Author/s:
Seah, JM;Kam, NM;Wong, L;Tanner, C;Shub, A;Houlihan, C;Ekinci, EI

Title:
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Date:
2021-01-01

Citation:
Seah, J. M., Kam, N. M., Wong, L., Tanner, C., Shub, A., Houlihan, C. & Ekinci, E. I. (2021). Risk factors for pregnancy outcomes in Type 1 and Type 2 diabetes. Internal Medicine Journal, 51 (1), pp.78-86. https://doi.org/10.1111/imj.14840.

Persistent Link:
https://hdl.handle.net/11343/298083

Tanner Cara (Orcid ID: 0000-0001-5528-3966)
Ekinci Elif (Orcid ID: 0000-0003-2372-395X)

Title:

Risk factors for pregnancy outcomes in type 1 and type 2 diabetes

Authors:

Jas-mine Seah [1 2 3] (MBBS), Ning Mao Kam [2 3] (MD), Lydia Wong [2] , Cara Tanner[2 3] (MD), Alexis Shub [1 3] (MBBS), Elif I. Ekinci [2 3] *(PhD), Christine Houlihan [1 2] (MD) *

* Equal contribution

1. *Department of Perinatal Medicine Mercy Health, Heidelberg, VIC, Australia*
2. *Department of Endocrinology Austin Health, Heidelberg, VIC, Australia*
3. *Department of Medicine Austin Health, The University of Melbourne, Melbourne, VIC, Australia*

Word Counts

Abstract: 247

Main text: 3109

Funding

RACP-JDRF Research Establishment Fellowship

Conflicts of Interest

None

BACKGROUND:

Adverse maternal and neonatal outcomes have been reported up to nine times higher in women affected by pre-gestational diabetes compared to those without. [1, 2] Pregnancy outcomes in women with type 1 diabetes have generally been a focus in the literature. However, the incidence of pregnancies affected by type 2 diabetes has surpassed that of type 1 diabetes in Australia. [3-5] This predominance of type 2 diabetes, to almost four times that of type 1 diabetes has also been shown in a large diabetes-pregnancy epidemiology study. [6] Suboptimal glycaemic management, particularly in the third trimester is associated with preeclampsia in women with type 1 diabetes. [7] Such a relationship has not been established in pregnancies of women with type 2 diabetes and the presence of pre-existing hypertension in this cohort complicates the picture. Furthermore, a major challenge in interpreting current literature in this field is the lack of homogeneity in outcome measures and determination of risk factors throughout pregnancy.

The aim of this study was to investigate the association of maternal and neonatal outcomes, with established risk factors throughout the pregnancy. We hypothesized

that in women attending a tertiary university hospital in metropolitan Melbourne, Australia, those affected by type 1 and type 2 diabetes will have greater risk of adverse outcomes compared to women without diabetes.

METHODS:

Women with type 1 and type 2 diabetes, who delivered in a tertiary obstetric medical centre, over a 10-year period from July 2004 to July 2014 were identified via hospital database. Diagnosis of type 1 and type 2 diabetes was confirmed on clinician entry. Patients with unclear diabetes diagnosis, gestational diabetes, and inconsistent or lack of baseline measures of glycaemia were excluded. One hundred and nineteen prospectively recruited healthy women as an extension from a separate study were included in the study as the control group. [8, 9] The prospective cohort were healthy pregnant women presenting at or prior to 13 weeks of gestation at the same tertiary obstetric hospital between 2006-2011. Exclusion criteria included women with known type 1 and type 2 diabetes, past history of thyroid disease and positive thyroid peroxidase antibodies, thyroid hormone replacement therapy, past history of intravenous drug abuse or the presence of major systemic illness

We excluded women with multiple-pregnancies, spontaneous or elective abortion within the first 20 weeks of pregnancy. Study investigators reviewed all medical record and pathology entries from the diagnosis of pregnancy until discharge following delivery. Mercy Health Human Research Ethics Committee approved this study.

Anthropometric and Pathology Data

We collected anthropometric data throughout pregnancy, starting from the first antenatal visit. The initial visit entries were considered as baseline data. Data were obtained by manual reviews of the patient medical record. Presence of pre-existing hypertension was based on clinician entry and use of anti-hypertensive agents. Women who were on anti-hypertensive agents solely for the purpose of reno-protection without hypertension were not classified as having pre-existing hypertension.

Blood pressure and all biochemical parameters from each trimester during routine, stable clinical assessments were averaged for each individual. Parameters from every trimester were included as means for each covariable, as the cumulative exposures throughout pregnancy were considered important for pregnancy outcomes. Biochemical and clinical data obtained during acute and intra-partum admissions were excluded. HbA_{1c} was used to represent glycaemic management. Renal function was measured by serum creatinine. Due to the lack of a direct measurement of glomerular filtration rate, estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Cohort (CKD-EPI) formula. [10]

The following risk factors were included in analyses: maternal age, body mass index (BMI), type of diabetes, mean HbA_{1c}, mean eGFR, and mean systolic and diastolic blood pressure. Rather than trimester specific values, the mean HbA_{1c}, blood pressure

and eGFR of the whole pregnancy were utilised in the analytical model to take into consideration the overall levels of these risk factors throughout pregnancy. The major obstetric outcome measures were: preeclampsia, preterm birth < 37 weeks and < 32 weeks, large for gestational age (LGA), small for gestational age (SGA) and neonatal intensive care (NICU) admission.

Outcome Measures

For the purpose of this study, maternal and perinatal outcomes were defined using The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) recommended guidelines [11] and clinician diagnosis. Pregnancy induced hypertension was based on the absence of a pre-existing diagnosis of hypertension, as well as systolic blood pressure (sBP) > 140 mmHg with or without diastolic blood pressure (dBP) > 90 mmHg, on three or more measurements. Preeclampsia was defined as a development of sBP > 140 mmHg with or without dBP > 90 mmHg, and proteinuria (> 0.3 g/24h or ≥30mg/mmol) after 20 weeks gestation. Primary postpartum haemorrhage was defined as a blood loss of either > 500 ml post vaginal delivery or > 1000 ml post caesarean delivery within 24 hours of delivery.

Preterm birth was categorised as delivery at 32-37 weeks and early preterm birth as prior to 32 weeks (with no separation between spontaneous and iatrogenic). Infant birthweight was measured at delivery using standard weighing scales. Birthweight percentiles and z-scores corrected for gestational age were calculated based on a

reference population at the same hospital. [12] The z-score was calculated as: (observed birthweight – mean birthweight for gestational age)/ standard deviation of the mean birthweight. LGA and SGA, were defined as birthweights > 90th centile and < 10th centile, respectively. Neonatal jaundice was defined as hyperbilirubinemia requiring phototherapy. Major congenital malformations were those responsible for death, those causing a significant future disability, or those requiring major surgery requiring correction. Neonatal hypoglycaemia was defined as blood glucose of < 2.6 mmol/l in the early neonatal period. Fetal death in utero was defined as fetal death later than 20 weeks gestation.

Statistical Analysis

Univariate analysis was performed with Wilcoxon rank sum test for continuous variables, and Chi-square tests or Fisher's exact tests for categorical variables. Comparisons were made between type 1 and type 2 diabetes pregnancies (Table 1 and 3), and healthy controls with the combined diabetes group (Table 2 and 4).

We undertook univariate logistic analyses to assess associations with established risk factors (including age, blood pressure, BMI, renal function and HbA1c) and four major outcomes of preeclampsia, preterm birth < 32 and 37 weeks, and neonatal intensive care admission in women with and without pregestational diabetes (combined type 1 and type 2 diabetes). Sub-group analysis was also performed comparing outcomes in women with type 1 diabetes to type 2 diabetes. The co-linearity of the model prohibited

appropriate inclusion of these risk factors into a multivariable analysis. Due to the multiple outcome measures, we corrected for multiplicity testing using the Bonferroni correction with a threshold of significance at $P = 0.03$.

RESULTS:

Maternal Characteristics

Over the ten-year period, 307 singleton pregnancies were included in the analysis: 119 healthy women without diabetes; 92 women with type 1 diabetes; and 106 women with type 2 diabetes (Table 1 & Figure 1).

Women with type 2 diabetes had more advanced age and higher BMI. Women with type 1 diabetes had statistically significant longer duration of diabetes, marginally higher HbA_{1c}, and higher prevalence of microvascular complications. Lower renal function as reflected by lower eGFR, and higher serum creatinine was evident in the type 1 diabetes cohort (Table 1). Longitudinal data across all three trimesters (Figure 1), demonstrated that women with type 2 diabetes had a significantly lower HbA_{1c} (Figure 1a) but a higher blood pressure (Figure 1b and 1c) compared to women with type 1 diabetes. Women without pre-gestational diabetes were younger and had a lower BMI compared to women with type 1 and type 2 diabetes (Table 2).

Maternal and Neonatal Outcomes

Pregnancy and neonatal outcomes are demonstrated comparing type 1 and type 2 diabetes (Table 3) individually. Furthermore, to illustrate the differences between healthy and pregnancies affected by diabetes, we combined type 1 and type 2 diabetes; comparing the collective diabetes cohort to controls (Table 4). Birth weight gestational centile (median 97.4% vs. 72.4%; $P < 0.001$) and LGA rates (63.4% vs. 35.8%; $P < 0.001$) were higher in women with type 1 diabetes compared to type 2 diabetes. Women with type 2 diabetes had an approximate doubling of SGA compared to type 1 diabetes (15.1% vs. 5.4%; $P = 0.02$). There was no statistically significant difference in other major perinatal and obstetrics outcomes between women with type 1 and type 2 diabetes (Table 3). Sixteen percent of women with diabetes (type 1 and type 2 combined) developed preeclampsia compared to four percent in the control group ($P = 0.003$).

Compared to healthy pregnancies (Table 4), the odds of preeclampsia (odds ratio [OR], 4.4; 95% confidence interval [CI], 1.7-11.6; $P = 0.003$), emergency caesarean delivery (OR, 2.7; 95% CI, 1.5-4.9; $P = 0.001$), LGA (OR, 2.8; 95% CI, 1.7-4.7; $P < 0.001$), Apgar score less than 7 (OR, 5.8; 95% CI, 1.3-25.7 $P = 0.02$), neonatal intensive care admission (OR, 5.2; 95% CI, 2.0-13.7; $P = 0.001$), preterm birth at less than 32 (OR, 12.5; 95% CI, 1.7-94.8; $p = 0.01$) and 37 weeks (OR, 6.3; 95% CI, 3.0-13.1; $P < 0.001$) were all significantly higher in women with diabetes. Only SGA and neonatal congenital malformation was not significantly different between the two groups.

Predictors of adverse pregnancy outcomes in women with pre-gestational diabetes

HbA_{1c} was not associated with major outcomes. A one mmHg increase in systolic and diastolic blood pressure was associated with higher odds of developing preeclampsia (OR of 1.1 [95% CI, 1.0-1.1; *P* = 0.001] and 1.1 [95% CI, 1.1-1.2; *P* < 0.001], respectively) and preterm birth at 37 weeks (OR of 1.1 [95% CI, 1.0-1.1; *P* < 0.001] and 1.1 [95% CI, 1.0-1.1; *P* = 0.005], respectively)

Higher BMI was associated with higher odds of developing pregnancy-induced hypertension (OR, 1.1; 95% CI, 1.0-1.1; *P* = 0.01) and preeclampsia (OR, 1.0; 95% CI, 1.0-1.1: *P* = 0.05). Increasing age (per year) was also associated with higher odds of developing preterm birth < 32 weeks (OR, 1.1; 95% CI, 1.0-1.2; *P* = 0.01). Each ml/min/1.73m^2 decrease in eGFR (*P* < 0.001) was associated with higher odds of developing preeclampsia (OR, 1.1; 95% CI, 1.0-1.1), preterm birth 32 (OR, 1.1; 95% CI, 1.0-1.1) and 37 weeks (OR, 1.0; 95% CI, 1.0-1.1) and neonatal intensive care admission (OR, 1.1; 95% CI, 1.0-1.1).

Smoking was not associated with any major outcomes apart from the higher odds of developing pre-eclampsia (OR, 1.9; 95% CI, 1.1, 3.1).

As limited by the co-linearity of the model, multivariable analyses for the above risk factors were not conducted.

DISCUSSION:

The most important findings in this study were that the rates of poor outcomes were comparable between type 1 and type 2 diabetes. The measures of poorer outcomes in pre-existing maternal diabetes were present across most (thirteen out of sixteen) of outcome measures, and consistent with current literature. [13] In addition, we identified maternal blood pressure, BMI, and renal function to be important predictors of risk for poor outcomes.

Comparison to Previous Studies

We found similar pregnancy outcomes in type 1 and type 2 diabetes. This is in contrast with some studies [13-16] suggesting more adverse consequences in pregnancies affected by type 2 diabetes. A study by Hillman and colleagues[17] attempting to address this concluded that pregnancy outcomes were better in type 2 diabetes when intensified glycaemic management, as gauged by HbA_{1c}, were as rigorous as in women with type 1 diabetes. In our study, we did not find better outcomes in women with type 2 diabetes despite lower HbA_{1c}. The glycaemic pattern throughout pregnancy from the study by Clausen et al. was not dissimilar to our study, along with others which failed to find any differences in outcomes between type 1 and type 2 diabetes. [14] Of note however, timely intensive glucose therapy was shown to reduce spontaneous abortion and congenital malformation in the diabetes in Complication and Control Trial (DCCT) in women with type 1 diabetes. [18]

Findings of LGA rates being significantly higher in pre-gestational diabetes compared to healthy women, supports glucose as a major mediator of growth. [19] Exaggeration of the physiological insulin resistance in pregnancy that occurs in maternal diabetes can promote hyperglycaemia. Independent association of HbA_{1c} with LGA, has been found in previous type 1 diabetes studies. [20, 21] However a mean HbA_{1c} of 6.5% (48 mmol/mol), which was found to be associated with other poor outcomes in previous studies including preterm birth before 37 weeks, composite neonatal outcomes and preeclampsia, [20] was not found in our cohort. A systemic review of 13 studies in relation to HbA_{1c} and outcomes identified overall poorer, but unpredictable and diverse outcomes from study to study. [22] Of note, in the presence of an acceptable HbA_{1c}, higher median glucose readings especially in the second trimester are closely related to LGA in type 1 diabetes. [21] These inconsistencies linking HbA_{1c} to adverse outcomes illustrate the limitation of using HbA_{1c} as an indicator of fetal glucose exposure during pregnancy. Targeting near normal glycaemia throughout the entire pregnancy is desirable [23, 24] and may be more enabled by further advances in technology of insulin delivery and intensive real time glucose monitoring. In fact, a recent multicentre randomized controlled trial [25] demonstrated improved neonatal outcomes for mothers with type 1 diabetes using continuous glucose monitoring during pregnancy, with lower incidence of large for gestational age, fewer neonatal intensive care admissions and fewer instances of neonatal hypoglycaemia.

Obesity has been linked with intra-uterine growth restriction, [26] which may partially explain the lower birthweight centile in infants born to type 2 diabetes women in our cohort, with a median BMI within the obese range. The effect of obesity and risk of SGA may be related to the inadequate weight gain of women [27] with the introduction of gestational weight gain guidelines which recommends a lower weight gain pregnancy threshold for women with elevated BMIs. [28] In contrast, a recent study has shown a different pattern, whereby there appears to be an association with maternal obesity and accelerated fetal growth, especially when combined with gestational diabetes. [29] In addition, a recent Australian study established a higher BMI in women with both type 1 and type 2 diabetes with infants more likely to be LGA compared to healthy controls. [30, 31] Whether BMI explains the significantly lower birth weight and smaller gestational age in our type 2 diabetes cohort will need to be further investigated, especially with the lack of documented gestational weight changes in our cohort of women, as well as being confounded by the increasing co-morbidities that accompany this, including hypertension. [32]

Hypertension has a combined additive effect with diabetes on SGA, [33] which may partly explain the higher rates of SGA in our type 2 diabetes cohort. Intensive blood pressure management in diabetic kidney disease has been shown to benefit outcomes in this group of high-risk pregnancy. [34, 35]

Supplementing current Australian Pre-gestational Outcome Data

The similar proportion of both type 1 and type 2 women with diabetes in our study may still reflect the under-recognition of the need to direct specialist care for these high-risk women. This is further highlighted with 25% of all type 2 diabetes and 3% of type 1 diabetes patients registered with the National Diabetes Service Scheme were from childbearing age of 21-39 years. [36, 37] From a study published in 2005, involving ten teaching hospitals in Australia [5] with comparable numbers (n = 180), the mean age of conception in our study was higher, particularly in type 2 diabetes reflecting current societal trends of deferred pregnancies. The incidence (4.6% vs. 8.1%) of major congenital malformations was also less, however, our study excluded women with spontaneous abortion of pregnancy before 20 weeks and elective terminations. Taking into consideration, findings of a New Zealand study, [16] which demonstrated higher perinatal mortality in type 2 diabetes and gestational diabetes compared to our study, exclusion of gestational diabetes in our study may potentially exclude very small number of undiagnosed late type 2 diabetes cases that may contribute to neonatal deaths.

In contrast to our findings, a 2010 report based on the National Hospital Morbidity Database [3] found that mothers with type 1 diabetes had higher rate of hypertension. We believe that manually obtaining blood pressure readings, as performed in our study, provided better overall representation of the presence of hypertension than that of a single documentation of self- or clinician reported diagnosis. The findings of higher preterm birth and caesarean-section in type 1 diabetes compare to type 2 diabetes were

not replicated by findings of our study. This may reflect different populations, with the fact that our study was conducted at a tertiary centre and possibly also due to improvements in clinical practice over time.

The most recent Australian study reporting pregnancy outcomes in type 1 [31] and type 2 diabetes [30] compared to the same cohort of healthy controls highlighted the adverse outcomes in this high risk group, underscoring the importance of HbA_{1c} and glycaemic management. Our study complements the literature by examining the association of outcomes with additional variables of blood pressure, eGFR and other clinical and biochemical data. Risk factors for patients with diabetes were also pooled in our study when compared to healthy controls, which may explain some of the discrepancies in our respective study findings.

Strengths and Limitations

This was an observational, retrospective study and we recognize that there may be incomplete data collection. For example, we excluded women with inconsistent and absent baseline glycaemia measurement. This may result in missing some cases of pre-gestational diabetes, but on the other hand allow for a low false positive rate on the diagnosis of type 2 diabetes. The cause of preterm birth was also not determined, which would have allowed insight into future management of these cases.

The applicability of findings outside of our institution may also be limited. This includes the relatively well-controlled blood pressure and reasonable glycaemic management which may reflect practices within a tertiary obstetric hospital and affect the overall outcomes. However, as the focus on the importance of obstetric blood pressure and glycaemic management is increasing, our findings may be applicable more broadly with time.

Finally, as this is one of the larger observational studies in Australia in recent years, our findings may be helpful in counselling women with diabetes regarding pregnancy outcomes in contemporary Australian practice.

CONCLUSION:

Both type 1 and type 2 diabetes carry a similar high risk for poorer maternal and fetal outcomes compared to healthy pregnancies. Although estimates of associations between the maternal risk factors and adverse outcomes should be regarded as exploratory in a cohort of this sample size, age, higher BMI, higher systolic and diastolic blood pressure, and lower eGFR predicted poorer outcomes.

CONTRIBUTION TO AUTHORSHIP:

JS, CH, EIE and AS designed the study and conceptualized the research question. JS, NK, LW was involved in data collection. JS, NK and LC analyzed the data. JS and NK drafted the article. All authors critically reviewed and approve the final version of the article.

REFERENCES:

1. Yang J, Cummings EA, O'Connell C, Jangaard K. Fetal and neonatal outcomes of diabetic pregnancies. Obstet Gynecol. 2006;108(3 Pt 1):644-50.
2. Jensen DM, Damm P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies: a nationwide, population-based study. Diabetes Care. 2004;27(12):2819-23.
3. Welfare AIoHa. Diabetes in pregnancy: its impact on Australian women and their babies. Canberra: AIHW; 2010.
4. 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.
5. 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.

6. Jovanovic L, Liang Y, Weng W, Hamilton M, Chen L, Wintfeld N. Trends in the incidence of diabetes, its clinical sequelae, and associated costs in pregnancy. Diabetes Metab Res Rev. 2015;31(7):707-16.

7. Holmes VA, Young IS, Patterson CC, Pearson DW, Walker JD, Maresh MJ, et al. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. Diabetes Care. 2011;34(8):1683-8.

8. Ekinci EI, Lu ZX, Sikaris K, Bittar I, Cheong KY, Lam Q, et al. Longitudinal assessment of thyroid function in pregnancy. Ann Clin Biochem. 2013;50(Pt 6):595-602.

9. Ekinci EI, Chiu WL, Lu ZX, Sikaris K, Churilov L, Bittar I, et al. A longitudinal study of thyroid autoantibodies in pregnancy: the importance of test timing. Clin Endocrinol (Oxf). 2015;82(4):604-10.

10. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

11. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Statements and Guidelines. Melbourne: RANZCOG [cited 12 May 2017]. Available from: https://www.ranzcog.edu.au/Statements-Guidelines/

12. Mongelli M, Figueras F, Francis A, Gardosi J. A customized birthweight centile calculator developed for an Australian population. Aust N Z J Obstet Gynaecol. 2007;47(2):128-31.

13. Boulot P, Chabbert-Buffet N, d'Ercole C, Floriot M, Fontaine P, Fournier A, et al. French multicentric survey of outcome of pregnancy in women with pregestational diabetes. Diabetes Care. 2003;26(11):2990-3.

14. Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. Diabetes Care. 2005;28(2):323-8.

15. Dunne F, Brydon P, Smith K, Gee H. Pregnancy in women with Type 2 diabetes: 12 years outcome data 1990-2002. Diabet Med. 2003;20(9):734-8.

16. Cundy T, Gamble G, Townend K, Henley PG, MacPherson P, Roberts AB. Perinatal mortality in Type 2 diabetes mellitus. Diabet Med. 2000;17(1):33-9.

17. 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.

18. Pregnancy outcomes in the Diabetes Control and Complications Trial. Am J Obstet Gynecol. 1996;174(4):1343-53.

19. Nahavandi S, Seah JM, Shub A, Houlihan C, Ekinci EI. Biomarkers for Macrosomia Prediction in Pregnancies Affected by Diabetes. Front Endocrinol (Lausanne). 2018;9:407.

20. Maresh MJ, Holmes VA, Patterson CC, Young IS, Pearson DW, Walker JD, et al. Glycemic targets in the second and third trimester of pregnancy for women with type 1 diabetes. Diabetes Care. 2015;38(1):34-42.

21. Kerssen A, de Valk HW, Visser GH. Increased second trimester maternal glucose levels are related to extremely large-for-gestational-age infants in women with type 1 diabetes. Diabetes Care. 2007;30(5):1069-74.

22. Inkster ME, Fahey TP, Donnan PT, Leese GP, Mires GJ, Murphy DJ. Poor glycated haemoglobin control and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: systematic review of observational studies. BMC Pregnancy Childbirth. 2006;6:30.

23. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, et al. HbA1c levels are significantly lower in early and late pregnancy. Diabetes Care. 2004;27(5):1200-1.

24. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. BMJ. 2008;337:a1680.

25. 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.

26. Radulescu L, Munteanu O, Popa F, Cirstoiu M. The implications and consequences of maternal obesity on fetal intrauterine growth restriction. J Med Life. 2013;6(3):292-8.

27. Xu Z, Wen Z, Zhou Y, Li D, Luo Z. Inadequate weight gain in obese women and the risk of small for gestational age (SGA): a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2017;30(3):357-67.

28. Lactation IoMUCoNSDPa. Nutrition During Pregnancy: Part I Weight Gain: Part II Nutrient Supplements. Washington (DC): National Academies Press (US); 1990.

29. Sovio U, Murphy HR, Smith GC. Accelerated Fetal Growth Prior to Diagnosis of Gestational Diabetes Mellitus: A Prospective Cohort Study of Nulliparous Women. Diabetes Care. 2016;39(6):982-7.

30. Abell SK, Boyle JA, de Courten B, Soldatos G, Wallace EM, Zoungas S, et al. Impact of type 2 diabetes, obesity and glycaemic control on pregnancy outcomes. Aust N Z J Obstet Gynaecol. 2017;57(3):308-14.

31. 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. The Medical journal of Australia. 2016;205(4):162-7.

32. Catov JM, Nohr EA, Olsen J, Ness RB. Chronic hypertension related to risk for preterm and term small for gestational age births. Obstet Gynecol. 2008;112(2 Pt 1):290-6.

33. Yanit KE, Snowden JM, Cheng YW, Caughey AB. The impact of chronic hypertension and pregestational diabetes on pregnancy outcomes. Am J Obstet Gynecol. 2012;207(4):333 e1-6.

34. 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.

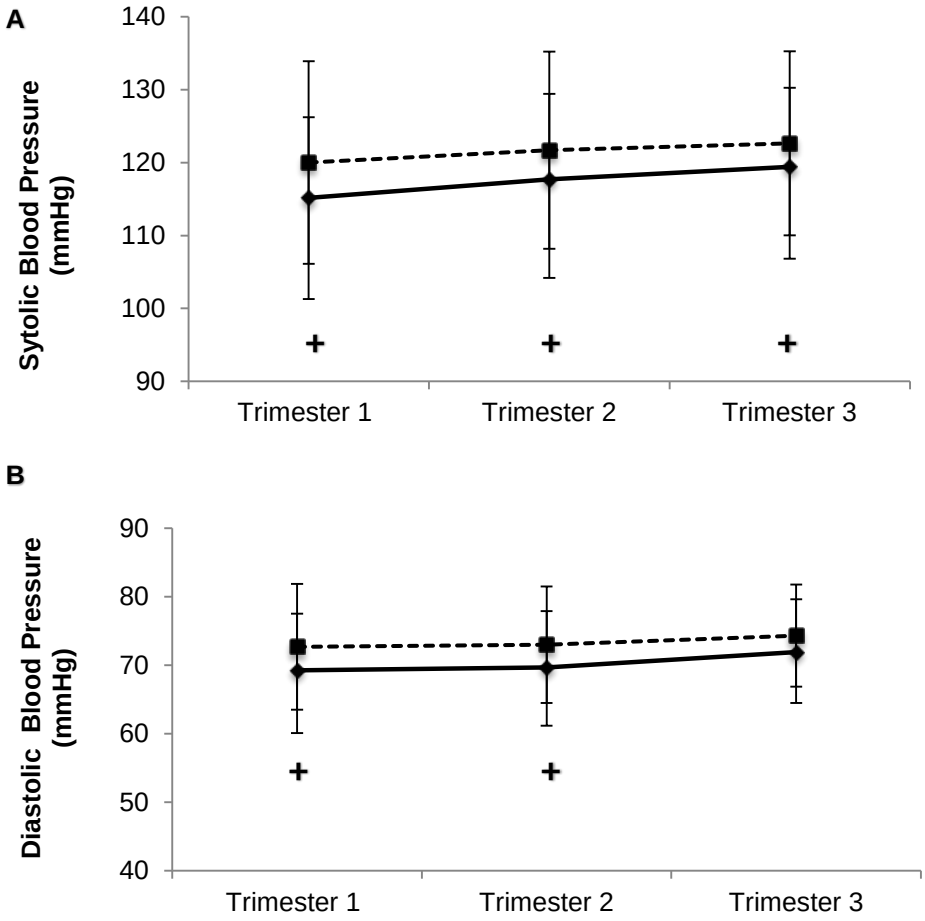
35. Carr DB, Koontz GL, Gardella C, Holing EV, Brateng DA, Brown ZA, et al. Diabetic nephropathy in pregnancy: suboptimal hypertensive control associated with preterm delivery. Am J Hypertens. 2006;19(5):513-9.

36. Diabetes Australia, Data Snapshot - Type 1 Diabetes in National Diabetes Service Scheme Statistics. 2018.

37. Diabetes Australia, Data Snapshot - Type 2 Diabetes in National Diabetes Service Scheme Statistics. 2018.

FIGURES

Figure 1. Comparison of (A) systolic blood pressure and (B) diastolic blood pressure and (C) glycosylated haemoglobin (HbA1c) in women with type 1 diabetes (-◆-) and type 2 diabetes (--■--) during pregnancy.



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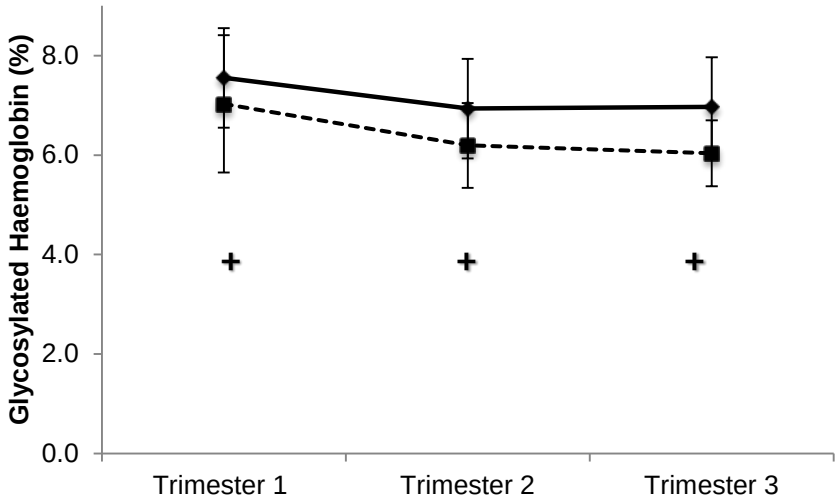

Data expressed as mean standard error of the mean.
Mann-Whitney U-tests were performed. $^{+}p < 0.05$

TABLES

Table 1. Maternal characteristics in women at baseline (type 1 diabetes vs. type 2 diabetes)

	Type 1 Diabetes	Type 2 Diabetes	*P* value
n	92	106	
Age (years)	31.0 (27.5, 34.3)	34.5 (31.0, 37.4)	< 0.001
BMI (kg/m^2)	27.2 (23.0, 31.0)	33.0 (29.0, 38.0)	< 0.001
Parity	1.0 (0.0,1.0)	1.0 (0.0,1.0)	0.1
Smoking status at conception			0.9
Current smoker	7 (9.8)	6 (5.7)	
Ex-smoker	9 (7.6)	11 (10.4)	
Non-smoker	76 (82.6)	89 (83.9)	
Duration of diabetes (years)	12.0 (5.0, 19.0)	3.0 (2.0, 5.0)	< 0.001
HbA_{1c} (%)	7.0 (6.5, 8.2)	6.9 (6.0, 7.8)	0.03
HbA_{1c} (mmol/mol)	53.0 (47.5, 66.1)	51.9 (42.1, 61.7)	0.03
Systolic blood pressure (mmHg)	115.0 (110.0, 120.0)	120.0 (110.0, 125.0)	0.02
Diastolic blood pressure (mmHg)	70.0 (65.0, 70.0)	70.0 (70.0, 80.0)	0.02
Serum creatinine (µmol/l)	54.0 (47.0, 59.0)	46.0 (40.5, 51.5)	< 0.001
CKD-EPI eGFR (ml/min/1.73m^2)	120.8 (116.7, 128.5)	124.8 (121.6, 130.6)	0.02
Pre-existing hypertension	10 (10.9)	23 (21.7)	0.04
Renin angiotensin aldosterone System Inhibition at conception	8 (8.7)	8 (7.6)	0.8

Statins therapy at conception	4 (4.4)	9 (8.5)	0.2
Metformin therapy at conception	0 (0)	55 (51.9)	< 0.01
Microvascular complications	21 (22.6)	8 (7.5)	< 0.01
Macrovascular complications	2 (2.2)	0 (0)	0.1

Data expressed median (interquartile range) or n (%)

Group comparisons were performed using Chi-square tests and Fisher exact tests for categorical variables and Mann-Whitney U tests for continuous variables

Body mass index = BMI; glycosylated hemoglobin = HbA_{1c}; Chronic Kidney Disease Epidemiology Collaboration equation for estimated glomerular filtration rate = CKD-EPI eGFR

Table 2. Selected maternal characteristics in women at baseline (diabetes vs. healthy control)

	Diabetes (Type 1 & Type 2)	Healthy Controls	*P*-value
N	198	119	
Age (years)	33.0 (28.9, 36.2)	31.0 (28.0, 35.0)	0.04
BMI (kg/m^2)	30.0 (26.0, 35.5)	25.0 (23.0, 32.0)	< 0.001
Serum creatinine (µmol/l)	49.5 (43.0, 57.0)	49.0 (44.0, 54.0)	0.8
CKD-EPI eGFR (ml/min/1.73m^2)	123.6 (118.2, 129.4)	125.3 (119.6, 130.6)	0.2
Albumin-to-creatinine ratio (mg/g)	7.1 (4.4, 21.2)	-	

Data expressed median (interquartile range) or n (%)

Group comparisons were performed using Chi-square tests and Fisher exact tests for categorical variables and Mann-Whitney U tests for continuous variables

Body mass index = BMI; Chronic Kidney Disease Epidemiology Collaboration equation for estimated glomerular filtration rate = CKD-EPI eGFR

Table 3. Comparison of obstetric and perinatal outcomes in women with type 1 and type 2 diabetes

	Type 1 diabetes	Type 2 diabetes	Odds ratio (95% CI)	P-value
n	92	106		
Obstetric outcomes				
Preeclampsia	12 (12.9)	20 (18.9)	0.6 (0.3, 1.4)	0.3
Pregnancy-induced hypertension	4 (4.3)	11 (10.4)	0.4 (0.1, 1.3)	0.1
Emergency caesarean delivery	32 (34.4)	33 (31.1)	1.2 (0.7, 2.3)	0.5
Postpartum haemorrhage	13 (14)	10 (9.4)	1.6 (0.7, 3.8)	0.3
Perinatal outcomes				
Gestational age (weeks)	37.4 (36.0, 38.1)	37.3 (38.3, 40.4)	-0.1 (-1.0, 0.8)	0.8
Preterm birth < 37 weeks gestation	31 (33.3)	36 (34)	1.0 (0.5, 1.8)	1.0
Preterm birth < 32 weeks gestation	10 (10.8)	9 (8.5)	1.3 (0.5, 3.4)	0.6
Birthweight gestational centile (%)	97.4 (79.2, 99.8)	72.4 (32.4, 94.4)	20.2 (11.7, 28.8)	< 0.001
Large for gestational age	59 (63.4)	38 (35.8)	3.2 (1.8, 5.7)	< 0.001
Small for gestational age	5 (5.4)	16 (15.1)	0.3 (0.1, 0.9)	0.03
Major congenital malformation	3 (3.2)	3 (2.8)	1.2 (0.2, 5.9)	0.9
Fetal death in utero/ in labour	2 (2.2)	3 (2.8)	0.8 (0.1, 4.7)	0.8

Neonatal jaundice	9 (9.7)	17 (16.0)	0.6 (0.2, 1.3)	0.2
Apgar score < 7 at 5 minutes	8 (8.6)	10 (9.4)	0.9 (0.3, 2.4)	0.9
NICU Admission	18 (19.4)	19 (17.9)	1.1 (0.5, 2.3)	0.8
Neonatal hypoglycaemia	25 (26.9)	24 (22.6)	1.3 (0.7, 2.4)	0.5

Data expressed median (interquartile range) or n (%)

Group comparisons were performed using logistic regression.

Data expressed as Odds ratio for categorical variables and Co-efficient variation for continuous variable.

Neonatal intensive care unit = NICU

Table 4. Comparison of obstetric and perinatal outcomes in women with and without diabetes

	Diabetes (Type 1 & Type 2)	Healthy controls	Odds ratio (95% CI)	P-value
n	198	119		
Obstetric outcomes				
Preeclampsia	32 (16.2)	5 (4.2)	4.4 (1.6, 11.6)	0.003
Pregnancy-induced hypertension	15 (7.6)	3 (2.5)	3.2 (0.9, 11.2)	0.07
Emergency caesarean delivery	65 (32.8)	18 (15.1)	2.7 (1.5, 4.9)	0.001
Postpartum haemorrhage	23 (11.6)	11 (9.2)	1.3 (0.6, 2.8)	0.5
Perinatal outcomes				
Gestational age (weeks)	37.3 (36, 38.1)	39.4 (38.3, 40.4)	-2.8 (-3.4, -2.1)	< 0.001
Preterm birth < 37 weeks gestation	67 (33.8)	9 (7.6)	6.3 (3.0, 13.1)	< 0.001
Preterm birth < 32 weeks gestation	19 (9.6)	1 1(0.8)	12.5 (1.7, 94.8)	0.01

Birthweight gestational centile (%)	89.5 (61.7, 98.7)	69.7 (41.0, 48.9)	10.8 (3.7, 18.0)	0.003
Large for gestational age	97 (49.5)	30 (25.2)	2.8 (1.7, 4.7)	< 0.001
Small for gestational age	21 (10.6)	9 (7.6)	1.5 (0.6, 3.3)	0.4
Major congenital malformation	6 (3)	4 (3.4)	0.9 (0.2, 3.3)	0.9
Fetal death in utero/ in labour	5 (2.5)	0 (0)	NA	NA
Neonatal jaundice	26 (13.1)	4 (3.4)	4.3 (1.5, 12.6)	0.008
Apgar score < 7 at 5 minutes	18 (9.1)	2 (1.7)	5.9 (1.3, 25.7)	0.02
NICU Admission	37 (18.7)	5 (4.2)	5.2 (2.0, 13.7)	0.001
Neonatal hypoglycaemia	49 (24.7)	4 (3.4)	9.5 (3.3, 27.0)	< 0.001

Data expressed median (interquartile range) or n (%)

Group comparisons were performed using logistic regression.

Data expressed as Odds ratio for categorical variables and Co-efficient variation for continuous variable.

Neonatal intensive care unit = NICU

Abstract:

Objective: Our aim was to explore differences in pregnancy outcomes between women with type 1 and type 2 diabetes, and healthy controls, and to examine the relationships between potential adverse risk factors and pregnancy outcomes in this cohort of women.

Study Design and Methods: This is a 10 year retrospective study of women with type 1 diabetes (n = 92), type 2 diabetes (n = 106) and healthy women without diabetes (controls) (n = 119) from a tertiary obstetric centre. Clinical and biochemical characteristics of women with type 1 and type 2 diabetes were determined and related to major obstetric outcomes using univariate analysis.

Results: Women with pre-existing diabetes had higher adverse pregnancy outcomes (preeclampsia, emergency caesarean section, preterm birth < 32 and 37 weeks, large for gestational age, neonatal jaundice, Apgar score < 7 at 5 minutes, neonatal intensive care admission and neonatal hypoglycaemia) compared to controls. A higher birth weight gestational centile (97.4% vs. 72.4%, P = 0.001) and large for gestational age rate (63.4% vs. 35.8%, P = 0.001) were observed in type 1 diabetes compared to type 2 diabetes. There were no differences in other outcomes between women with type 1 and 2 diabetes.

Conclusion:

In this exploratory study, risk factors for maternal adverse outcomes differ between type 1 and type 2 diabetes. Maternal and fetal adverse outcomes were higher in

pregnancies affected by diabetes compared to healthy women but occurred with similar frequency in women with type 1 and type 2 diabetes.

Title:

Risk factors for pregnancy outcomes in type 1 and type 2 diabetes

Authors:

Jas-mine Seah [1 2 3] (MBBS), Ning Mao Kam [2 3] (MD), Lydia Wong [2] , Cara Tanner[2 3] (MD), Alexis Shub [1 3] (MBBS), Elif I. Ekinci [2 3] *(PhD), Christine Houlihan [1 2] (MD) *

* Equal contribution

1. *Department of Perinatal Medicine Mercy Health, Heidelberg, VIC, Australia*
2. *Department of Endocrinology Austin Health, Heidelberg, VIC, Australia*
3. *Department of Medicine Austin Health, The University of Melbourne, Melbourne, VIC, Australia*

Word Counts

Abstract: 247

Main text: 3109

Funding

RACP-JDRF Research Establishment Fellowship

Conflicts of Interest

None