

Supplementary table S7-1. Principal Component Factor Loadings for the 4-Component of CADEES Items

CADEES item (its Health Belief Model construct)	Component*			
	1	2	3	4
Having an eye exam once a year can help me prevent losing my eyesight (Be)	**0.56**	0.04	0.04	-0.01
I would benefit from having an eye exam every year. (Be)	**0.79**	-0.15	0.14	-0.01
I think it is important to have an eye exam every year (Be)	**0.75**	-0.10	0.07	0.04
Having a yearly eye exam will help me to save the eyesight I have now (Be)	**0.57**	0.08	0.26	-0.08
I want to get an eye exam every year (O)	**0.79**	-0.10	-0.01	0.02
I do not want to know if I have an eye disease (Ba)	-0.14	**0.53**	-0.12	-0.18
There is no treatment for diabetic eye diseases (Ba)	-0.05	**0.55**	-0.04	0.18
My family members or friends help me make doctor appointments (E)	0.27	**0.56**	0.10	-0.09
I cannot afford an eye exam (Ba)	-0.12	**0.67**	-0.28	0.00
I only seek eye care when I am having trouble with my vision (C)	-0.25	**0.67**	0.10	-0.14
I know a lot about diabetes and the effect it can have on health (E)	-0.09	-0.07	**0.66**	0.16
Diabetes can result in a loss of visual function (e.g., difficulty reading, driving) (Se)	0.04	0.06	**0.67**	-0.08
Diabetes can cause severe eye problems (Se)	0.20	-0.10	**0.54**	0.18
Diabetes can damage the blood vessels in the eye (Se)	0.22	-0.09	**0.59**	-0.10
Eye exams can find many different kinds of eye problems (Be)	0.30	-0.24	**0.56**	-0.04
Diabetic eye diseases often cause blindness (Se)	0.06	0.35	**0.51**	-0.08
My eyes are healthy (Su)	0.22	0.02	0.07	**0.53**
My overall general health is excellent (O)	-0.02	0.03	-0.02	**0.61**
I am confident I can control my blood sugar (E)	-0.02	-0.08	0.21	**0.64**
I have medical problems from diabetes (Se)	0.14	0.04	-0.02	**-0.63**

* loading cut-off 0.5

Abbreviations: Ba, Barriers; Be, Benefits; C, Cues to action; CADEES, Compliance with Annual Diabetic Eye Exams Survey; E, self-efficacy; O, others; Se, Severity; Su, susceptibility.

Supplementary table S7-2. Association of CADEES items with adherence to NHMRC guidelines (agreed in any strength compared to those who answered disagree or neutral), adjusted for self-reported DR status

Compliance with Annual Diabetic Eye Exams Survey Item	Odds of adherence, given that participant agreed with the item statement	
	Model 5	
	OR (95% CI)	*p*-value
NHMRC guidelines		
There are many eye doctors where I live (Q27)	***0.31 (0.14 - 0.67)***	***0.003***
My family members or friends help me make doctor appointments (Q28)	***2.57 (1.10 - 6.02)***	***0.029***
Study protocol		
I am confident I can control my blood sugar (Q30)	***0.23 (0.08 - 0.64)***	***0.005***
Getting an eye exam every year is not one of my top priorities (Q40)	***0.17 (0.04 - 0.77)***	***0.021***

Abbreviations: CADEES, Compliance with Annual Diabetic Eye Exams Survey; CI, confidence interval; NHMRC, National Health and Medical Research Council; OR, odds ratio.

Supplementary table S7-3. Health appointment priority ranking, by ethnicity groupings

	Asian (median [IQR])	**Caucasian (median [IQR])**	**Other (median [IQR])**	***p*-value**
Eye	5 (4 - 6)	4 (4 - 5)	5 (4 - 6)	0.897
Obstetrician	1 (1 - 2)	1 (1 - 2)	2 (1 - 3)	0.291
GP	4 (1 - 6)	4 (3 - 6)	4 (3 - 6)	0.165
Endocrinologist	***2 (2 - 5)***	***2 (1 - 2)***	***2 (1 - 3)***	***0.006***
Dietician	***4 (3 - 5)***	***6 (5 - 6)***	***5 (4 - 6)***	***0.002***
Diabetes educator	3 (3 - 5)	3 (3 - 5)	3 (2 - 4)	0.408
Podiatrist	7 (6 - 7)	7 (5 - 7)	6.5 (5 - 7)	0.511

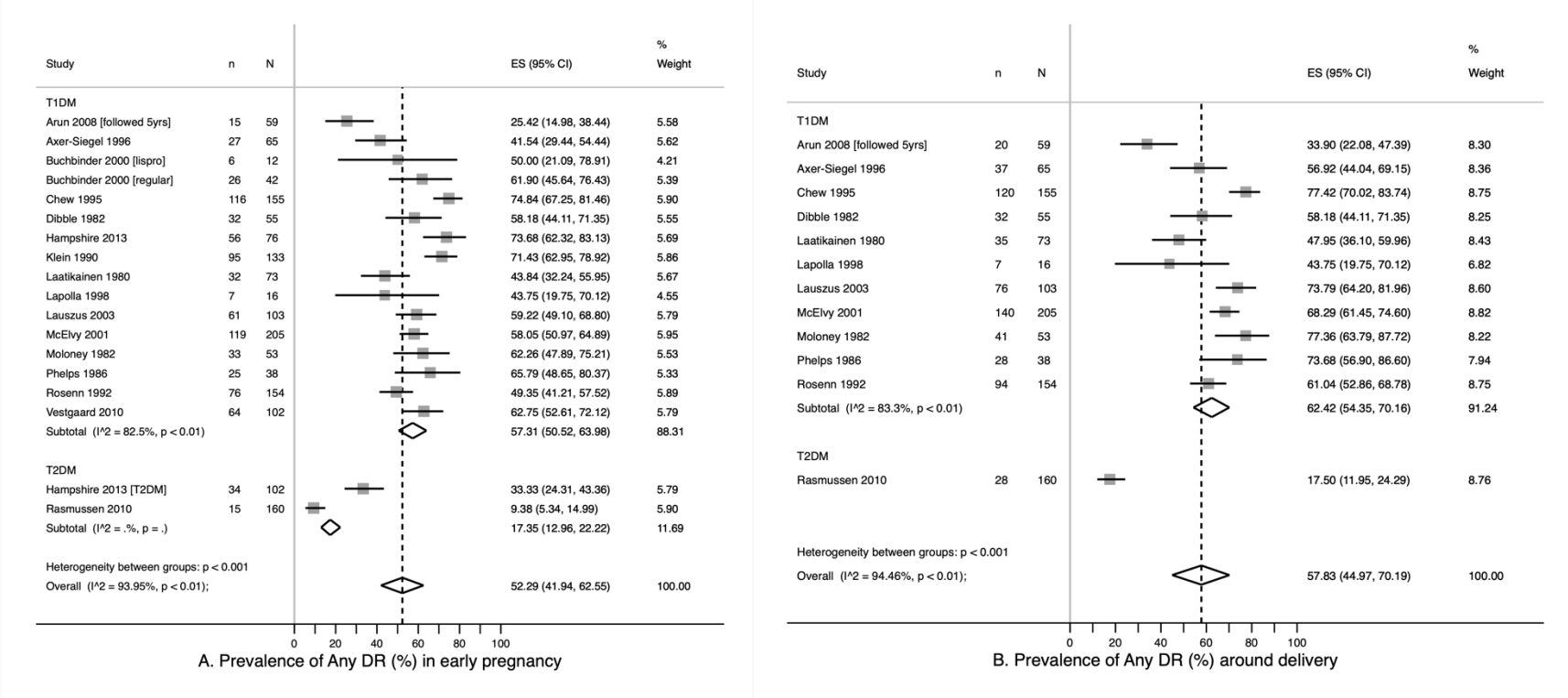
Abbreviations: GP, general practitioner; IQR, interquartile range.

Supplementary table S7-4. Health appointment priority ranking, by adherent and non-adherent groups

	NHMRC guidelines			**Study protocol**		
	Non-Adherent	**Adherent**	***p*-value**	**Non-adherent**	**Adherent**	***p*-value**
Eye	***5 (4 - 6)***	***4 (4 - 5)***	***0.024***	***5 (4 - 6)***	***4 (3 - 5)***	***0.004***
Obstetrician	1 (1 - 2)	2 (1 - 2)	0.479	1 (1 - 2)	2 (1 - 2)	0.291
GP	4 (3 - 6)	4 (3 - 6)	0.196	***4 (2 - 6)***	***5 (4 - 6.5)***	***0.019***
Endocrinologist	2 (2 - 3)	2 (1 - 3)	0.064	***2 (2 - 3)***	***1.5 (1 - 2)***	***0.002***
Dietician	5 (4 - 6)	6 (4 - 6)	0.803	5 (4 - 6)	5.5 (4 - 6)	0.986
Diabetes educator	3 (3 - 4)	4 (3 - 5)	0.260	3 (3 - 5)	4 (3 - 5)	0.327
Podiatrist	7 (6 - 7)	7 (6 - 7)	0.932	7 (6 - 7)	7 (6 - 7)	0.555

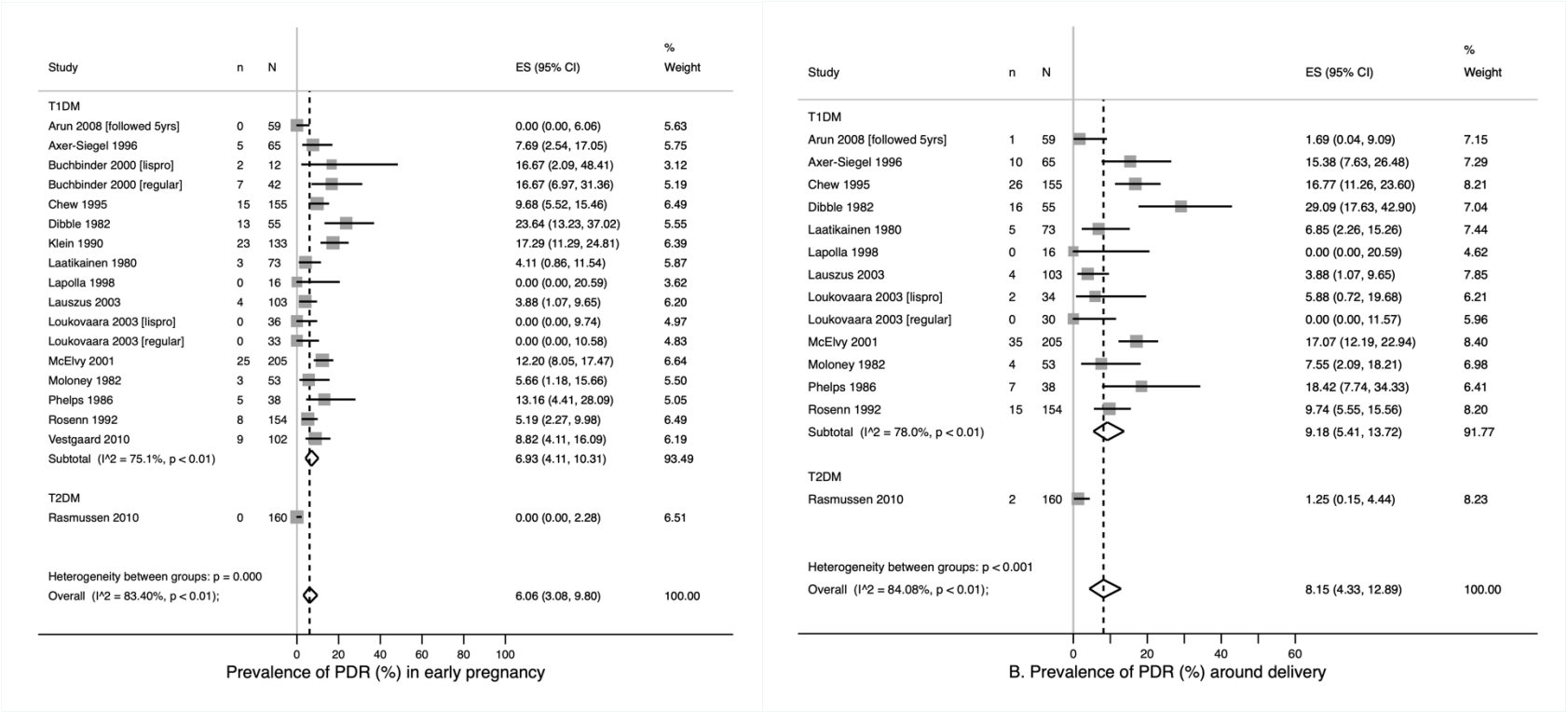
Abbreviations: GP, general practitioner; NHMRC, National Health and Medical Research Council.

SUPPLEMENTARY FIGURES



Supplementary figure S3-1. Forest plots of prevalence of any DR

A) In early pregnancy and **B**) around delivery using studies with similar quality (quality score for prevalence ≥ 9), by type of diabetes. Weights are from random effects analysis. Abbreviations: DR, diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.



Supplementary figure S3-2. Forest plots of prevalence of PDR

A) In early pregnancy and **B**) around delivery using studies with similar quality (quality score for prevalence ≥ 9), by type of diabetes. Weights are from random effects analysis. Abbreviations: DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; T1DM, type 1 diabetes; T2DM, type 2 diabetes.

APPENDICES

A1. Systematic Review Search Strategy

Medline/OVID

1 diabetic retinopathy.ti,ab. or diabetic retinopathy/ti, ab or diabetic retinopathy/
2 (pregnant or pregnancy).ti,ab. or pregnancy/
3 1 AND 2
4 limit 3 to (english language and humans)
5 limit 4 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or journal article or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or twin study)

Embase

1 diabetic retinopathy.ti,ab. or diabetic retinopathy/ti, ab or diabetic retinopathy/
2 (pregnant or pregnancy).ti,ab. or pregnancy/
3 1 AND 2
4 limit 3 to (human and english language and embase)
5 limit 4 to (article and journal)

Scopus

1 TITLE-ABS-KEY ("diabetic retinopathy")
2 TITLE-ABS-KEY (pregnant OR pregnancy)
3 #1 AND #2
4 #3 (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO(SRCTYPE,"j")) AND (LIMIT-TO (LANGUAGE, "English"))

A2. Methodological Quality Scoring

Item	Quality Criteria	Score
1	Appropriate method of **ascertaining diabetes prior to conception**. Appropriate inclusion of all persons with diabetes is important for accurate DR prevalence estimates. This may be defined based on a positive laboratory test (i.e. an oral glucose tolerance test or fasting blood glucose) and/or a self-reported history of physician's diagnosis and current diabetes treatment. A review of medical records or use of a national health registry to identify individuals with diabetes is also appropriate	**1 point** if method specifically described and prior to conception **0 points** if not described *(not included if not prior to conception, GDM excluded)*
2	Diabetes type is described and, if a mixture of types included in a study, the **data could be extracted separately for T1DM and T2DM**	2 points if type is described and DR grading data is published separately by DM type 1 point if type described and data can be extracted by type 0 if not described
3	Appropriate assessment of outcome. In this case, **retinal photography** must be **performed on all study participants** diagnosed with diabetes. *Retinal photography should not be limited to participants who have been diagnosed with DR from a clinical examination or where photographs served only as documentation of clinical findings*	2 points if all subjects 1 point if >=90% of subjects 0 if not performed for 90% of subjects or not at all
4	DR assessment: number **of eyes per person and retinal fields photographed**. *Studies that photographed only 1 randomly selected eye may miss detecting DR in the opposite eye. Studies that captured 1 field of 50 to 60-degree of retinal photos, they equal to more than 3 fields*[228]	**3 points** for 3 or more fields/eye and both eyes for <u>all subjects with fundus photography;</u> **2 points** for 3 or more fields/eye and both eyes for <u>>=90% subjects with fundus photography;</u> **2 points** of 2 fields/eye and both eyes for <u>all subjects with fundus photography</u>; **1 point** if only 1 field per eye, and both eyes for <u>all subjects with fundus photography</u>; **0 points** if no photos or only 1 eye per patient
5	Photos were graded more than once to reach **consensus**	1 point if graded by graders for consensus 0 point if not, or no photos.
6	DR grading was carried out by a dedicated, **trained grader or team of trained graders**	1 point if use of consistent, trained grader/team for all images 0 if many random graders 0 if not described

7	Grading of DR based on **standardized protocols** and definitions that can be comparable* to analysis categories 'none', 'NPDR', 'PDR', such as the ETDRS, modified Airlie House, WESDR, AAO or EURODIAB classification schemes. **(National Screening Committee retinopathy standards (UK) specifically not listed as their 'maculopathy' category confuses the retinopathy status)*	2 points if a well-accepted, comparable*, grading scheme was used 1 point if clearly describes their method but it is some other protocol 0 if not described
8	The **timing of baseline eye exam data/results** was specifically **described**	1 point if described 0 if not described
		Max total, prevalence: 13 pts
Extra elements relevant to the progression outcomes		
9	Appropriate assessment of outcome. In the case of progression outcomes, retinal photography/exam must be **performed at the same frequency** on all study participants. *Retinal photography during follow-up should not be limited to participants who had diagnosed DR at baseline or the frequency of follow-up photography should be the same in those with and without DR at baseline*	1 point if same frequency for all subjects 0 if frequency varied by initial clinical findings 0 if unclear or not described
10	**NPDR details**. DR grading scale has enough subtlety to detect the difference between mild and more severe grades of NPDR (thus the ability to detect progression/worsening <u>*within*</u> the NPDR grades)	2 points if follow-up data reported for differing severities of NPDR 0 if not reported or not described
11	DR grading was carried out **over follow-up time** by a dedicated, **trained grader or team of trained graders**	1 point if use of consistent, trained grader/team for all images 0 if many random graders 0 if not described
12	The **timing of follow-up** eye examination data/results was specifically described	2 points if described and baseline was 1st trimester (<14 weeks) and follow-up was in the 3rd trimester 1 point if timing described and baseline was mostly <22 weeks and follow-up was in the 3rd trimester or just after delivery (<12 weeks post-partum) 0 points if not described *(other timepoints were excluded)*
		Max total, progression: 19 pts

A3. Ethical Approvals and Amendments

The Behavioural and Social Sciences Human Ethics Sub-Committee, University of Melbourne

THE UNIVERSITY OF MELBOURNE

08 August 2017

A/Prof L.L. Lim
Ophthalmology Eye and Ear Hospital
The University of Melbourne

Dear A/Prof Lim

I am pleased to advise that the Behavioural and Social Sciences Human Ethics Sub-Committee has approved the following Project:

Project title:	**Natural History of Diabetic Retinopathy in Pregnant Women**
Researchers:	**A/Prof L L Lim, Dr S H Qureshi, A/Prof D J Guest, A/Prof A J Nankervis, A/Prof J J Conn, Dr R C Symons, F Widyaputri**
Ethics ID:	**1749108**

The Project has been approved for the period: **08-Aug-2017 to 31-Dec-2017**

It is your responsibility to ensure that all people associated with the Project are made aware of what has actually been approved.

Research projects are normally approved to 31 December of the year of approval. Projects may be renewed yearly for up to a total of five years upon receipt of a satisfactory annual report. If a project is to continue beyond five years a new application will normally need to be submitted.

Please note that the following conditions apply to your approval. Failure to abide by these conditions may result in suspension or discontinuation of approval and/or disciplinary action.

(a) **Limit of Approval:** Approval is limited strictly to the research as submitted in your Project application.

(b) **Variation to Project:** Any subsequent variations or modifications you might wish to make to the Project must be notified formally to the Human Ethics Sub-Committee for further consideration and approval. If the Sub-Committee considers that the proposed changes are significant, you may be required to submit a new application for approval of the revised Project.

(c) **Incidents or adverse effects:** Researchers must report immediately to the Sub-Committee anything which might affect the ethical acceptance of the protocol including adverse effects on participants or unforeseen events that might affect continued ethical acceptability of the Project. Failure to do so may result in suspension or cancellation of approval.

(d) **Monitoring:** All projects are subject to monitoring at any time by the Human Research Ethics Committee.

(e) **Annual Report:** Please be aware that the Human Research Ethics Committee requires that researchers submit an annual report on each of their projects at the end of the year, or at the conclusion of a project if it continues for less than this time. Failure to submit an annual report will mean that ethics approval will lapse.

(f) **Auditing:** All projects may be subject to audit by members of the Sub-Committee.

If you have any queries on these matters, or require additional information, please contact me using the details below.

Please quote the ethics ID number and the title of the Project in any future correspondence.

On behalf of the Sub-Committee I wish you well in your research.

Yours sincerely

Mr Tony Callahan
Secretary, Behavioural and Social Sciences HESC
Phone: 8344 2067, Email: t.callahan@unimelb.edu.au

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The Human Research Ethics Committee (HREC) of Royal Women's Hospital

Mr Arthur Hui
Manager
Research and Ethics Secretariat
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www.thewomens.org.au

16.11.17

Dr F Widyaputri
Centre for Eye Research Australia
Royal Victorian Eye and Ear Hospital
Peter Howson Wing, Level 7
32 Gisborne Street, East Melbourne Vic 3002

Dear Dr Widyaputri,

Re: Project 17/26 – Natural history of Diabetic Retinopathy in pregnant women

Thank you for submitting the amendments as requested by the RWH Human Research Ethics Committee.

I confirm the project is now approved.

Enclosed please find Project Approval and Notification of Project Commencement Forms for your record.

Please note that the RWH Human Research Ethics Committee has now agreed that GCP training should be mandatory for all principal investigators. The Committee also strongly encourages GCP training for other associate investigators and student researchers.

To this end, please forward a copy of your and other Investigators' (Principal & Associate Investigators as well as Student researchers) current GCP Training Certificate for my record.

Please return the completed Notification of Project Commencement Form to me when the project begins.

Yours sincerely,

A. C. B. Hui
Manager
Research and Ethics Secretariat

Encl:

THE ROYAL WOMEN'S HOSPITAL

RESEARCH AND HUMAN RESEARCH ETHICS COMMITTEES

PROJECT APPROVAL

PROJECT NO:	**17/26**
PROJECT TITLE:	Natural history of Diabetic Retinopathy in pregnant women
INVESTIGATOR (S):	L Lim, A Symons, D Guest, A Nankervis, J Conn, F Widyaputri
DATE OF APPROVAL:	16 November 2017
ANTICIPATED DURATION:	Thirty six (36) months

SIGNED 16.11.2017

Secretary, Research & Human Research Ethics Committees **DATE**

CONDITIONS OF APPROVAL

The Principal Investigator is reminded of the following:-

1. ***GCP training is mandatory for all principal investigators. The Human Research Ethics Committee also strongly encourages GCP training for other associate investigators and student researchers.***
2. ***Prior to commencement of the project, you must contact the relevant RWH Divisional Directors / Department Heads to confirm your actual commencement date. Failure to inform these RWH personnel may jeopardise their approval and support for your project.***
3. ***A Project may commence once the Principal Investigator has received written confirmation that the Human Research Ethics Committee has approved the Project.***
4. ***Substantial changes in protocols must be submitted to the Research/Human Research Ethics Committees for approval.***
5. ***Progress reports must be submitted annually. A request will be forwarded to the Principal Investigator. If no report is supplied, permission to continue the project may lapse.***
6. ***The Research/Human Research Ethics Committees must be notified IMMEDIATELY of any untoward or unexpected complications or side affects arising during the project or of any ethical or medico-legal problems that may arise.***
7. ***Consent forms must be available for audit and retained on file for at least five (5) years.***
8. ***Raw data and details of analysis must be retained by the Principal Investigator for at least five (5) years.***
9. ***Principal Investigator MUST upon leaving the Institution, inform the Human Research Ethics Committee as to the nominated person to replace him/her.***

PLEASE QUOTE PROJECT NO. AND TITLE FOR ALL CORRESPONDENCE

Mr Arthur Hui
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Research and Ethics Secretariat
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29.4.19

Dr F Widyaputri
Centre for Eye Research Australia
Royal Victorian Eye and Ear Hospital
Peter Howson Wing, Level 7
32 Gisborne Street, East Melbourne Vic 3002

Dear Dr Widyaputri,

Re: Project 17/26 – Natural history of Diabetic Retinopathy in pregnant women

Thank you for the letter dated 1.3.19 from Associate Professor L Lim requesting to add an optional survey to all current participants who have agreed to attend ophthalmic screening and to those who decline to attend ophthalmic visits but are agreeable to complete a short survey (new recruits).

I wish to inform you that this was approved by the RWH Human Research Ethics Committee at its meeting held on 17.4.19 subject to the following suggestions.

In relation to the Survey Participant Information Sheet and Consent Form, the RWH Human Research Ethics Committee made the following suggestions:

1. Under Section 'What will I be asked to do?' --- Second last sentence

   Suggest consider amending "The survey will take no more than 10 minutes of your time" to "The survey will take approximately 10 to 15 minutes of your time."

2. Under Section 'What will happen to information about me?' --- Second sentence, last paragraph

   Suggest amending it to read "If you agree, your anonymous data may also be used in the future for studies with a similar purpose."

3. Please consider adding the details of a RWH contact person in the Statement.

Please therefore amend the Participant Information Sheet and Consent Form and send me an amended copy for my record.

Yours sincerely,

A C B Hui
Manager
Research and Ethics Secretariat

The HREC of Melbourne Health

MELBOURNE HEALTH

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MELBOURNE HEALTH HUMAN RESEARCH ETHICS COMMITTEE

ETHICAL APPROVAL

A/Prof Lyndell Lim

09 March 2018 (Updated 16 March 2018)

Dear A/Prof Lyndell Lim,

HREC Reference Number: HREC/17/MH/430

Melbourne Health Site Reference Number: 2018.019

Project Title: Natural History of Diabetic Retinopathy in Pregnant Women

---

I am pleased to advise that the above project has **received ethical approval** from the Melbourne Health Human Research Ethics Committee (HREC). The HREC confirms that your proposal meets the requirements of the National Statement on Ethical Conduct in Human Research (2007). This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Human Research (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

HREC Approval Date: 1 March 2018

Ethical approval for this project applies at the following sites:

Site
The Royal Melbourne Hospital
Austin Hospital

Approved Documents:

The following documents have been reviewed and approved:

Document	Version	Date
Protocol	4.2	21 February 2018
Master Participant Information Sheet and Consent Form	4.1	25 January 2018
Follow-up Form	4.1	25 January 2018
GP Consultant Info Sheet	4.1	25 January 2018
Poster	4.1	25 January 2018
Serious Adverse Event Report	4.1	25 January 2018
Questionnaire	4.1	25 January 2018

First in Care, Research and Learning

The Royal Melbourne Hospital

NorthWestern Mental Health

Doherty Institute

Referral Letter	4.1	25 January 2018
Report Letter	4.1	25 January 2018
Summary of the Study	2	25 January 2018

Governance Authorisation:

Governance Authorisation is required at each site participating in the study before the research project can commence at that site.

You are required to provide a copy of this HREC approval letter to the principal investigator for each site covered by this ethics approval for inclusion in the site specific assessment application.

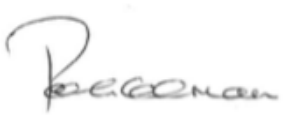
Conditions of Ethics Approval:

- You are required to submit to the HREC:
    - An Annual Progress Report (that covers all sites listed on approval) for the duration of the project. This report is due on the anniversary of HREC approval. Continuation of ethics approval is contingent on submission of an annual report, due within one month of the approval anniversary. Failure to comply with this requirement may result in suspension of the project by the HREC.
    - A comprehensive Final Report upon completion of the project.
- Submit to the reviewing HREC for approval any proposed amendments to the project including any proposed changes to the Protocol, Participant Information and Consent Form/s and the Investigator Brochure.
- Notify the reviewing HREC of any adverse events that have a material impact on the conduct of the research in accordance with the NHMRC's Safety Monitoring and Reporting in Clinical Trials Involving Therapeutic Goods (2016) guideline.
- Notify the reviewing HREC of your inability to continue as Coordinating Principal Investigator.
- Notify the reviewing HREC of the failure to commence the study within 12 months of the HREC approval date or if a decision is taken to end the study at any of the sites prior to the expected date of completion.
- Notify the reviewing HREC of any matters which may impact the conduct of the project.
- If your project involves radiation, you are legally obliged to conduct your research in accordance with the Australian Radiation Protection and Nuclear Safety Agency Code of Practice 'Exposure of Humans to Ionizing Radiation for Research Purposes' Radiation Protection series Publication No.8 (May 2005)(ARPANSA Code).

Please note: Template forms for reporting Amendments, safety reporting, Annual/Final reports, etc. can be accessed from: https://www2.health.vic.gov.au/about/clinical-trials-and-research/clinical-trial-research/monitoring-reporting

The HREC may conduct an audit of the project at any time.

Yours sincerely,



Prof Peter Colman
Chair – Melbourne Health Human Research Ethics Committee (HREC)

MELBOURNE HEALTH

Office for Research
The Royal Melbourne Hospital
Level 2 South West
300 Grattan Street
Parkville VIC 3050
Australia

Telephone: +61 3 9342 8530
Facsimile: +61 3 9342 8548
Email: research@mh.org.au
thermh.org.au
ABN 73 802 706 972

APPROVAL OF AMENDMENT

10 October 2018

Dear A/Prof. Lyndell Lim,

HREC Reference Number: HREC/17/MH/430
Local Project Number: 2018.019

Research Title: Natural History of Diabetic Retinopathy in Pregnant Women

Type of review: Ethics Review Only

I am pleased to advise that the amendment to the above project has been reviewed and approved by the Melbourne Health HREC. This approval applies to all sites for which the Melbourne Health HREC has issued ethical approval. This HREC is organised and operates in accordance with the National Health and Medical Research Council's (NHRMC) National Statement on Ethical Conduct in Human Research (2007), and all subsequent updates, and in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988 (and subsequent Guidelines).

Amendment Approval Date: 10 October 2018

Approved Documents: Ethics approval

- Protocol, Version 5, dated 10 October 2018
- Modified Compliance with Annual Diabetic Eye Exams Survey, Version 1.2, dated 17 July 2018
- PICF, Version 5.1, dated 02 March 2018
- Survey PICF, Version 1.0, dated 10 September 2018

Please refer to the Melbourne Health Office for Research website to access guidelines and other information and news concerning research at: https://www.thermh.org.au/research/researchers

Please Note: Template forms for reporting Amendments, Adverse Events, Annual Report/Final Reports, etc. can be accessed from: https://www2.health.vic.gov.au/about/clinical-trials-and-research/clinical-trial-research/monitoring-reporting

For any queries about this matter, please contact the HREC Manager on 03 9342 8530 or via email on: research@mh.org.au

Yours sincerely,

Professor Peter Colman
Chair – Melbourne Health Human Research Ethics Committee (HREC)

First in Care, Research and Learning

The Royal Melbourne Hospital

Doherty Institute

The HREC of Mercy Health

Mercy Hospitals Victoria Ltd
Level 2, 12 Shelley Street
Richmond Vic 3121
Phone: +61 3 8416 7777
Fax: +61 3 8416 7888
mercyhealth.com.au

14 May 2018

Dr Felicia Widyaputri
PhD student
Centre for Eye Research Australia
Level 7, Peter Howson Wing
32 Gisborne Street
East Melbourne VIC 3002

Dear Dr Widyaputri,

Re: 2018-009: Natural History of Diabetic Retinopathy in Pregnant Women.

I am pleased to advise that the Mercy Health Human Research Ethics Committee meeting held on the 8th of May **endorsed the approval** of the above research proposal. It was noted that the study had formerly received expedited approval from the Mercy Health HREC Expedited Review Working Party.

The Mercy Health Human Research Committee has granted approval of research until **27th of April 2019**.

The Human Research Ethics Committee is constituted and functions in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007- updated May 2015).

In accordance with the NHMRC Guidelines, approval is subject to:

1. Immediate notification to the Administrative Officer, Human Research Ethics Committee and sponsor, of any unforeseen events that may affect the continuing ethical acceptability of the project;
2. Notification and reasons for ceasing the project prior to its expected date of completion;
3. The completion of a progress report at 6 months and then annually for the duration of the project.
4. Human Research Ethics Committee approval of any proposed modifications to the project;
5. The submission of a final report and papers published on completion of the project.

Please also note:

6. The Principal Investigator upon leaving the Institution must inform the Human Research Ethics Committee as to the nominated person to replace him/her.

In future correspondence please quote the given project number: **2018-009.**

Extensions:

If an extension of ethics approval is required, the HREC office must be contacted before the ethics approval runs out. Your request must be accompanied with a current progress report.

Continuation of ethics approval is contingent on submission of an annual progress report. Failure to comply with this requirement may result in suspension of this research. A progress report form has been emailed with this letter.

Amendments:

Amendments to approved research can be made at any time. Amendments must be submitted with a Mercy Health Amendment Request Form and copies of any additional or amended documentation with tracked changes. A blank copy has been emailed with this letter.

If you have any queries, please do not hesitate to contact Ms Natasha Rooney, Administrative Officer Mercy Health Human Research Ethics Committee on 8458 4808 or email ethics@mercy.com.au.

Yours sincerely,

Mr Tim O'Leary

Chair, Mercy Health Human Research Ethics Committee

Mercy Hospitals Victoria Ltd
Level 2, 12 Shelley Street
Richmond Vic 3121
Phone: +61 3 8416 7777
Fax: +61 3 8416 7888
mercyhealth.com.au

10th September 2019

Dr Alexis Shub
Diabetes and Endocrine Clinic
Mercy Women Hospital
163 Studley Road
Heidelberg
Vic 3084

Dear Dr Shub,

Re. **2018-009:** Natural History of Diabetic Retinopathy in Pregnant Women

I am pleased to advise that the amendments to this approved research was approved by the HREC meeting on 13th August 2019.

This approval is effective immediately.

In particular, the following documents were approved:

Document	Version	Date
• Patient Information Sheet and Consent Form Research Protocol	Version 6.1	21/5/19
• Participant Information Sheet and Consent Form	Version 1.1	10/5/19
• Form for Withdrawal of Participation	Version 1.1	10/5/19
• Modified CADEES Survey,	Version 1.2	17/7/18

This approval is effective immediately and enables you to continue the study.

Continuation of ethics approval is contingent on submission of an annual report. Failure to comply with this requirement may result in suspension of this research.

Should you require an extension of ethics approval, the HREC office must be contacted before the ethics approval runs out and your request must be accompanied with a current progress report.

Mercy Health
Care first

In accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007- updated 2018), approval is subject to:

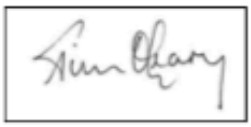
- Immediate notification to the Administrative Officer, Human Research Ethics Committee and sponsor, of any serious adverse effects on participants;
- Immediate notification of any unforeseen events that may affect the continuing ethical acceptability of the project;
- Notification and reasons for ceasing the project prior to its expected date of completion;
- The completion of a progress report annually for the duration of the project;
- Human Research Ethics Committee approval of any proposed modifications to the project;
- The submission of a final report and papers published on completion of the project.

Please also note:

- Consent Forms must be available for audit by the Human Research Ethics Committee and retained for the period required by law;
- The Principal Investigator upon leaving the Institution must inform the Human Research Ethics Committee as to the nominated person to replace him/her.

If you have any queries, please do not hesitate to contact Rati Ramnauth, Administrative Officer on 8458 4808 or email ethics@mercy.com.au.

Yours sincerely,



Mr Tim O'Leary

Chair, Mercy Health Human Research Ethics Committee

search Ethics Committee

Compassion Hospitality Respect Innovation Stewardship Teamwork

A4. Patient information and consent form

Royal Women's Hospital site

Participant Information Sheet

Natural History of Diabetic Retinopathy in Pregnant Women

Department of Surgery, Department of Optometry and Vision Sciences
University of Melbourne
Diabetes and Endocrine Service, Royal Women's Hospital

Coordinating Investigator	**A/Prof. Lyndell Lim** Department of Surgery (Ophthalmology) The University of Melbourne Email: limllp@unimelb.edu.au
Principal Investigator	**A/Prof. Andrew Symons** Department of Surgery (Ophthalmology) Department of Optometry and Vision Sciences The University of Melbourne Email: andrew.symons@mh.org.au
Principal Investigator	**A/Prof. Daryl Guest** Department of Optometry and Vision Sciences The University of Melbourne Email: daryl.guest@unimelb.edu.au
Principal Investigator	**A/Prof. Alison Nankervis** Diabetes and Endocrine Service The Royal Women's Hospital Email: alison.nankervis@mh.org.au
Co-Investigator	**A/Prof. Jennifer Conn** Diabetes and Endocrine Service The Royal Women's Hospital Email: jjconn@unimelb.edu.au
Co-Investigator (PhD student)	**Dr. Felicia Widyaputri** Department of Surgery (Ophthalmology) The University of Melbourne Email: widyaputrif@unimelb.edu.au

Introduction

Thank you for your interest in participating in this research project which aims to investigate the nature of Diabetic Retinopathy (a form of diabetic eye disease) during pregnancy.

The following few pages will provide you with further information about the project, the possible risks and benefits of participating this study, so that you can decide if you would like to take part in this research.

Please note that your participation is **voluntary**. If you don't wish to take part, you don't have to. If you join the study you can stop at any time. Your decision to participate (or not) in this study will have no influence on the clinical care and management that you will receive.

What is this research about?

Diabetic Retinopathy (DR) is a sight threatening disease, which may occur in people with type 1 or type 2 diabetes. This disease results from diabetes causing damage to a delicate part of the eye called the retina, which functions inside your eye to make an image similarly to the way a film acts within a camera. Your retina can become severely damaged before you notice any problems with your eyes or vision. It is thought that in some people this damage may occur even faster during pregnancy. However, we are not yet sure whether this is definitely the case. We are also not sure if there are any risk factors, or reasons, that may cause diabetic retinopathy to worsen faster in some pregnant women than in others.

The aim of our study is to address these knowledge gaps by collecting routine clinical data from pregnant diabetic patients who attend routine, standard eye examinations throughout their pregnancy and after delivery. These eye examinations are exactly as recommended by the NHMRC, a government organisation that oversees healthcare in Australia. By taking part in this study, we will therefore help ensure that you get the eye care that you need.

Approximately 100 participants will be recruited in this study.

What will I be asked to do?

Should you agree to participate, your General Practitioner (GP) or Obstetrician will refer you to University of Melbourne Eye Clinic, UMeyecare (located at Shop 2, 800 Swanston Street, Carlton, Victoria, 3053), to get comprehensive eye examinations during your pregnancy and for up to 1 year after delivery. If you cannot travel to UMeyecare, the eye examinations can be done at Royal Melbourne Hospital. Also, if you wish, you may continue to have your eye examinations at the University of Melbourne clinic or Royal Melbourne Hospital after your involvement in the study is complete. The examination will be scheduled once in each trimester (3-monthly of the pregnancy) and at 3, 6 and 12 months after delivery. If you are recruited during your pre-pregnancy care, an additional eye examination will be done during this period. To help organise and remind you of these appointments, Dr Felicia Widyaputri, our study co-ordinator, or a representative of the UMeyecare clinic will make contact by email or SMS or phone prior to each of your scheduled appointments.

At your first visit, you will be asked to read and sign this Patient Information and Consent Form. If you decide to participate you will need to sign the consent form. After consenting, you will be asked about your general medical history, including your diabetic and pregnancy status, in addition to details regarding your vision and eye health. We will also obtain other information regarding your diabetes control and other medical data from your GP or Obstetrician.

At every visit, your weight and blood pressure will be measured, and your eye examination will be performed (detailed in table). Routine blood and urine tests will also be scheduled in conjunction with your GP or Obstetrician. We will use either the Royal Women's Hospital pathology service or any other pathology service of your choice. As it is standard routine care, the testing will be covered by Medicare.
Please note: all procedures are part of routine clinical care of pregnant diabetic patient and will take approximately an hour to complete.

Procedure	Things to do
Vision (visual acuity) test	You will be tested by reading letters on a screen.
Eye examination	The front part of your eyes and your retinas will be examined using standard techniques using a "slit lamp" and by ophthalmoscopy. Your pupils will be dilated as part of this study, if there is no contraindication (A condition which makes the procedure potentially inadvisable).
Fundus (retina) imaging	We will take photos of the retina. This is a non-invasive imaging technique (i.e. it does not require any injections or radiation). You will be asked to position your chin on the chin rest of a retina camera and stare directly ahead at the blinking spot inside the camera. There will be a flashing light when the examiner captures the image of your retina. It will be done in both eyes.
Optical coherence tomography (OCT) & Optical coherence tomography Angiography (OCTA)	These are specialised photos of the retina that make use of a non-invasive imaging technique that is very similar to retinal photography detailed above. This image helps us to determine whether there is any swelling of the retina due to diabetes and examines the blood vessels in the eye to detect early signs of vessel abnormalities. The procedure is much the same as fundus (retina) imaging detailed above.

What are the possible benefits?

By participating in this study, you will receive diabetic eye-screening examinations in pre-pregnancy state (if applicable), in each trimester of pregnancy and until 12-months after delivery for free. Having eye screening early in your pregnancy can benefit you by providing not only information about your eye health, but also about the impact of your sugar control on your body. If we detect any sign of new, or progressive diabetic retinopathy we will inform your GP or Obstetrician so your diabetic management can be adjusted where appropriate. If potentially sight threatening diabetic retinopathy is

detected that needs review by an ophthalmologist or treatment, you will be immediately referred to the Ophthalmology Department at the Royal Melbourne Hospital to receive treatment. The UMeyecare clinic can refer you to another ophthalmologist if that is your preference.

There may or may not be benefits to you for participating in this study. There will be no reimbursement of travel expenses or any other reward. You will however be receiving, at minimum, standard of care for your condition. Broadly, this study will benefit society by providing findings that may help inform the future care of pregnant patients with diabetes and diabetic retinopathy by:

1. Determining the number of people with diabetic retinopathy during pregnancy and early post delivery period. This will in turn inform the development of updated specific guidelines on ophthalmic screening and care during pregnancy.
2. Identification of risk factors that may accelerate the progression of diabetic retinopathy. This in turn will also contribute to the development of updated screening procedures and may also identify factors that may be treatable in order to reduce the risk of diabetic retinopathy progression.
3. Determining the rate of progression of diabetic retinopathy during pregnancy and whether it spontaneously improves after delivery may help inform how aggressively sight threatening diabetic retinopathy is treated at different stages of pregnancy.

What are the possible risks?

In case you haven't done your standard routine blood and urine examination, your GP or Obstetrician will ask the research team to organize it. The test will be taken by the pathology service of your choice. You may feel some pain when the blood is drawn (<5ml, or the volume of a tablespoon, will be taken). There is a small chance that the needle will cause bleeding, a bruise or an infection at the puncture site. Some people may feel faint or dizzy, when blood is drawn but this usually passes very quickly.

As part of the testing the pupils of your eyes will be dilated using eye-drops. You may experience reduced ability to focus and increased glare and difficulty with your vision for about three hours after your visit. It would be preferable for you not to drive during this period. Pupil dilatation very occasionally causes the development of high pressures in the eyes. Therefore, pupil dilatation will only be performed after examination of your eyes has shown that the risk of this occurring is negligible.

The dilating eye drops (1% Tropicamide) have been assessed by Australian Government Department of Health and does not carry additional risk to your baby. The use of this eye-drop is included in standard care for diabetic eye screening examination as recommended by National Health and Medical Research Council of Australia. To further minimise the risk, you will be asked to close your eyes and press the inner corner of your eyes immediately after the eye drop is given.

Do I have to take part?

No. Participation is **completely voluntary**. You are able to withdraw (quit) at any time without penalty and it will not affect your care. You may still have eye examinations at UMeyecare even if you are not part of the study.

Will I hear about the results of this project?

The result of this study may be published as journal articles and/or presented at conferences. We will also make copies of these articles available to you either in print (posted) or via email.

What will happen to information about me?

By signing the consent form you consent to the researchers collecting and using personal information about you for the research project. Full confidentiality of your medical data will be kept by the researchers, your GP or Obstetrician, the pathology service and by the staff of UMeyecare and Royal Melbourne Hospital - that is, by all people involved with the study. All personal data used in the research study will be anonymous and will be coded with a study identity and patient number (Example: DRP001) that will be assigned to you at the beginning of the study.

Study records will be retained for 15 years after the completion of the study and only can be accessed by the researchers. Your anonymous data may also be used in the future for studies with a similar purpose. A report may be published; however, you will not be able to be identified in any publications or reports that arise from this study, as your identity will always be kept confidential in any such publication(s).

Where can I get further information?

If you have any further questions about this project or any medical problems which may be related to your involvement in the project (for example, any side effects), please contact the researchers; A/Prof Lyndell Lim (Email: limllp@unimelb.edu.au) or Dr. Felicia Widyaputri (Ph: 0424902612, email: widyaputrif@unimelb.edu.au)

Who can I contact if I have any concerns about the project?

This research project has been approved by the Human Research Ethics Committee of The University of Melbourne (Ethics ID: 1749108), The Royal Women's Hospital (Ethics ID: 17/26), and The Royal Melbourne Hospital (Ethics ID: 2018.019). If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact:

1. The Manager, Human Research Ethics, Office for Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Email: HumanEthics-complaints@unimelb.edu.au.
   Or
2. Royal Women's Hospital Consumer Advocate. Tel: +61 3 8345 2290
   Or
3. The Complaints Manager, Director Research Governance and Ethics, Royal Melbourne Hospital. Tel: +61 3 9342 8530 or email: Research@mh.org.au

All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project.

Consent Form

Natural History of Diabetic Retinopathy in Pregnant Women

Departments of Surgery, Department of Medicine
Department of Optometry and Vision Sciences
University of Melbourne

Coordinating Investigator: A/Prof. Lyndell Lim

Name of Participant: _____

1. I consent to participate in this project, the details of which have been explained to me, and I have been provided with a written patient information to keep.
2. I understand that the purpose of this research is to investigate the nature of Diabetic Retinopathy (a form of diabetic eye disease) during pregnancy and after delivery.
3. I understand that my participation in this project is for research purposes.
4. I acknowledge that the possible effects of participating in this research project have been explained to my satisfaction.
5. I understand that this project will involve scheduled visits throughout my pregnancy and for up to one year after delivery. These visits will generally occur at the University of Melbourne eye clinic, UMeyecare, but in special circumstances may be able to be scheduled at The Royal Melbourne Hospital. Routine eye examination will be done and all the procedures have been explained to me. I will provide relevant medical data that is required in the study. I also understand that my previous medical data may be provided by my GP or Obstetrician.
6. I understand that my participation is voluntary and that I am free to withdraw from this project at anytime without explanation or prejudice and to withdraw any unprocessed data that I have provided.
7. I understand that the data from this research will be stored at the University of Melbourne for a minimum of fifteen years after the completion of the study.
8. I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements; my data will be password protected and accessible only by researchers approved by the Human Research Ethics Committee.
9. I am aware and give my approval for my anonymous data to be used in the future for studies with a similar purpose?

   ☐ **Yes** ☐ **No** (please tick)
10. I understand that after I sign and return this consent form, it will be retained by the University.

I have read, or have had read to me, and I understand the Participant Information and Consent Form for persons participating in a research project, Version 4.1 dated 25 January 2018.

If available, I wish to receive a copy of the summary report on the research findings?

☐ **Yes** ☐ **No** (please tick)

If Yes, please provide us with an email address to send this to:

_____

Participant Signature: _____ Date: _____

Printed name of researcher _____

Signature _____ **Date** _____

(To be signed and dated by the person who conducted the informed consent process)

Form for Withdrawal of Participation

Natural History of Diabetic Retinopathy in Pregnant Women

Departments of Surgery, Department of Medicine
Department of Optometry and Vision Sciences
University of Melbourne

Coordinating Investigator: A/Prof. Lyndell Lim

Declaration by Person Responsible

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me.

Participant's Name (printed) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the person responsible for the participant has understood that explanation.

Researcher's Name (printed) _____

Signature _____ Date _____

[†] A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

Mercy Hospital for Women site

Participant Information Sheet

Natural History of Diabetic Retinopathy in Pregnant Women

Departments of Surgery (Ophthalmology), Optometry and Vision Sciences
University of Melbourne Diabetes and Endocrine Clinic, Mercy Hospital
Department of Surgery (Ophthalmology), Austin Hospital

Coordinating Investigator	**A/Prof. Lyndell Lim** Department of Surgery (Ophthalmology) The University of Melbourne Email: limllp@unimelb.edu.au
Principal Investigator	**A/Prof. Andrew Symons** Department of Surgery (Ophthalmology) Department of Optometry and Vision Sciences The University of Melbourne Email: andrew.symons@mh.org.au
Principal Investigator	**Dr. Alexis Shub** Diabetes and Endocrine Clinic The Mercy Hospital for Women Email: ashub@unimelb.edu.au
Principal Investigator	**Dr. Xavier Fagan** Department of Surgery (Ophthalmology) The Austin Hospital Email: xavier.fagan@unimelb.edu.au
Principal Investigator	**A/Prof. Daryl Guest** Department of Optometry and Vision Sciences The University of Melbourne Email: daryl.guest@unimelb.edu.au
Co-Investigator	**Dr. Christine Houlihan** Diabetes and Endocrine Clinic The Mercy Hospital for Women Email: houlihan@bigpond.net.au
Co-Investigator	**Dr. Li Ping Chow** Department of Surgery (Ophthalmology) The Austin Hospital Email: drlpchow@gmail.com

Co-Investigator	**Mr. Angelo Rando** Department of Surgery (Ophthalmology) The Austin Hospital Email: angelo.rando@austin.org.au
Co-Investigator (Study Coordinator)	**Dr. Felicia Widyaputri** Department of Surgery (Ophthalmology) The University of Melbourne Email: widyaputrif@unimelb.edu.au

Introduction

Thank you for your interest in participating in this research project which aims to investigate the nature of Diabetic Retinopathy (a form of diabetic eye disease) during pregnancy.

The following few pages will provide you with further information about the project, the possible risks and benefits of participating this study, so that you can decide if you would like to take part in this research.

Please note that your participation is **voluntary**. If you don't wish to take part, you don't have to. If you join the study you can stop at any time. Your decision to participate (or not) in this study will have no influence on the clinical care and management that you will receive.

What is this research about?

Diabetic Retinopathy (DR) is a sight threatening disease, which may occur in people with type 1 or type 2 diabetes. This disease results from diabetes causing damage to a delicate part of the eye called the retina, which functions inside your eye to make an image similarly to the way a film acts within a camera. Your retina can become severely damaged before you notice any problems with your eyes or vision. It is thought that in some people this damage may occur even faster during pregnancy. However, we are not yet sure whether this is definitely the case. We are also not sure if there are any risk factors, or reasons, that may cause diabetic retinopathy to worsen faster in some pregnant women than in others.

The aim of our study is to address these knowledge gaps by collecting routine clinical data from pregnant diabetic patients who attend routine, standard eye examinations throughout their pregnancy and after delivery. These eye examinations are exactly as recommended by the NHMRC, a government organisation that oversees healthcare in Australia. By taking part in this study, we will therefore help ensure that you get the eye care that you need.

Approximately 120 participants will be recruited in this study.

What will I be asked to do?

Should you agree to participate, your General Practitioner (GP) or Obstetrician will refer you to the photographic diabetic retinopathy screening clinic at Austin Hospital (located at The Austin Hospital - Repatriation Campus, Tobruk Building, Clinic E. A map will be

provided to guide the you travel between Mercy and Austin Hospital) or University of Melbourne Eye Clinic, UMeyecare (located at Shop 2, 800 Swanston Street, Carlton, Victoria, 3053), to get comprehensive eye examinations during your pregnancy and for up to 1 year after delivery. If you wish, you may continue to have your eye examinations at the Austin Hospital or University of Melbourne clinic after your involvement in the study is complete. The examination will be scheduled once in each trimester (3-monthly of the pregnancy) and at 3, 6 and 12 months after delivery. If you are recruited during your pre-pregnancy care, an additional eye examination will be done during this period. To help organise and remind you of these appointments, Dr Felicia Widyaputri, our study co-ordinator, will make contact by email or SMS or phone prior to each of your scheduled appointments.

At your first visit, you will be asked to read and sign this Patient Information and Consent Form. If you decide to participate you will need to sign the consent form. After consenting, you will be asked about your general medical history, including your diabetic and pregnancy status, in addition to details regarding your vision and eye health. We will also obtain other information regarding your diabetes control and other medical data from your GP or Obstetrician or Endocrinologist.

At every visit, your weight and blood pressure will be measured, and your eye examination will be performed (detailed in table). Routine blood and urine tests will also be scheduled in conjunction with your GP or Obstetrician or Endocrinologist. We will use either the Mercy Hospital pathology service or any other pathology service of your choice. As it is standard routine care, the testing will be covered by Medicare.
Please note: all procedures are part of routine clinical care of pregnant diabetic patient and will take approximately 30 minutes to complete.

Procedure	Things to do
Vision (visual acuity) test	You will be tested by reading letters on a screen.
Eye examination	The front part of your eyes and your retinas will be examined using standard techniques using a “slit lamp” and by ophthalmoscopy. Your pupils will be dilated as part of this study, if there is no contraindication (A condition which makes the procedure potentially inadvisable).
Fundus (retina) imaging	We will take photos of the retina. This is a non-invasive imaging technique (i.e. it does not require any injections or radiation). You will be asked to position your chin on the chin rest of a retina camera and stare directly ahead at the blinking spot inside the camera. There will be a flashing light when the examiner captures the image of your retina. It will be done in both eyes.

Optical coherence tomography (OCT) & Optical coherence tomography Angiography (OCTA)*	These are specialised photos of the retina that make use of a non-invasive imaging technique that is very similar to retinal photography detailed above. This image helps us to determine whether there is any swelling of the retina due to diabetes and examines the blood vessels in the eye to detect early signs of vessel abnormalities. The procedure is much the same as fundus (retina) imaging detailed above.

*The OCTA will only be performed if you have the examinations at the UMeyecare clinic.

What are the possible benefits?

By participating in this study, you will receive diabetic eye-screening examinations in pre-pregnancy state (if applicable), in each trimester of pregnancy and until 12-months after delivery for free. Having eye screening early in your pregnancy can benefit you by providing not only information about your eye health, but also about the impact of your sugar control on your body. If we detect any sign of new, or progressive diabetic retinopathy we will inform your GP or Obstetrician or Endocrinologist so your diabetic management can be adjusted where appropriate. If potentially sight threatening diabetic retinopathy is detected that needs review by an ophthalmologist or treatment, you will be immediately referred to our ophthalmologist at the Austin Melbourne Hospital to receive treatment.

There may or may not be benefits to you for participating in this study. There will be no reimbursement of travel expenses or any other reward. You will however be receiving, at minimum, standard of care for your condition. Broadly, this study will benefit society by providing findings that may help inform the future care of pregnant patients with diabetes and diabetic retinopathy by:

1. Determining the number of people with diabetic retinopathy during pregnancy and early post delivery period. This will in turn inform the development of updated specific guidelines on ophthalmic screening and care during pregnancy.
2. Identification of risk factors that may accelerate the progression of diabetic retinopathy. This in turn will also contribute to the development of updated screening procedures and may also identify factors that may be treatable in order to reduce the risk of diabetic retinopathy progression.
3. Determining the rate of progression of diabetic retinopathy during pregnancy and whether it spontaneously improves after delivery may help inform how aggressively sight threatening diabetic retinopathy is treated at different stages of pregnancy.

What are the possible risks?

In case you haven't done your standard routine blood and urine examination, your GP or Obstetrician or Endocrinologist will ask the research team to organize it. The test will be taken by the pathology service of your choice. You may feel some pain when the blood is drawn (<5ml, or the volume of a tablespoon, will be taken). There is a small chance that the needle will cause bleeding, a bruise or an infection at the puncture site. Some people may feel faint or dizzy, when blood is drawn but this usually passes very quickly.

As part of the testing the pupils of your eyes will be dilated using eye-drops. You may experience reduced ability to focus and increased glare and difficulty with your vision for

about three hours after your visit. It would be preferable for you not to drive during this period. Pupil dilatation very occasionally causes the development of high pressures in the eyes. Therefore, pupil dilatation will only be performed after examination of your eyes has shown that the risk of this occurring is negligible.

The dilating eye drops (1% Tropicamide) have been assessed by Australian Government Department of Health and does not carry additional risk to your baby. The use of this eye-drop is included in standard care for diabetic eye screening examination as recommended by National Health and Medical Research Council of Australia. To further minimise the risk, you will be asked to close your eyes and press the inner corner of your eyes immediately after the eye drop is given.

Will I be reimbursed for my time?

There are no additional costs associated with participating in this study, nor will you be paid. All examinations required as part of the research project will be provided to you free of charge.

You may be reimbursed for parking expenses associated with the study visit to a maximum of $5 AUD per visit.

Do I have to take part?

No. Participation is **completely voluntary**. You are able to withdraw (quit) at any time without penalty and it will not affect your care. You may still have eye examinations at Austin Hospital or UMeyecare even if you are not part of the study.

Will I hear about the results of this project?

The result of this study may be published as journal articles and/or presented at conferences. A copy of these articles will be available to you if you request them.

What will happen to information about me?

By signing the consent form you consent to the researchers collecting and using personal information about you for the research project. Full confidentiality of your medical data will be kept by the researchers, your GP or Obstetrician or Endocrinologist, the pathology service and by the staff of UMeyecare and Austin Hospital - that is, by all people involved with the study. All personal data used in the research study will be anonymous and will be coded with a study identity and patient number (Example: DRP001) that will be assigned to you at the beginning of the study.

Study records will be retained for 15 years after the completion of the study and only can be accessed by the researchers. Your anonymous data may also be used in the future for studies with a similar purpose. A report may be published; however, you will not be able to be identified in any publications or reports that arise from this study, as your identity will always be kept confidential in any such publication(s).

In accordance with the National Medical Health and Research Council guidelines, the Human Research Ethics Committee is required to conduct audits of research projects from time to time. It may therefore be possible that the Human Research Ethics Committee

which has approved this research, will seek to view a copy of your signed consent form, or to contact you, to ensure that the research is being conducted according to the ethical standards required by these guidelines.

Where can I get further information?

If you have any further questions about this project or any medical problems which may be related to your involvement in the project (for example, any side effects), please contact the researchers; A/Prof Lyndell Lim (Email: limllp@unimelb.edu.au) or Dr. Alexis Shub (Email: ashub@unimelb.edu.au) or Dr. Xavier Fagan (Email: xavier.fagan@unimelb.edu.au) or Dr. Felicia Widyaputri (Ph: 0424902612, email: widyaputrif@unimelb.edu.au)

Who can I contact if I have any concerns about the project?

This research project has been approved by the Human Research Ethics Committee of The University of Melbourne (Ethics ID: 1749108), The Royal Women's Hospital (Ethics ID: 17/26), The Melbourne Health (Ethics ID: 2018.019), The Mercy Health (Ethics ID: 2018-009), and the Austin Health (SSA ID: SSA/18/Austin/185). If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact:

1. The Manager, Human Research Ethics, Office for Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Email: HumanEthics-complaints@unimelb.edu.au.
   Or
2. The Complaints Manager, Director Research Governance and Ethics, Royal Melbourne Hospital. Tel: +61 3 9342 8530 or email: Research@mh.org.au
   Or
3. The Administrative Officer, Human Research Ethics Committee, Mercy Hospital for Women. Tel: 8458 4808
   Or
4. The Complaints Officer of Austin Health. Tel: (03) 94964090 or (03) 94963248 or Email: ethics@austin.org.au

All complaints will be treated confidentially. In any correspondence, please provide the name of the research team or the name or ethics ID number of the research project.

Consent Form

Natural History of Diabetic Retinopathy in Pregnant Women

Departments of Surgery (Ophthalmology), Optometry and Vision Sciences
University of Melbourne Diabetes and Endocrine Clinic, Mercy
Hospital Department of Surgery (Ophthalmology), Austin Hospital

Coordinating Investigator: A/Prof. Lyndell Lim

Name of Participant
(or barcode): _____

1. I consent to participate in this project, the details of which have been explained to me, and I have been provided with a written patient information to keep.
2. I understand that the purpose of this research is to investigate the nature of Diabetic Retinopathy (a form of diabetic eye disease) during pregnancy and after delivery.
3. I understand that my participation in this project is for research purposes.
4. I acknowledge that the possible effects of participating in this research project have been explained to my satisfaction.
5. I understand that this project will involve scheduled visits throughout my pregnancy and for up to one year after delivery. These visits will generally occur at the Austin Hospital - Repatriation Campus, but in special circumstances may be able to be scheduled at The University of Melbourne eye clinic, UMeyecare. Routine eye examination will be done and all the procedures have been explained to me. I will provide relevant medical data that is required in the study. I also understand that my previous medical data may be provided by my GP or Obstetrician.
6. I understand that my participation is voluntary and that I am free to withdraw from this project at any time without explanation or prejudice and to withdraw any unprocessed data that I have provided.
7. I understand that the data from this research will be stored at the University of Melbourne for a minimum of fifteen years after the completion of the study.
8. I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements; my data will be password protected and accessible only by researchers approved by the Human Research Ethics Committee.
9. I consent to the Mercy Health and Austin Health Human Research Ethics Committee which approved this study to access my information, or to contact me to ask about my research experience, in order to ensure that the project is being run in accordance with government standards.
10. I am aware and give my approval for my anonymous data to be used in the future for studies with a similar purpose?

    ☐ **Yes** ☐ **No** (please tick)
11. I understand that after I sign and return this consent form, it will be retained by the University.

I have read, or have had read to me, and I understand the Participant Information and Consent Form for persons participating in a research project, Version 5.1 dated 2 March 2018.

If available, I wish to receive a copy of the summary report on the research findings?

☐ **Yes** ☐ **No** (please tick)

If Yes, please provide us with an email address to send this to:

_____

Participant Signature: _____ **Date:** _____

Printed name of researcher _____

Signature _____ **Date** _____

(To be signed and dated by the person who conducted the informed consent process)

Form for Withdrawal of Participation

Natural History of Diabetic Retinopathy in Pregnant Women

Departments of Surgery (Ophthalmology), Optometry and Vision Sciences
University of Melbourne Diabetes and Endocrine Clinic, Mercy Hospital
Department of Surgery (Ophthalmology), Austin Hospital

Coordinating Investigator: A/Prof. Lyndell Lim

Declaration by Person Responsible

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me.

Participant's Name (printed) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the person responsible for the participant has understood that explanation.

Researcher's Name (printed) _____

Signature _____ Date _____

[†] A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

A5. Basic medical data and risk factors questionnaire

CONFIDENTIAL

ONLY FOR RESEARCH PURPOSE

NATURAL HISTORY OF DIABETIC RETINOPATHY IN PREGNANT WOMEN

Department of Surgery, Department of Optometry and Vision Sciences
University of Melbourne
Diabetes and Endocrine Service, Royal Women's Hospital

BASIC MEDICAL DATA AND RISK FACTOR

ID Number : _____

Date : _____

Directions:

Answer the questions in the blank space for each question. Please, give the information as precise as you can, since it will influence the study result. If you forget the exact date of the questioned event, please fill with at least the month and/or year. For multiple choices questions, fill the small box with the number of your answer. If you find any difficulty, please ask for guidance.

I. IDENTITY

1.	Name		
2.	Date of Birth/ Age	/ /	years
3.	Address	_____ _____ _____ Postcode: _____	
4.	Phone number		
5.	Email		
6.	Ethnicity	1. Aboriginal & Torres Strait Islander People 2. South Pacific Islanders 3. Caucasian: - North-west European - Southern & Eastern European 4. North African & Middle Eastern 5. Asian 6. Peoples of The Americas 7. Sub-Saharan African	☐
7.	Level of education	1. Primary school 2. Secondary school 3. Trade certificate 4. Diploma 5. University degree	☐
8.	Occupation		

II. DIABETIC STATUS

1.	Type of Diabetes	1. Type 1 2. Type 2	☐
2.	Time of Diagnosis	Month:	Year:
3.	Insulin Medication	1. Yes 2. No	☐
	If Yes, for how long?		
4.	Oral Diabetes Medicine	1. Yes 2. No	☐
	If Yes, which one(s) and for how long?	Drugs: 1. 2. 3.	Period: 1. 2. 3.
5.	Other medication?	1. Yes 2. No	☐
	If Yes, please list the medications & indicate how long you have been taking them	Drugs: 1. 2. 3.	Period: 1. 2. 3.
6.	Managing diet	1. Yes 2. No	☐
	Have you ever experienced:		
7.	Diabetic Coma	1. Yes 2. No	☐
8.	Hypoglycemia (“Hypos”)	1. Yes 2. No	☐
9.	Heart disease	1. Yes 2. No	☐
10.	Neuropathy (Problems with feeling your feet due to nerve damage from your diabetes)	1. Yes 2. No	☐
11.	Nephropathy (kidney problems from your diabetes)	1. Yes 2. No	☐

12.	Foot ulcers	1. Yes 2. No	☐
13.	Eye diseases	1. Yes 2. No	☐
	If Yes, please list, including any treatments you may have received for them	Diseases: 1. 2. 3. 4.	Therapies: 1. 2. 3. 4.
14.	Do you have a family history of diabetes?	1. Yes 2. No	☐
	If Yes, which type?	1. Type 1 2. Type 2 3. Gestational 4. Other type	☐
15.	How often do you go to a doctor regarding your diabetes?	1. Every week 2. Every month 3. Every 3 month 4. Every 6 month 5. Every year 6. Infrequent	☐
16.	How often do you have your eyes checked?	1. Every month 2. Every 3 month 3. Every 6 month 4. Every year 5. Every 2 year 6. Infrequent	☐
17.	When was your last eye check?	/ /	
18.	Have you been diagnosed with diabetic eye disease (diabetic retinopathy)	1. Yes 2. No	☐
	If Yes, when?	/ /	
19.	Have you ever had any treatment for diabetic eye disease (diabetic retinopathy)	1. Yes 2. No	☐
	If Yes, please provide details		

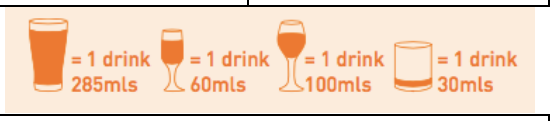
III. MATERNITY STATUS

1.	Validated pregnancy	1. Yes 2. No	☐

2.	Date last menstrual period	/ /	
3.	Gestational age	weeks	
4.	Expected due date	/ /	
5.	Attendance at pre-pregnancy care	1. Yes 2. No	☐
6.	Number of prior Pregnancies		
7.	Number of deliveries		
8.	Date of birth of your children	(DD/MM/YY)	I. II. III. IV.
9.	Birth weight of each child?	(on gram)	I. II. III. IV.
10.	Gestational age on delivery of each child?	(on weeks)	I. II. III. IV.
11.	Were there any complications during pregnancy or birth? If yes, please list	(Y/N)	I. II. III. IV.
12.	Current or past health problems of your children (if any)	(write N, if there wasn't)	I. II. III. IV.
13.	Did you have your eyes checked during your previous pregnancies?	1. Yes 2. No	☐

IV. GENERAL MEDICAL HISTORY

1.	Have you been a smoker	1. Yes 2. No	☐
	If Yes, since when? If you are an ex-smoker, please list when you quit & for how many years you were a smoker previously	Year: or Age:	
	Number of cigarettes daily		piece(s) / packet(s)
2.	How many standard drinks of alcohol do you currently drink per week?		drinks/week
	How many standard drinks of alcohol did you drink per week before pregnancy?		drinks/week



	Do you have or have you had any of the following:		
3.	High blood pressure (hypertension)	1. Yes 2. No	☐
4.	Heart attack	1. Yes 2. No	☐
5.	Renal (kidney) disease	1. Yes 2. No	☐
6.	Dyslipidemia (high cholesterol and/or high triglycerides)	1. Yes 2. No	☐
7.	Neuropathy (nerve disorder)	1. Yes 2. No	☐
8.	Surgery	1. Yes 2. No	☐
	If Yes, mention and when	Type of surgery:	Time:

A6. REDCap Data Instrument

A6.1. Demographics

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Record number	text	integer				
Study ID	text			y		
Eye exam location:	checkbox		1, UMEyecare | 2, Repat Hospital | 3, RMH | 9, Elsewhere | 0, No eye exam			y
SUNIX ID	text	integer		y	[eye_exam_loc(1)] = '1'	
UR number	text	integer		y	[eye_exam_loc(2)] = '1' or [eye_exam_loc(3)] = '1'	
Date subject signed consent	text	date_dmy				y
Today's Gestational Age	calc		Formula in **A6.11**			
Upload the patient's consent form	file			y		
First Name	text			y		y
Last Name	text			y		y
Date of birth	text	date_dmy				y
Age (years)	calc		Formula in **A6.11**			
Address	notes			y		y

Phone number	text	integer		y		y
E-mail	text	email		y		
Ethnicity	dropdown		1, Aboriginal & Torres Strait Islander People | 2, South Pacific Islanders | 3, Caucasian (North-west European, Southern & Eastern European) | 4, North Africa & Middle Eastern | 5, Asian and Indian | 6, Peoples of the Americas | 7, Sub-Saharan African | 99, Other			y
Please mention	text				[ethnicity] = '99'	
Level of Education	dropdown		1, Primary school | 2, Secondary school | 3, Trade certificate | 4, Diploma | 5, University Degree | 99, Other			y
Please mention	text				[education] = '99'	
Occupation	text					
Referral source	checkbox		1, GP | 2, Endocrinologist | 3, Diabetic Educator | 4, Dietician | 5, Optometrist | 6, Outreach Primary Health Service | 7, Royal Melbourne Hospital | 8, Royal Women's Hospital | 9, Mercy Hospital | 10, Austin Hospital | 11, Research Study | 99, Other	y		y
Other referral source?	text				[referral_source(99)] = '1'	
Comments	notes					

A6.2. Baseline data

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Type of DM	radio		1, Type I | 2, Type II | 3, Gestational			y
When did you were diagnosed with diabetes?	radio		1, less than 2 years ago | 2, more than 2 years ago			
Duration of diabetes/time since diagnosis:	text	number			[when_diagnosed] = '1'	
Duration months to years	calc		Formula in **A6.11**			
Duration of diabetes/time since diagnosis:	text	number			[when_diagnosed] = '2'	
Treatment for DM	checkbox		1, Diet | 2, Oral | 3, Insulin			
Duration of insulin use:	text	number			[treatment_dm(3)] = '1'	
Type of oral medication:	text				[treatment_dm(2)] = '1'	
Duration of oral medication:	text	number			[treatment_dm(2)] = '1'	
Other Medications	notes					
How regular are your doctor visits	dropdown		1, Weekly | 2, Monthly | 3, Every 3 months | 4, Every 6 months | 5, Yearly | 6, Infrequently			

regarding your diabetes?				
A family history of diabetes?	yes/no			
Family Type of diabetes	checkbox		1, Type I | 2, Type II | 3, Gestational | 9, Other	[famhistory_dm] = '1'
Please mention	text			[famhistory_dmtype(9)] = '1'
Do you currently smoke?	yes/no			
Were you previously a smoker?	yes/no			[smoke_currently] = '0'
How long have you stop smoking?	text	number		[smoke_previously] = '1'
Number of cigarettes per day (on average):	text	integer		[smoke_currently] = '1' or [smoke_previously] = '1'
Number of years since started smoking?	text	number		[smoke_currently] = '1' or [smoke_previously] = '1'
Do you currently drink alcohol?	yes/no			
Did you drink alcohol before pregnant?	yes/no			[alcohol] = '0'
How many standard drinks do you currently drink per week?	text	integer		[alcohol] = '1'
How many standard drinks did you drink	text	integer		[alcohol_beforepreg] = '1'

per week before pregnancy?					
Complications	checkbox		1, None | 2, Diabetic Ketoacidosis (DKA) | 3, Hypoglycaemia | 4, Heart disease | 5, Neuropathy | 6, Nephropathy | 7, Foot ulcers		y
Comorbidities	checkbox		1, None | 2, Hypertension | 3, Heart attack | 4, Kidney disease | 5, Dyslipidaemia | 6, Neuropathy | 7, Thyroid problem | 8, Other		y
Please specify:	text			[comorbidities(8)] = '1'	
Have you had any previous surgery?	yes/no				
Detail type & time/date of surgery	notes			[have_you_had_any_previous] = '1'	
How often are your eyes examined?	dropdown		1, Monthly | 2, Every 3 months | 3, Every 6 months | 4, Yearly | 5, Two yearly | 6, Infrequently/Never		
What date was last eye examination? (if known)	text	date_dmy			
When was last eye examination?	text	integer			
Last eye examination months	calculation		Formula in **A6.11**		
Previously diagnosed eye conditions:	yes/no				
Eye conditions:	notes			[previously_diagnosed_eye_c] = '1'	

Previously diagnosed diabetic retinopathy?	yes/no				[previously_diagnosed_eye_c] = '1'	
When was the diagnosis?	text	integer			[previously_diagnosed_diabe] = '1'	
Previous treatment for diabetic retinopathy?	yes/no				[previously_diagnosed_diabe] = '1'	
Details of DR treatment:	notes				[previous_drtreatment] = '1'	

A6.3. Pre-pregnancy data

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Currently pregnant?	yes/no					
Attendance at pre-pregnancy care?	yes/no					

A6.4. Pregnancy data

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Currently pregnant?	yes/no					y

Expected due date	text	date_dmy		[pregnant] = '1'
Gestational Age	text	integer		[pregnant] = '1'
Gestational Age calculated	calculation		Formula in **A6.11**	[pregnant] = '1'
Attendance at pre-pregnancy care?	yes/no			
Pre-pregnancy weight (or early pregnancy)	text	number		
Has the patient had pregnancy before?	yes/no			
How many pregnancies that she has had?	radio		1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7 | 8, 8 | 9, more	[previous_pregnancy] = '1'
Mention:	text	integer		[numb_preg] = '9'
How many times has the patient given birth?	radio		0, None | 1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7 | 8, 8 | 9, more	[previous_pregnancy] = '1'
Mention:	text	integer		[numb_children] = '9'
Date of birth of your 1st child:	text	date_dmy		[numb_children] = '1' or [numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or

			[numb_children] = '8' or [numb_children] = '9'
Birth weight of 1st child:	text	number	[numb_children] = '1' or [numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Gestational age at delivery of 1st child:	text	integer	[numb_children] = '1' or [numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Any complication during pregnancy or birth of your 1st child?	yes/no		[numb_children] = '1' or [numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Please mention:	notes		[complic_preg_first_child] = '1'
Date of birth of your 2nd child:	text	date_dmy	[numb_children] = '2' or [numb_children] = '3' or

			[numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Birth weight of 2nd child:	text	number	[numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Gestational age at delivery of 2nd child:	text	integer	[numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Any complication during pregnancy or birth of your 2nd child?	yes/no		[numb_children] = '2' or [numb_children] = '3' or [numb_children] = '4' or [numb_children] = '5' or [numb_children] = '6' or [numb_children] = '7' or [numb_children] = '8' or [numb_children] = '9'
Please mention:	notes		[complic_preg_second_child] = '1'

A6.5. Eye examinations

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Today's Gestational Age	calculation		Formula in **A6.11**			
Date of visit	text	date_dmy				y
Location	radio		1, UMeyecare | 2, Repatriation hospital | 3, Royal Melbourne Hospital | 4, Elsewhere			y
Give details	notes				[eye_exam_location] = '4'	
Patient's pregnancy status on exam day:	radio		0, pre-pregnancy | 1, still pregnant | 2, post delivery			y
Gestational Age on exam day	calculation		Formula in **A6.11**		[preg_status_examday] = '1'	
Baby's age on exam day	calculation		Formula in **A6.11**		[preg_status_examday] = '2'	
Height (cm)	text	number				
Weight (kilograms)	text	number				
BMI	calculation		Formula in **A6.11**			
Systolic blood pressure	text					

Diastolic blood pressure	text			
R VA	dropdown		1, NPL | 2, PL | 3, HM | 4, CF | 5, 6/120 | 6, 6/96 | 7, 6/75 | 8, 6/60 | 9, 6/48 | 10, 6/36 | 11, 6/24 | 12, 6/19 | 13, 6/15 | 14, 6/12 | 15, 6/9.5 | 16, 6/7.5 | 17, 6/6 | 18, 6/4.8	
L VA	dropdown		1, NPL | 2, PL | 3, HM | 4, CF | 5, 6/120 | 6, 6/96 | 7, 6/75 | 8, 6/60 | 9, 6/48 | 10, 6/36 | 11, 6/24 | 12, 6/19 | 13, 6/15 | 14, 6/12 | 15, 6/9.5 | 16, 6/7.5 | 17, 6/6 | 18, 6/4.8	
R Sphere	text			
R cylinder	text			
R axis	text			
L Sphere	text			
L cylinder	text			
L axis	text			
Pupils normal?	yes/no			
Pupil abnormality:	text			[pupils_normal] = '0'
R	radio		1, normal | 2, NVI | 3, NVA	
L	radio		1, normal | 2, NVI | 3, NVA	
R IOP	text	number		
L IOP	text	number		
Right	checkbox		1, AMD | 2, Glaucoma | 3, External eye disease | 4, Cataract	

Left	checkbox	1, AMD | 2, Glaucoma | 3, External eye disease | 4, Cataract		
Both	checkbox	1, AMD | 2, Glaucoma | 3, External eye disease | 4, Cataract		
R	radio	1, 1% Trop. | 2, 1% Trop. & 2.5% Phenyl. | 3, Unsafe		
L	radio	1, 1% Trop. | 2, 1% Trop. & 2.5% Phenyl. | 3, Unsafe		
DR Grading R:	dropdown	1, None | 2, Mild NPDR | 3, Moderate NPDR | 4, Severe NPDR | 5, Very Severe NPDR | 6, PDR | 7, PDR high risk | 8, PDR advanced		
DR grading L:	dropdown	1, None | 2, Mild NPDR | 3, Moderate NPDR | 4, Severe NPDR | 5, Very Severe NPDR | 6, PDR | 7, PDR high risk | 8, PDR advanced		
Edema R:	dropdown	1, None | 2, Lipid Only | 3, Non-CSMO | 4, Non-centre involved CSMO | 5, Centre involved CSMO		
Edema L:	dropdown	1, None | 2, Lipid Only | 3, Non-CSMO | 4, Non-centre involved CSMO | 5, Centre involved CSMO		
Notes	notes			
R	checkbox	1, Photo | 2, OCT | 3, OCTA		
L	checkbox	1, Photo | 2, OCT | 3, OCTA		
Fundus photo field has taken:	checkbox	1, macula-centered | 2, disc-centered	[r_scans(1)] = '1' or [l_scans(1)] = '1'	y

fundus photo RE, macula-centered	file				[r_scans(1)] = '1' and [fundus_field(1)] = '1'
fundus photo RE, disc-centered	file				[r_scans(1)] = '1' and [fundus_field(2)] = '1'
fundus photo LE, macula-centered	file				[l_scans(1)] = '1' and [fundus_field(1)] = '1'
fundus photo LE, disc-centered	file				[l_scans(1)] = '1' and [fundus_field(2)] = '1'
R OCT good quality?	yes/no				[r_scans(2)] = '1'
R CSFT	text	integer			[r_scans(2)] = '1'
R mac volume	text	number			[r_scans(2)] = '1'
OCT RE report	file			y	[r_scans(2)] = '1'
L OCT good quality?	yes/no				[l_scans(2)] = '1'
L CSFT	text	integer			[l_scans(2)] = '1'
L mac volume	text	number			[l_scans(2)] = '1'
OCT LE report	file			y	[l_scans(2)] = '1'
OCTA has taken:	checkbox		1, 3x3 macula | 2, 6x6 macula | 3, 6x6 disc | 4, 3x3 disc		[r_scans(3)] = '1' or [l_scans(3)] = '1'
R OCTA 3x3 mm good quality for VESSEL	yes/no				[r_scans(3)] = '1' and [octa_captured(1)] = '1'

DENSITY analysis?					
How many?	radio		0, both | 1, only 1 | 2, only taken 1	[r_octa_3x3_vdquality] = '1'	
Image 1 time stamp at IMAGEnet:	text	time		[r_octa_3x3_vdquality] = '1' or [n_goodqual_rocta_vd] = '0' or [n_goodqual_rocta_vd] = '1' or [n_goodqual_rocta_vd] = '2'	y
R central vessel density image 1	text	number		[r_octa_3x3_vdquality] = '1' or [n_goodqual_rocta_vd] = '0' or [n_goodqual_rocta_vd] = '1' or [n_goodqual_rocta_vd] = '2'	
R nasal vessel density image 1	text	number		[r_octa_3x3_vdquality] = '1' or [n_goodqual_rocta_vd] = '0' or [n_goodqual_rocta_vd] = '1' or [n_goodqual_rocta_vd] = '2'	
R temporal vessel density image 1	text	number		[r_octa_3x3_vdquality] = '1' or [n_goodqual_rocta_vd] = '0' or [n_goodqual_rocta_vd] = '1' or [n_goodqual_rocta_vd] = '2'	
R superior vessel density image 1	text	number		[r_octa_3x3_vdquality] = '1' or [n_goodqual_rocta_vd] = '0' or [n_goodqual_rocta_vd] = '1' or [n_goodqual_rocta_vd] = '2'	
R inferior vessel density image 1	text	number		[r_octa_3x3_vdquality] = '1' or [n_goodqual_rocta_vd] = '0' or [n_goodqual_rocta_vd] = '1' or [n_goodqual_rocta_vd] = '2'	
Image 2 time stamp at IMAGEnet:	text	time		[r_octa_3x3_vdquality] = '1' and [n_goodqual_rocta_vd] = '0'	y

R central vessel density image 2	text	number		[r_octa_3x3_vdquality] = '1' and [n_goodqual_rocta_vd] = '0'	
R nasal vessel density image 2	text	number		[r_octa_3x3_vdquality] = '1' and [n_goodqual_rocta_vd] = '0'	
R temporal vessel density image 2	text	number		[r_octa_3x3_vdquality] = '1' and [n_goodqual_rocta_vd] = '0'	
R superior vessel density image 2	text	number		[r_octa_3x3_vdquality] = '1' and [n_goodqual_rocta_vd] = '0'	
R inferior vessel density image 2	text	number		[r_octa_3x3_vdquality] = '1' and [n_goodqual_rocta_vd] = '0'	
R OCTA 3x3 mm good quality for FAZ analysis?	yes/no			[octa_captured(1)] = '1' AND [r_scans(3)] = '1'	
How many?	radio		0, both | 1, only 1 | 2, only taken 1	[r_octa_3x3_fazquality] = '1'	
Image 1 time stamp at IMAGEnet:	text	time		[r_octa_3x3_fazquality] = '1' or [n_goodqual_rocta_faz] = '0' or [n_goodqual_rocta_faz] = '1' or [n_goodqual_rocta_faz] = '2'	y
R FAZ area image 1	text	number		[r_octa_3x3_fazquality] = '1' or [n_goodqual_rocta_faz] = '0' or [n_goodqual_rocta_faz] = '1' or [n_goodqual_rocta_faz] = '2'	
Image 2 time stamp at IMAGEnet:	text	time		[r_octa_3x3_fazquality] = '1' and [n_goodqual_rocta_faz] = '0'	y

R FAZ area image 2	text	number		[r_octa_3x3_fazquality] = '1' and [n_goodqual_rocta_faz] = '0'	
Overall R FAZ area	text			[r_octa_3x3_fazquality] = '1'	y
L OCTA 3x3 mm good quality for VESSEL DENSITY analysis?	yes/no			[octa_captured(1)] = '1' and [l_scans(3)] = '1'	
How many?	radio		0, both | 1, only 1 | 2, only taken 1	[l_octa_3x3_vdquality] = '1'	
Image 1 time stamp at IMAGEnet:	text	time		[l_octa_3x3_vdquality] = '1' or [n_goodqual_locta_vd] = '0' or [n_goodqual_locta_vd] = '1' or [n_goodqual_locta_vd] = '2'	y
L central vessel density image 1	text	number		[l_octa_3x3_vdquality] = '1' or [n_goodqual_locta_vd] = '0' or [n_goodqual_locta_vd] = '1' or [n_goodqual_locta_vd] = '2'	
L nasal vessel density image 1	text	number		[l_octa_3x3_vdquality] = '1' or [n_goodqual_locta_vd] = '0' or [n_goodqual_locta_vd] = '1' or [n_goodqual_locta_vd] = '2'	
L temporal vessel density image 1	text	number		[l_octa_3x3_vdquality] = '1' or [n_goodqual_locta_vd] = '0' or [n_goodqual_locta_vd] = '1' or [n_goodqual_locta_vd] = '2'	
L superior vessel density image 1	text	number		[l_octa_3x3_vdquality] = '1' or [n_goodqual_locta_vd] = '0' or [n_goodqual_locta_vd] = '1' or [n_goodqual_locta_vd] = '2'	

L inferior vessel density image 1	text	number		[l_octa_3x3_vdquality] = '1' or [n_goodqual_locta_vd] = '0' or [n_goodqual_locta_vd] = '1' or [n_goodqual_locta_vd] = '2'	
Image 2 time stamp at IMAGEnet:	text	time		[l_octa_3x3_vdquality] = '1' and [n_goodqual_locta_vd] = '0'	y
L central vessel density image 2	text	number		[l_octa_3x3_vdquality] = '1' and [n_goodqual_locta_vd] = '0'	
L nasal vessel density image 2	text	number		[l_octa_3x3_vdquality] = '1' and [n_goodqual_locta_vd] = '0'	
L temporal vessel density image 2	text	number		[l_octa_3x3_vdquality] = '1' and [n_goodqual_locta_vd] = '0'	
L superior vessel density image 2	text	number		[l_octa_3x3_vdquality] = '1' and [n_goodqual_locta_vd] = '0'	
L inferior vessel density image 2	text	number		[l_octa_3x3_vdquality] = '1' and [n_goodqual_locta_vd] = '0'	
L OCTA 3x3 mm good quality for FAZ analysis?	yes/no			[octa_captured(1)] = '1' and [l_scans(3)] = '1'	
How many?	radio		0, both | 1, only 1 | 2, only taken 1	[l_octa_3x3_fazquality] = '1'	
Image 1 time stamp at IMAGEnet:	text	time		[l_octa_3x3_fazquality] = '1' or [n_goodqual_locta_faz] = '0' or [n_goodqual_locta_faz] = '1' or [n_goodqual_locta_faz] = '2'	y

L FAZ area image 1	text	number			[l_octa_3x3_fazquality] = '1' or [n_goodqual_locta_faz] = '0' or [n_goodqual_locta_faz] = '1' or [n_goodqual_locta_faz] = '2'	
Image 2 time stamp at IMAGEnet:	text	time			[l_octa_3x3_fazquality] = '1' and [n_goodqual_locta_faz] = '0'	y
L FAZ area image 2	text	number			[l_octa_3x3_fazquality] = '1' and [n_goodqual_locta_faz] = '0'	
Overall L FAZ area	text				[l_octa_3x3_fazquality] = '1'	y
Referral required?	yes/no					
Treatment provided:	radio		1, monitoring | 2, laser | 3, intravitreous injection		[referral] = '1'	
Give details:	notes				[treatment_dr] = '2' or [treatment_dr] = '3'	

A6.6. Pathology results

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Test date	text	date_dmy				
Gestational age on exam day	calculation		Formula in **A6.11**			

What kind of pathology test?	checkbox		1, HbA1c | 2, blood chemistry | 3, urine - Albumin creatinine ratio | 4, urine - Protein creatinine ratio | 99, other	
HbA1c (%)	text	number		[pathology_test(1)] = '1'
Blood urea (mmol/l)	text	number		[pathology_test(2)] = '1'
Blood creatinine (micromol/l)	text	number		[pathology_test(2)] = '1'
Random blood glucose (mmol/l)	text	number		[pathology_test(2)] = '1'
Fasting blood glucose (mmol/l)	text	number		[pathology_test(2)] = '1'
Blood albumin (g/L)	text	number		[pathology_test(2)] = '1'
Uric Acid (mmol/l)	text	number		[pathology_test(2)] = '1'
Type of urine sample	dropdown		1, Random | 2, First morning | 3, 24-hour collection | 4, mid-stream	[pathology_test(3)] = '1' or [pathology_test(4)] = '1'
Urine Albumin (mg/L)	text	number		[pathology_test(3)] = '1'
Is the Albumin documented as < and value i.e. <3	radio		0, No | 1, Yes	[pathology_test(3)] = '1'
Urine Protein (mg/l)	text	number		[pathology_test(4)] = '1'
Is the Protein documented as <	radio		0, No | 1, Yes	[pathology_test(4)] = '1'

and value i.e. < 40						
Urine Creatinine (mmol/L)	text	number			[pathology_test(3)] = '1' or [pathology_test(4)] = '1'	
Urine Albumin: Creatinine Ratio (mg/mmol)	text	number			[pathology_test(3)] = '1' and [urinealbumin_below_3] = '0'	
Urine Protein: Creatinine Ratio (mg/mmol)	text	number			[pathology_test(4)] = '1' and [urineprotein_below_40] = '0'	

A6.7. Pregnancy outcomes

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Date of birth of the baby	text	date_dmy		y		y
Fetal number	dropdown		1, Singleton | 2, Twins | 3, Triplets | 4, Other			
Sex	radio		1, Female | 2, Male			
Birth weight	text	number				
Birth length	text	number				
Gestational age at delivery	text	integer				

Gestational age at delivery (calculated)	calculation		Formula in **A6.11**		
Last weight before delivery	text	number			
Type of Labour	dropdown		1, Spontan | 2, Inducted		
Type of Birth	dropdown		1, Normal | 2, Forceps | 3, Ventouse | 4, Breech | 5, Caesarian section		
Did it plan?	radio		0, planned | 1, unplanned	[type_of_birth] = '5'	
APGAR 1 minute	text	integer			
APGAR 5 minutes	text	integer			
Admitted to NICU/SCN?	radio		0, No | 1, SCN | 2, NICU		
For how long?	text	number		[nicu_scn] = '1' or [nicu_scn] = '2'	

A6.8. Post-delivery follow-up

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Baby's health problem?	yes/no					

Issues;	checkbox	1, respiratory distress | 2, hypoglycemia | 3, susp. sepsis | 4, jaundice | 9, other	[baby_s_health_problem] = '1'
Phototherapy?	yes/no		[baby_health_problem(4)] = '1'
If yes, details?	notes		[baby_s_health_problem] = '1'
Mother's health problems?	yes/no		
Issues:	checkbox	1, Postpartum haemorrhage | 2, Preeclampsia | 3, Sepsis | 4, Perineal tear | 9, other	[mother_s_health_problems] = '1'
Degree of tear	radio	1, 1 | 2, 2 | 3, 3 | 4, 4	[mother_heath_problem(4)] = '1'
If yes, details?	notes		[mother_s_health_problems] = '1'
Breastfeeding?	yes/no		
Baby's health problem?	yes/no		
Issues;	checkbox	1, respiratory distress | 2, hypoglycemia | 3, susp. sepsis | 4, jaundice | 9, other	[baby_s_health_problem] = '1'
Phototherapy?	yes/no		[baby_health_problem(4)] = '1'
If yes, details?	notes		[baby_s_health_problem] = '1'
Mother's health problems?	yes/no		
Issues:	checkbox	1, Postpartum haemorrhage | 2, Preeclampsia | 3, Sepsis | 4, Perineal tear | 9, other	[mother_s_health_problems] = '1'
Degree of tear	radio	1, 1 | 2, 2 | 3, 3 | 4, 4	[mother_heath_problem(4)] = '1'
If yes, details?	notes		[mother_s_health_problems] = '1'

Breastfeeding?	yes/no					

A6.9. Completion data

Field Label	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
Which participation did the patient involve?	radio		1, Full study | 2, CADEES and share data | 3, CADEES only			y
Comments	notes					
Has patient completed study?	dropdown		0, No | 1, Yes			
Date of last visit	text	date_dmy				
Put a date if patient withdrew study	text	date_dmy				
Reason patient withdrew from study	dropdown		0, Non-compliance | 1, Did not wish to continue in the study | 2, Miscarriage | 3, Not illegible | 4, Other			
Mention:	notes				[withdraw_reason] = '4'	
Did the patient comply with the eye screening recommendation?	yes/no					

Has the patient do the CADEES survey?	yes/no	
Gestational Age when completing the survey:	calculation	Formula in **A6.11**
Did the patient want to get the study publications?	yes/no	

A6.10. Survey data

Variable / Field Name	Field Type	Text Validation Type or Show Slider Number	Choices, Calculations, or Slider Labels	Identifier?	Branching Logic (Show field only if...)	Required Field?
survey_participation	yes/no					y
surveydate	text	date_dmy			[survey_participation] = '1'	y
last_eye_exam_survey	dropdown		0, Never | 1, Within the past month | 2, within the past 2-3 months | 3, within the past 4-6 months | 4, within the past 7-12 months | 5, within the past 1-2 years | 6, within the past 2-5 years | 7, More than 5 years ago | 8, More than a year ago, but unsure of the exact time | 9, Don't know		[survey_participation] = '1'	y
survey1	radio		1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree		[survey_participation] = '1'	y

survey2	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey3	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey4	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey5	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey6	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey7	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey8	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey9	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey10	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y

survey11	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey12	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey13	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey14	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey15	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey16	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey18	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey19	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey20	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y

survey17	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree | 6, No provider	[survey_participation] = '1'	y
survey21	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey22	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey23	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey24	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey25	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey26	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey27	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey28	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y

survey29	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey30	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey34	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree | 6, No insurance	[survey_participation] = '1'	
survey31	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey32	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey33	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey35	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey36	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey37	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y

survey38	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey39	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey40	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1'	y
survey41	yes/no		[survey_participation] = '1'	y
survey42	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1' and [survey41] = '1'	
survey43	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1' and [survey41] = '1'	
survey44	radio	1, Strongly disagree | 2, Disagree | 3, No opinion/ Don't know | 4, Agree | 5, Strongly agree	[survey_participation] = '1' and [survey41] = '1'	
survey45	notes		[survey_participation] = '1'	
more_often_eyecheck	yes/no		[survey_participation] = '1'	y
eyeexam_provider	checkbox	1, Optometrist | 2, Eye doctor/ Ophthalmologist | 3, GP/ Local doctor | 4, Nurse | 5, Health Worker | 6, Ophthalmic Nuse/ Technician | 9, Other	[survey_participation] = '1'	y
eyeexam_provider_other	text		[eyeexam_provider(9)] = '1'	
pre_preg_attendance	yes/no		[survey_participation] = '1'	y

obs_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
eye_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
gp_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
endo_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
diet_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
educator_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
podiatrist_appointment	radio	1, 1 | 2, 2 | 3, 3 | 4, 4 | 5, 5 | 6, 6 | 7, 7	[survey_participation] = '1'	y
health_insurance	yes/no		[survey_participation] = '1'	y
relationship_status	dropdown	0, Single | 1, Married | 2, Separated | 3, Divorced | 4, Widowed | 5, Domestic partnership	[survey_participation] = '1'	y
annual_income	dropdown	1, Less than $15,000 | 2, $15,000 to $24,999 | 3, $25,000 to $34,999 | 4, $35,000 to $49,999 | 5, $50,000 to $74,999 | 6, $75,000 to $99,999 | 7, $100,000 or more | 0, Do not want to answer	[survey_participation] = '1'	y

A6.11. REDCap calculation field type formula

Instruments	Field Label	Formula
Demographics	Today's Gestational Age	rounddown((280-(datediff("today",[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0)
	Age (years)	round(datediff([dob],[enrolment_arm_1][date_consent],'y','DMY'),0)

Baseline Data	Duration months to years	round([duration_dm_month]/12,1)
	Last eye examination months	round(datediff([enrolment_arm_1][date_consent],[enrolment_arm_1][last_eye_exam_yr],"M","dmy"),0)
Pregnancy Data	Gestational Age calculated	rounddown((280-(datediff([enrolment_arm_1][date_consent],[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0)
Examinations	Today's Gestational Age	rounddown((280-(datediff("today",[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0)
	Gestational Age on exam day	if([preg_status_examday]=1,rounddown((280-(datediff([followup_visit],[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0),0)
	Baby's age on exam day	if([preg_status_examday] = 2, round((datediff([followup_visit],[6_week__3_month_po_arm_1][dob_baby],"d","dmy"))/7,0),0)
	BMI	round(([weight]*10000)/(([height])^(2)),1)
Pathology Results	Gestational age on exam day	rounddown((280-(datediff([test_date],[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0)
Pregnancy Outcomes	Gestational age at delivery (calculated)	rounddown((280-(datediff([6_week__3_month_po_arm_1][dob_baby],[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0)
Completion Data	Gestational Age when completing the survey:	rounddown((280-(datediff([final_followup_arm_1][cadeesdate],[enrolment_arm_1][expected_due_date_preg_con],"d","dmy")))/7,0)

A7. Foveal Avascular Zone Area Automatic Measurement Algorithm (ImageJ)

```
//Housekeeping code to ensure that macro runs smoothly
//ensure black background
manualmode = 0; //default = 0 i.e. turn off manual mode/ leave on Auto-FAZ mode
        if (manualmode) {
                autowidth = 0;
        }
run("Colors...", "foreground=white background=black selection=yellow");
run("Options...", "iterations=1 count=1 black");
run("Input/Output...", "jpeg=85 gif=-1 file=.csv use_file copy_column copy_row save_column
save_row");
//remove scale and previous ROIs
run("Set Scale...", "distance=0");
run("Select None");

//get image directory
dir = getDirectory("image");
        saveDir = dir+"Analysed"+ File.separator;
        File.makeDirectory(saveDir);
    pretitle = getTitle();
    title=replace(pretitle,".jpg","");
    print(title);

run("Duplicate...", " ");
run("Smooth");
```

```
roiManager("Reset"); //do not reset if want to keep all


//Objective: Isolate the FAZ from the vessels
//Step 1: threshold the image to convert grey intensity vessels into binary
//Input a tissue threshold percentage 0-100. Default 77% validated by manual segmentation
desiredpercent = 77;
print("User selected: " + desiredpercent + "% threshold");
        tissueThreshPrec = 100 - desiredpercent;
        nBins = 256;
        getHistogram(values, count, nBins);
        size = count.length;
        //find cumulative sum
        cumSum = 0;
        for (i = 0; i<count.length; i++)
        {
        cumSum += count[i];
        }
        tissueValue = cumSum * tissueThreshPrec / 100;
        //cumulative sum of before
        cumSumValues = count;
        for (i = 1; i<count.length; i++)
        {
        cumSumValues[i] += cumSumValues[i-1];
        }
        //find tissue Value
        for (i = 1; i<cumSumValues.length; i++)
        {
```

```
        if (cumSumValues[i-1] <= tissueValue && tissueValue <= cumSumValues[i])
        //output tissue threshold:
        userthreshold = i-2;
         }
        print("Threshold: " + userthreshold + " out of 255");
    setThreshold(userthreshold, 255);
    setOption("BlackBackground", true);
    run("Convert to Mask");


run("Select None");
run("Dilate");
run("Dilate");
run("Invert");


if (manualmode == 0){
//NEW AUTO FAZ SEARCH ALGORITHM **updated 17/07/2019
//auto determine location of FAZ by sampling region starting from x = 20 - 300 steps of 10, y = 80 to 200, steps 5
run("Select None");
autowidth = 0; //if auto fails, manual overwrite available
for (k = 0; k < 24; k++) { //y-axis (vertical)
        for (i = 0; i < 28; i++) { //x-axis (horizontal)
                        doWand(20+i*10, 80+k*5); //x starting point =20,step 10,y starting point =80, y=steps 5
                        getSelectionBounds(x, y, width, height);
                        a = width;
                                if (a < 320) { //only register area if its less than the whole image size...
```

```
                                        if (a > 20) { //...and more than a spot (biologically
impossible FAZ sizes)
                                        autowidth = x+width/2;
                                        autoheight = y+height/2;
                                        }
                                }
                        }
}
}
//if auto fails, manual overwrite available
if (autowidth ==0){
        setTool("wand");
        waitForUser("Unable to locate FAZ. Please manually click on FAZ before clicking OK");
        getSelectionBounds(x, y, width, height);
        autowidth = x+width/2;
        autoheight = y+height/2;
        doWand(autowidth, autoheight);
}
else {doWand(autowidth, autoheight);
}
//**********end of auto faz detection**********


        run("Fill Holes");//clear central debris from FAZ
                doWand(autowidth,autoheight);
run("Enlarge...", "enlarge=4"); //enlarge and shrink back to make edges round
run("Enlarge...", "enlarge=-2");//shrink back 2 less than enlarge
run("Create Mask");
```

```
run("Fill Holes");//clear paracentral debris from FAZ
        doWand(autowidth,autoheight);
roiManager("Add");
        run("Select None");
        roiManager("deselect"); roiManager("Show None");
roiManager("select", roiManager("count")-1);roiManager("rename", "FAZ "+title);

//Measure FAZ parameters and size
//set scale & measurements to include circularity
run("Set Scale...", "distance=320 known=3000 unit=um");
run("Set Measurements...", "area mean min bounding shape feret's integrated area_fraction
redirect=None decimal=3");
        roiManager("Select", roiManager("count")-1);
                i = nResults;
                roiManager("Measure");
                c = getResult("Area", i);
                        setResult("Area(pixels)", i, pow(sqrt(c)*320/3000,2));
roiManager("select", roiManager("count")-1)));
                setResult("ID", i, title);
print("Results for "+title+ " density.txt"+" saved!");

//Print FAZ x,y coordinate for the next step of the macro
//fit circle around FAZ and get centre of FAZ coordinates
        run("Fit Ellipse");
        getSelectionBounds(x, y, width, height);
                FAZx = x+width/2;
                FAZy = y+height/2;
```

```
print("FAZ x="+FAZx+" y="+FAZy);
run("Select None");
roiManager("Deselect");
selectWindow("Mask");
close();//close Mask window


//close duplicate window after adding ROI to manager
list = getList("image.titles");
if (list.length > 1){
	close(list[list.length-1]);
}
roiManager("Select", roiManager("count")-1);


roiManager("Save",saveDir + " FAZ ROI compilation.zip");
saveAs("Results", saveDir + " compiled density.txt");
```

A8. Survey Study's Participant Information Sheet and Consent Form

Participant Information Sheet

Natural History of Diabetic Retinopathy in Pregnant Women
SURVEY OF DIABETIC EYE SCREENING EXAMINATION COMPLIANCE DURING PREGNANCY

Coordinating Investigator	**A/Prof. Lyndell Lim** Department of Surgery (Ophthalmology) The University of Melbourne Email: limllp@unimelb.edu.au
Principal Investigator	**A/Prof. Andrew Symons** Department of Surgery (Ophthalmology) Department of Optometry and Vision Sciences The University of Melbourne Email: andrew.symons@mh.org.au
Principal Investigator	**Dr. Alexis Shub** Diabetes and Endocrine Clinic The Mercy Hospital for Women Email: ashub@unimelb.edu.au
Principal Investigator	**A/Prof. Alison Nankervis** Diabetes and Endocrine Service The Royal Women's Hospital Email: alison.nankervis@mh.org.au
Principal Investigator	**A/Prof. Daryl Guest** Department of Optometry and Vision Sciences The University of Melbourne Email: daryl.guest@unimelb.edu.au
Principal Investigator	**Dr. Xavier Fagan** Department of Surgery (Ophthalmology) The Austin Hospital Email: xavier.fagan@unimelb.edu.au
Co-Investigator	**A/Prof. Jennifer Conn** Diabetes and Endocrine Service The Royal Women's Hospital Email: jjconn@unimelb.edu.au

Co-Investigator (PhD student)	**Dr. Felicia Widyaputri** Department of Surgery (Ophthalmology) The University of Melbourne Email: widyaputrif@unimelb.edu.au

Introduction

Thank you for your interest in participating in this survey which aims to determine the barriers that may prevent pregnant women from attending recommended diabetic eye examinations. It is part of a larger study where we are examining how the eyes may worsen during pregnancy in women with pre-existing diabetes.
The following few pages will provide you with further information about the survey, and any possible risks and benefits of participating this survey, so that you can decide if you would like to take part.
Please note that your participation is **voluntary**. If you don't wish to take part, you don't have to. If you join the survey you can stop at any time. Your decision to participate (or not) will have no influence on the clinical care and management that you will receive.

What is this survey about?

Diabetic Retinopathy (DR) is a sight threatening disease, which may occur in people with type 1 or type 2 diabetes. This disease results from diabetes causing damage to a delicate part of the eye called the retina, which functions inside your eye to make an image similarly to the way a film acts within a camera. Your retina can become severely damaged before you notice any problems with your eyes or vision. It is thought that in some people this damage may occur even faster during pregnancy. However, we are not yet sure whether this is definitely the case. We are also not sure if there are any risk factors, or reasons, that may cause diabetic retinopathy to worsen faster in some pregnant women than in others.

The aim of our main study is to address these knowledge gaps by collecting routine clinical data from pregnant diabetic patients who attend routine, standard eye examinations throughout their pregnancy and after delivery. These eye examinations are exactly as recommended by the National Health and Medical Research Council (NHMRC), a government organisation that oversees healthcare in Australia. By taking part in this main study, we will therefore help ensure that you get the eye care that you need.

As part of this main study, we are also keen to gather information on the barriers that may be encountered by pregnant women with diabetes that may prevent them from attending these NHMRC recommended eye screenings through a short survey. This will help the future development of a more accessible eye screening program and may contribute to the development of updated screening guidelines.

What will I be asked to do?

Should you agree to participate in the survey, you will be asked to read and sign this Patient Information and Consent Form. You will be offered to choose between two options. The FIRST option is to **only** do the survey without sharing any other data (demographic and clinical data), and the SECOND is to do the survey **and** consent to

share your data regarding your diabetes control and other medical data that relates to your pregnancy from your Endocrinologist or Obstetrician or Ophthalmologist or Optometrist. This data will be analysed to determine potential barriers to diabetic eye screening examinations in regard to your health status. After consenting, Dr Felicia Widyaputri, our study co-ordinator, will ask you to complete the survey whilst you wait for your regular ante-natal appointment. The survey will take approximately 10 to 15 minutes of your time. There are no 'right' or 'wrong' answers.

What are the possible benefits?

There may or may not be any direct benefits to you for participating in this survey. There will be no reimbursement for your time. As it is hoped that this study may help inform the future care of pregnant patients with diabetes and diabetic retinopathy, it may be of benefit to you in the future. This patient-centered approach might help to develop improved eye screening programs that are easier for patients to adhere to.

What are the possible risks?

We do not think there are any risks involved with participating in this survey. You may find some of the questions in the survey confronting (eg. The risk of vision loss due to diabetes; personal questions), however these are questions that can determine your understanding on diabetic retinopathy and your potential barriers to have the routine eye examinations.

There may be a risk of privacy breach in the data collection. However, this will be avoided by de-identifying all response and data that gathered during this survey. Also, the study records will be stored in locked storage and digital data will be kept in the password-protected software.

Do I have to take part?

No. Participation is **completely voluntary**. You are able to withdraw (quit) at any time without penalty and it will not affect your care.

Will I hear about the results of this survey?

The result of this survey may be published as journal articles and/or presented at conferences. We will also make copies of these articles available to you if you request them.

What will happen to information about me?

By signing the consent form you consent to the researchers collecting and using personal information about you for the research project. Full confidentiality of your medical data will be kept by the researchers, your Endocrinologist or Obstetrician - that is, by all people involved with the study. All personal data used in this survey will be de-identified and will be coded with a study identity and patient number (Example: DRP001) that will be assigned to you at the beginning of the survey. The study records will be stored in secured location and digital information will be kept in the software password protected.

Study records will be retained for 15 years after the completion of the study and only can be accessed by the researchers. If you agree, your anonymous data may also be used in the future for studies with a similar purpose. A report may be published; however, you will not be able to be identified in any publications or reports that arise from this study, as your identity will always be kept confidential in any such publication(s).

Where can I get further information?

If you have any further questions about this project, please contact the researchers; A/Prof Lyndell Lim (Email: limllp@unimelb.edu.au) or A/Prof Alison Nankervis (Email: alison.nankervis@mh.org.au) or Dr. Felicia Widyaputri (Ph: 0424902612, email: widyaputrif@unimelb.edu.au)

Who can I contact if I have any concerns about the project?

This survey has been approved by the Human Research Ethics Committee of The Melbourne Health (Ethics ID: 2018.019). If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact:

1. The Complaints Manager, Director Research Governance and Ethics, Royal Melbourne Hospital. Tel: +61 3 9342 8530 or email: Research@mh.org.au
   Or
2. Royal Women's Hospital Consumer Advocate. Tel: +61 3 8345 2290

All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project.

Consent Form

Natural History of Diabetic Retinopathy in Pregnant Women

SURVEY OF DIABETIC EYE SCREENING EXAMINATION DURING PREGNANCY

Coordinating Investigator: A/Prof. Lyndell Lim

Name of Participant: _____

1. I consent to participate in this survey, the details of which have been explained to me, and I have been provided with a written patient information to keep.
2. I understand that the purpose of this survey is to analyse the barriers and predict the adherence to diabetic eye screening examination in pregnant women.
3. I understand that my participation in this survey is for research purposes.
4. I acknowledge that the possible effects of participating in this survey have been explained to my satisfaction.
5. I understand that this survey will involve collection of my medical data from my medical records during my pregnancy if I choose option 2.
6. I understand that my participation is voluntary and that I am free to withdraw from this project at any time without explanation or prejudice and to withdraw any unprocessed data that I have provided.
7. I understand that the data from this survey will be stored at the University of Melbourne for a minimum of fifteen years after the completion of the project.
8. I have been informed that the confidentiality of the information I provide will be safeguarded subject to any legal requirements; my data will be password protected and accessible only by researchers approved by the Human Research Ethics Committee.
9. I am aware and give my approval for my anonymous data to be used in the future for studies with a similar purpose?

   ☐ **Yes** ☐ **No** (please tick)
10. I understand that after I sign and return this consent form, it will be retained by the University.

I have read, or have had read to me, and I understand the Survey Participant Information and Consent Form, Version 1.0 dated 10 September 2018.

Hereby, I consent to participate in this survey for option number:

☐ **1**: Only completing the survey questionnaire **without** sharing any of my data outside the questionnaire.

☐ **2**: Completing the survey questionnaire **and** sharing my medical data from my medical records during my pregnancy.

If available, I wish to receive a copy of the summary report on the survey findings?

☐ **Yes** ☐ **No** (please tick)

If Yes, please provide us with an email address to send this to:
_____

Participant Signature: _____ **Date:** _____

Printed name of researcher _____
Signature _____ **Date** _____
(To be signed and dated by the person who conducted the informed consent process)

Form for Withdrawal of Participation

Natural History of Diabetic Retinopathy in Pregnant Women

SURVEY OF DIABETIC EYE SCREENING EXAMINATION DURING PREGNANCY

Coordinating Investigator: A/Prof. Lyndell Lim

Declaration by Person Responsible

I wish to withdraw from participation in the above project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me.

Participant's Name (printed) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher[†]

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the person responsible for the participant has understood that explanation.

Researcher's Name (printed) _____

Signature _____ Date _____

[†] A senior member of the research team must provide the explanation of, and information concerning, withdrawal from the research project.
Note: All parties signing the consent section must date their own signature.

A9. Modified Compliance with Annual Diabetic Eye Exams Survey

CONFIDENTIAL

ONLY FOR RESEARCH PURPOSE

NATURAL HISTORY OF DIABETIC RETINOPATHY IN PREGNANT WOMEN

MODIFIED COMPLIANCE WITH ANNUAL DIABETIC EYE EXAMS SURVEY (CADEES)

ID Number : _____

Date : _____

Please answer each question by checking or circling the correct answer.

A. Have you ever had an eye exam when the doctor put drops in your eyes that made your pupils large? *If yes*, when was your last exam like that?

	Never
	Within the past month
	Within the past 2 – 3 months
	Within the past 4 – 6 months
	Within the past 7 – 12 months
	Within the past 1 – 2 years
	Within the past 2 – 5 years
	More than 5 years ago
	More than a year ago, but unsure of the exact time
	Don't know

Please read the following statements. For each statement, circle the number that best represents how you feel.

		Strongly disagree	**Disagree**	**No opinion/ Don't know**	**Agree**	**Strongly agree**
1.	My eyes are healthy.	1	2	3	4	5
2.	Early diabetic eye disease usually causes changes in vision.	1	2	3	4	5
3.	Having an eye exam is not pleasant.	1	2	3	4	5
4.	I am confident in my ability to make an appointment for an eye exam.	1	2	3	4	5
5.	Having an eye exam once a year can help me prevent losing my eyesight.	1	2	3	4	5
6.	I have trouble reading a book or newspaper, even if I use my glasses or contacts.	1	2	3	4	5

		Strongly disagree	Disagree	No opinion/ Don't know	Agree	Strongly agree
7.	Over the past 4 weeks I have felt blue, downhearted, or depressed.	1	2	3	4	5
8.	I know someone who has lost some or all of his/her eyesight because of problems from diabetes.	1	2	3	4	5
9.	I know a lot about diabetes and the effect it can have on health.	1	2	3	4	5
10.	Diabetes can result in a loss of visual function (e.g., difficulty reading, driving).	1	2	3	4	5
11.	I think I will lose some or all of my eyesight because of diabetes.	1	2	3	4	5
12.	I am confident I can keep a scheduled appointment with an eye doctor.	1	2	3	4	5
13.	I do not want to know if I have an eye disease.	1	2	3	4	5
14.	People who have good control of their diabetes are unlikely to have eye problems.	1	2	3	4	5
15.	Diabetes can cause severe eye problems.	1	2	3	4	5
16.	I would benefit from having an eye exam every year.	1	2	3	4	5

		Strongly disagree	Disagree	No opinion/ Don't know	Agree	Strongly agree	
17.	My medical provider (i.e., doctor, nurse, nurse practitioner) talks to me about the importance of eye exams.	1	2	3	4	5	6 No provider
18.	Eye exams cost too much.	1	2	3	4	5	
19.	There is no treatment for diabetic eye diseases.	1	2	3	4	5	
20.	It is hard for me to travel to an eye doctor.	1	2	3	4	5	
21.	There are many things that make it hard to get an eye exam every year.	1	2	3	4	5	
22.	I do not like having my eyes dilated with eye drops that make my pupils large.	1	2	3	4	5	
23.	I think it is important to have an eye exam every year.	1	2	3	4	5	
24.	My overall general health is excellent.	1	2	3	4	5	
25.	Diabetic eye disease can be seen with an eye exam.	1	2	3	4	5	
26.	Diabetes can damage the blood vessels in the eye.	1	2	3	4	5	
27.	There are many eye doctors where I live.	1	2	3	4	5	
28.	My family members or friends help me make doctor appointments.	1	2	3	4	5	

		Strongly disagree	Disagree	No opinion/ Don't know	Agree	Strongly agree	
29.	Eye exams can find many different kinds of eye problems.	1	2	3	4	5	
30.	I am confident I can control my blood sugar.	1	2	3	4	5	
31.	Having a yearly eye exam will help me to save the eyesight I have now.	1	2	3	4	5	
32.	People with diabetes are unlikely to get an eye disease.	1	2	3	4	5	
33.	I cannot afford an eye exam.	1	2	3	4	5	
34.	My insurance covers most of the cost of an eye exam.	1	2	3	4	5	6 No insurance
35.	There are things I can do to prevent losing my vision from diabetes.	1	2	3	4	5	
36.	Diabetic eye diseases often cause blindness.	1	2	3	4	5	
37.	I have medical problems from diabetes.	1	2	3	4	5	
38.	I want to get an eye exam every year.	1	2	3	4	5	
39.	I only seek eye care when I am having trouble with my vision.	1	2	3	4	5	
40.	Getting an eye exam every year is not one of my top priorities.	1	2	3	4	5	

41. I have an eye doctor I can go to for diabetic eye exams.

	Yes (Go to Q42)
	No (Go to Q45)

If **YES**

		Strongly disagree	**Disagree**	**No opinion/ Don't know**	**Agree**	**Strongly agree**
42.	I receive a reminder from my eye doctor's office when it is time to schedule an exam.	1	2	3	4	5
43.	I am happy with the care I get from my eye doctor.	1	2	3	4	5
44.	Visiting the eye doctor takes too much time.	1	2	3	4	5

45. We are interested in why some people do not have routine eye exams during pregnancy. Can you think of any reasons we did not ask about in this survey?

_____

_____

B. Do you know that during pregnancy, you should have your eyes checked more often?

	Yes
	No

C. Who did you see for your eye examination? *Tick all that apply*

	Optometrist
	Eye Doctor/ Ophthalmologist
	GP/ Local Doctor
	Nurse
	Health Worker
	Ophthalmic Nurse/ Technician
	Other, please specify _____

D. Did you attend pre-pregnancy care for your current pregnancy?

	Yes
	No

E. Please rank each of the following appointments in order of importance with **#1** being the **most important** appointments during your pregnancy to **#7** being the **least important** appointments during your pregnancy.

	Obstetrician
	Eye Doctor/ Ophthalmologist, Optometrist
	GP/ Local Doctor
	Endocrinologist
	Dietitian
	Diabetes Educator
	Podiatrist

F. When were you diagnosed with diabetes?

	Months (if under one year)
	Years

G. Do you have Type I or Type II diabetes?
Type I is often known as juvenile onset or insulin-dependent diabetes, and Type II is often known as adult onset diabetes that sometimes is insulin-dependent and sometimes is not.

	Type 1
	Type 2
	Uncertain

H. Do you use insulin?

	Yes, since _____ months ago
	Yes, since _____ years ago
	No

I. Do you have problems with any of the following?

Y/N	Condition	Comments
	Diabetic coma	
	Hypoglycemia (“Hypos”)	
	Heart disease, heart attack	
	High blood pressure	
	Stroke	
	High cholesterol	
	Kidney disease	
	Thyroid problems	
	Problems with the nerves in your feet	
	Other health issue, please specify _____ _____ _____	

J. Have you been diagnosed with diabetic eye disease (diabetic retinopathy)?

	Yes, when? _____
	No

If yes, have you had any treatment for it?

	Yes
	No

K. Do you have health insurance?

	Yes
	No

L. What is your year of birth?
_____ [enter the year]

M. What is your relationship status?

	Single
	Married
	Separated
	Divorced
	Widowed
	Domestic partnership

N. What is the highest level of education you have finished?

	No education
	Primary education incomplete
	Completed primary education
	Completed primary and some years of secondary education
	Completed primary and secondary education
	Attending/completing trade school or TAFE
	University student
	Completed university degree
	Undertaking/completed post graduate study

O. The next few questions will ask about your race and ethnicity.

Y/N	**Ethnicity**
	Aboriginal & Torres Strait Islander People
	South Pacific Islanders
	Caucasian
	North African & Middle Eastern
	Asian
	Peoples of The Americas
	Sub-Saharan African
	Others, please specify _____

P. What is the total combined annual income, before taxes and deductions, of everyone who lives in your home?

Tick one	Yearly Annual Income
	Less than $15,000
	$15,000 to $24,999
	$25,000 to $34,999
	$35,000 to $49,999
	$50,000 to $74,999
	$75,000 to $99,999
	$100,000 or more
	Do not want to answer

A10. Online Survey Invitation and Reminder Scripts

A10.1. Invitation

Email

Subject: Diabetic Retinopathy in Pregnancy Study - Survey

Dear [name]

Thank you for your participation in our research project entitled "Natural History of Diabetic Retinopathy in Pregnant Women".

As part of the study, we aim to gather information on the barriers that may be encountered by pregnant women with diabetes that may prevent them from attending the diabetic eye screenings as recommended by the National Health and Medical Research Council (NHMRC), a government organisation that oversees healthcare in Australia. This will help the future development of a more accessible eye screening program and may contribute to the development of updated screening guidelines. You have consented to participate in the survey study on [DATE]; however, **our records show that you have not yet completed your survey.**

The survey will take **about 5 minutes** of your time. There are no 'right' or 'wrong' answers. Participation in this survey is voluntary. If you do not want to continue with the survey, please open the survey link below and tick the option "No" in the first question (*Do you wish to continue with the survey?*).

You may open the survey in your web browser by clicking the link below: Modified Compliance with Annual Diabetic Eye Exams Survey (*hyperlink*)

If the link above does not work, try copying the link below into your web browser:

https://redcap.healthinformatics.unimelb.edu.au/surveys/?s=I5NoWGK2us

Please make sure that you click SUBMIT button at the end. This link is unique to you and should not be forwarded to others. All of the information you provide in this survey will be kept confidential.

The survey will remain open until 30 August 2019.

We will share the results of this study with you next year (if you chose to receive a copy of the summary in your consent form). If you have any questions, please do not hesitate to contact me by replying to this email.

We look forward to your participation in this survey. Thank you in advance.
Kind regards,
Dr. Felicia Widyaputri
Study Coordinator
Centre for Eye Research Australia Opthalmology, University of Melbourne

SMS

Dear [name]
Thank you for your participation in the research project "Natural History of Diabetic Retinopathy in Pregnant Women". As part of the project, we aim to gather information on the barriers that you may experience that prevent you from attending the recommended eye screenings. You have consented to participate in the survey study on [DATE]; however, **our records show that you have not yet completed your survey.** Please go to this link to complete the survey:

https://redcap.healthinformatics.unimelb.edu.au/surveys/?s=I5NoWGK2us

It will take about 5 minutes of your time. Please reply to this SMS if you need assistance. Thank you, Dr. Felicia Widyaputri, Centre for Eye Research Australia, Ophthalmology, University of Melbourne.

A10.2. Reminder

Email

Dear [name]
Thank you for your participation in our research project entitled "Natural History of Diabetic Retinopathy in Pregnant Women". This is a reminder for you to participate in our survey.

As part of the study, we recently sent you an invitation via email to complete a survey that aims to gather information on the barriers that may be encountered by pregnant women with diabetes that may prevent them from attending the National Health and

Medical Research Council (NHMRC) recommended eye screenings. **Our records show that you have not yet submitted the survey.** Your participation in this survey will help the future development of a more accessible eye screening program and may contribute to the development of updated screening guidelines.

The survey will take **about 5 minutes** of your time. There are no 'right' or 'wrong' answers. Participation in this survey is voluntary. If you do not want to continue with the survey, please open the survey link below and tick the option "No" in the first question (*Do you wish to continue with the survey?*).

You may open the survey in your web browser by clicking the link below: Modified Compliance with Annual Diabetic Eye Exams Survey (*hyperlink*)
If the link above does not work, try copying the link below into your web browser:
https://redcap.healthinformatics.unimelb.edu.au/surveys/?s=I5NoWGK2us
Please make sure that you click SUBMIT button at the end. This link is unique to you and should not be forwarded to others. All of the information you provide in this survey will be kept confidential.

The survey will remain open until 30 August 2019.

We will share the results of this study with you next year (if you chose to receive a copy of the summary in your consent form). If you have any questions, please do not hesitate to contact me by replying to this email.

We look forward to your participation in this survey. Thank you in advance.
Kind regards,
Dr. Felicia Widyaputri
Study Coordinator
Centre for Eye Research Australia Ophthalmology, University of Melbourne

SMS

Dear [name]
This is a reminder for you to participate in our survey for the "Natural History of Diabetic Retinopathy in Pregnant Women" study. As part of the study, we recently sent you an

invitation via SMS to complete a survey that aims to gather information on the barriers that you may experience that prevent you from attending the recommended eye screenings. **Our records show that you have not yet submitted your survey.** Please go to this link to complete the survey:

https://redcap.healthinformatics.unimelb.edu.au/surveys/?s=I5NoWGK2us

It will take about 5 minutes of your time. Your participation will really be appreciated. If you do not want to continue with the survey, please reply "NO" to this SMS. Please reply this SMS if you need assistance. Thank you, Dr. Felicia Widyaputri, Centre for Eye Research Australia, Ophthalmology, University of Melbourne.