Title: Pregnancy outcomes for women with pre-pregnancy diabetes mellitus in Australian populations, rural and metropolitan: A review

Short title: Pregnancy outcomes for women with pre-pregnancy DM

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ajo.12913

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Article type : Review

Pregnancy outcomes for women with pre-pregnancy diabetes mellitus in Australian populations, rural and metropolitan: A review

Short Title: Pregnancy outcomes for women with pre-pregnancy DM

Word count: Abstract 251, main text 4594

Tables: Two

Figures: Three

Keywords: Diabetes Mellitus, Type 1, Diabetes mellitus, type 2, Pregnancy outcome, Rural Health, Social Determinants of Health, Oceanic Ancestry Group

Abstract

Background

Historically, pre-pregnancy diabetes (PPDM) is a recognised risk factor for poor pregnancy outcome. Co-existing pathology and adverse social determinants, including rural-metropolitan inequities in health and healthcare access may confer additional risks.

Multi-disciplinary care before, during and after pregnancy can improve outcomes for women with PPDM and their infants. The extent to which rural Australian women and their families share in improved outcomes is unknown.

We aimed to summarise maternal characteristics and pregnancy outcomes for women with PPDM, including women in rural settings and examine applications of existing clinical guidelines to rural Australian practice.

Methods

We sought English language population and cohort studies about PPDM using Medline, Embase, Pubmed, Australian epidemiological and international clinical practice guidelines.

Results

Women with PPDM are changing; older, more obese, of lower parity, less likely to smoke, more likely to have type 2 rather than type 1 diabetes and shorter duration of PPDM. Women with PPDM continue to experience excess adverse pregnancy outcomes, including maternal morbidity, complicated birth, perinatal loss, congenital anomalies and mother-infant separation.

On face value, clinical guidelines appear relevant to women living in rural settings but there are only a few, conflicting outcome studies for rural women with PPDM.

Conclusions

PPDM is changing. A significant minority live in rural locations, and although perinatal mortality/morbidity seems to be improving, it is unclear if this is also true for rural women due to a lack of recent Australian studies. Further research is necessary to achieve excellence everywhere for women with PPDM and their babies.

1. Background and rationale for review

As long ago as 1989, international goals were set to achieve safe and healthy childbirth for women with diabetes with outcomes equivalent to those for individuals who do not live with diabetes mellitus (DM) [1].

The United Kingdom Confidential Enquiry into Maternal and Child Health (CEMACH) carried out a large prospective survey pregnant women with diabetes in 2002 and 2003 [2] noting that the goals from 1989 had not yet been achieved.

International goals [1] and rigorous audit [2] remain relevant to maternity units of all sizes, including small rural units [3]. While modern transport and communications go some way to bringing healthcare to rural and remote Australia, disparate health outcomes still exist in maternal and infant health [4-7].

We describe maternal characteristics and pregnancy outcomes for women with pre-pregnancy diabetes, with a particular focus on Australian settings. We also examined how applicable are existing clinical guidelines to rural-remote Australia. By identifying gaps in research and practice which need to be filled, we aim to improve health for rural Australian women with diabetes and for their families.

2. Methods

2.1. Literature search, inclusion and exclusion criteria

We searched Medline, Embase and Pubmed in May 2018 using English language publications for population and cohort studies using terms:

Pre#gestation*, pre#pregnancy, diabetes, type #, pregnancy outcome*, combined with body mass index (BMI), overweight, obes*, parity, nullipara*, smok*, hypertens*, eye or retina* or ophthalmol*, renal or kidney or proteinuria* or albuniuri*, migrant*, indigenous, aboriginal, rural, remote, metropolitan, women's experiences.

We also consulted reference lists from recent Australian epidemiologic data [8], Australian [9-11], North American [12-14] and European guidelines [11 15 16]. We recognise that restricting to English language publications may limit generalisability.

We excluded studies of gestational diabetes (GDM) or where pre-pregnancy diabetes (PPDM) was not distinguished from GDM.

Table 1 tabulates included studies grouped by how they contribute information about maternal characteristics, exposures and outcomes for women with pre-pregnancy diabetes and their infants. Salient features of Australian studies are summarised in Table 2 .

2.2 Outcomes

While the International Association of Diabetes in Pregnancy Study Groups' (IADPSG) work on a core outcome set which will inform future meta-analysis [17 18], the current review is largely descriptive. We chose maternal and infant outcomes which we judged to be clinically important. Quantitative pooling is not yet appropriate for studies of pregnancy outcomes for women with pre-pregnancy diabetes because the studies covered a prolonged period, some women had several pregnancies listed in the same study and other possible exposures and outcomes of interest were variably defined or undefined, limiting comparability and making data pooling inappropriate.

3. Results

3.1. Exposures which may impact on maternal and infant outcomes for women with pre-pregnancy diabetes.

3.1.1. Rural residence and/or place of childbirth

Many Australian publications report from endocrine-obstetric services of large urban hospitals: see Table 2. Two Australian populations studies reported 6.5% [19] and 12.3% [20] of women with PPDM give birth in a rural setting. A national study did not report on rural-dwelling mothers and infants separately from other Australians [8]. Of note, women with PPDM who gave birth in rural New South Wales hospitals had better outcomes than women in larger hospitals, possibly reflecting appropriate referrals of higher risk pregnancies from smaller to larger hospitals [19]. A late 20th century South Australian study found that while diabetes in pregnancy increased the risk of congenital anomaly, the rate was further increased for births in rural hospitals [20]. The authors cautioned that this observation related to only a small number of births [20].

Canada shares with Australia some of the challenges of providing health care to people living in remote and rural locations. In Ontario, rural based women with PPDM suffered an excess of perinatal loss and higher rates of congenital abnormalities compared with women living in an urban setting [21]. In the era before the Irish Atlantic-DIP network was established, women cared for at peripheral hospitals has less regular pre-pregnancy care and poorer pregnancy outcomes compared with those cared for at the referral hospital [22], however, distances are smaller and population denser in Ireland, compared with Australia.

3.1.2. Body mass index (BMI), smoking, maternal age and parity

An upward trend in BMI has been noted among women with PPDM [23 24] as well as more generally in Australia [25]. Figure 1 shows varying, but generally increasing, BMI among women with PPDM. A median BMI of 23.0 kg/m^2 in one group of women with type 1 diabetes [26] contrasts with mean BMI 34.4 kg/m^2 in a group with high rates of type 2 diabetes [27]. Women with type 2 diabetes tend to have higher BMI, and higher maternal age than women without diabetes conferring additional perinatal risks: See Table 2.

Published cigarette smoking rates varied between 0% [28] or 4.2% [29] among women with type 2 diabetes in Australian specialist care, up to 28.4% in the late 20th century in urban Australia [28]. Trends to reduced smoking among women with pre-pregnancy diabetes (see Figure 2) have also been observed more generally in Australia [30].

Internationally, nulliparous women comprised between 16.4% [27] and 67.0% [31] of women with PPDM. Australian studies report between 1/3 and ½ of women with PPDM are nulliparous (see Table 2 [8 19 32 33] and Figure 2), similar to 45% nulliparity among unselected mothers [34].

High BMI [34] and smoking [34] are both more prevalent in rural compared with urban Australia.

3.1.3. **Diabetes type and duration**

All types of diabetes in pregnancy are becoming more common in Australia [35] and elsewhere [21 23 36-40].

Type 2 diabetes is increasingly recognised as an important risk factor for poor pregnancy outcomes [2 41-45] and is becoming more common. Diabetes type for women giving birth between 2007 and 2017 was type 2 for 12,787 participant women and type 1 for 23,664 participant women, thus more than 1 in 3 women had type 2 diabetes [21 23 24 29 31-33 38 43 46-62]. The comparable numbers of participant women with type 1 and type 2 diabetes were 15,407 and 1,662 for publications about births between 1987 and 2006: thus in this earlier era, fewer than 1 in 10 women with diabetes were reported as having type 2[19 20 26-28 36 63-76]. An unusual study based on USA insurance claims reported that type 2 diabetes in pregnancy was 10 times as common as type 1 diabetes [38]. This contrasts with Australian studies where type 2 DM remains slightly less common than type 1 DM: See Table 2.

Women with Type 2 diabetes tend to a shorter time from diagnosis to pregnancy, compared to women with Type 1 diabetes, because of the older age at diagnosis. See Figure 3.

3.1.4. **Pre-pregnancy hypertension, renal and retinal complications**

Women with PPDM have high rates of essential hypertension, underlying renal disease and diabetic retinopathy. Internationally, pre-existing hypertension prevalence ranged between 2.1% [70] and 17.2% of women with PPDM [60]. Three of nine Australian studies shown in Table 2 reported pre-pregnancy hypertension: 12.3% [33], 5.5% [19], 4% for women with type 1 DM [8] and 6% for women with type 2 DM [8]. Figure 3 illustrates the world-wide trend to more prevalent pre-pregnancy hypertension.

Retinal or renal complications, variously defined, were reported in four of nine Australian studies [28 29 32 33]: see Table 2. Figure 3 illustrates international trends in kidney and eye disease prevalence, plotted on a log-scale against the mid time point in published case series. Included studies used various definitions, testing strategies and classifications of maternal renal and retinal disease.

Cohorts representing many women with > 10 year duration of pre-pregnancy diabetes report some degree of retinopathy in 30 to 45% of women [31 42 60 62]: the majority are non-proliferative and a minority (5 to 10%) are proliferative [26 42]. In these cohorts 10 to 15% of women have microalbuminuria [31 42 60] and fewer (2 to 7%) have macroalbuminuria [26 42 60]. At least one report found higher rates of pre-pregnancy proteinuria in women with type 2 diabetes compared with type 1 diabetes despite much shorter recognised disease duration [62]. Information reported about type of eye or kidney disease and diabetes duration varies. IADPSG recommend future research categorises renal complications of diabetes as: no nephropathy, microalbuminuria, overt proteinuria with or without decreased renal function at baseline [17]. Similarly, IADPSG recommends retinal complications be classified according to Early Treatment Diabetic Retinopathy Study (ETDRS) scale of retinopathy [77].

3.1.5. **Pre-pregnancy preparation**

Pre pregnancy care has been variably defined by asking women if the pregnancy was planned, whether they had consulted a general or specialist health practitioner or achieved other aspects of optimal preparation [70]. The majority of papers included HbA1c as a measure of preconception glycaemic control [2 22 23 31 36 46 47 55 56 58-62 69 72 73 78]. Others relied on clinical notes about the purpose of outpatient consultations [26 28 44 65 79] or whether a pregnancy was planned [29 74]. Other studies were limited to using pre-pregnancy folic acid use as a surrogate of pregnancy planning [27 67].

Measuring the effectiveness of pre-conceptual care (PCC) is challenging since women accessing PCC are often different from women not accessing PCC: differing according to health literacy, socio-economic advantage [69] and incidence of diabetes complications and co-morbidities. Acknowledging these challenges, Wahabi's group nevertheless identified 11 prospective cohort studies and one randomised trial at sufficiently low risk of bias, with similar or statistically adjustable baseline characteristics [80]. From their meta-analysis, they estimated that for every 8 women receiving PCC, one preterm birth is prevented, for every 17 women receiving PCC, there is one less congenital anomaly case and for every 32 women receiving PCC, one less baby succumbs to stillbirth or neonatal death [80]. None of the included PCC studies was set in a rural Australian setting.

Twenty-seven international studies made some assessment of pre-pregnancy preparation in PPDM. (See Table 1 for included studies) The largest study was the CEMACH survey from 2002 in the United Kingdom which found that about 1 in 3 women had recorded pre-pregnancy counselling, 1 in 3 women had an assessment of glycaemic control in the 6 months prior to pregnancy and less than two-fifths of women took folic acid supplements before their last menstrual period[2]. Some markers of pre-pregnancy care had improved on repeat audit in 2015: more women took folic acid and had early pregnancy glycaemic control assessed [78].

Australian urban-based studies also report improved PCC rates over the last 2 decades (see Table 2) but whether this reaches rural based women is unknown. Markedly high rates of pregnancy planning have been reported for some European women with type 1 diabetes: 66% in Finland [60] and 84% in the Netherlands [74]. In contrast, prior to implementation of a preconception community care programme in the North of England, only 5.8% of women with type 2 diabetes were considered to have optimal pregnancy preparation, defined as taking folic acid, not taking harmful medications (such as angiotensin converting enzyme inhibitors or statins), optimal first trimester HbA1c and pregnancy booking at less than 8 weeks of amenorrohoea [55].

3.1.6. **Cultural, linguistic or ethnic group.**

Immigrants to high income countries often experience worse health compared with non-immigrants. This was recognised for women with PPDM in the late 20th and early 21st centuries in Norway [81] and UK [2]. Women giving birth in Australia who migrated from high diabetes prevalence countries - Polynesia, Asia and the Middle East – had a slightly

increased prevalence of T2DM and substantially higher incidence of gestational diabetes compared with Australian born women [8].

Indigenous women bear a higher burden of diabetes in pregnancy in Australia and elsewhere [8 27 51 82]. About 4% of Australians identify as indigenous, varying from region to region: around 1% in Victoria [83 84], more than 1 in 4 in Northern Territory [84] and more than 1 in 2 in the Cape York region of Far North Queensland [85]. Rural-remote compared with urban domicile appears to confer additional health risk for Aboriginal infants born to mothers with diabetes in pregnancy [86].

3.2. **Maternal outcomes**

3.2.1. **Maternal death and life-threatening morbidity**

Two studies reported on deaths or mothers with PPDM. There were 5 maternal deaths in 3733 women with diabetes up to 12 months after childbirth in the United Kingdom [2]. This is increased compared with 13.1 maternal deaths per 100,000 maternities for the triennium 2000 – 2002 [36]. Another death of a woman in midtrimster without cause specified was reported from a Dutch series [74].

Shand's Australian study reported a composite of major maternal morbidity or mortality, occurring in 7.9% of women with PPDM. Although no maternal deaths occurred, the authors pre-specified severe morbidity by diagnoses and procedures common to maternal mortality cases: severe haemorrhage, thrombo-embolism, hypertension, sepsis and organ failure and admission to intensive care. This rate was increased compared with women without any diabetes: odds ratio 3.17 (95% confidence interval (CI) 2.56, 3.92) [19]. Kekalainen reported 8.3% of Finnish women with type 1 DM had significant hypoglycaemia and 0.7% had diabetic keto-acidosis in pregnancy [60]. Clausen reported that 3.3% of women required intensive care in a Danish study [42].

3.2.2. **Pre-eclampsia**

Twenty-three studies reported pre-eclampsia in women with PPDM: See Table 1. Australian population studies recorded pre-eclampsia in 13.8% [19] and 17.0% [8] of women, similar to 3 Nordic populations [26 68 70] and higher than 2 Canadian province-wide studies [51 57]. A single centre Australian study recorded one of the lowest rates of pre-eclampsia among women with T1DM: 5% [33]. This point estimate was double the rate for non-diabetic women, although not statistically different.

Early compared with late preeclampsia were not distinguished in any of the Australian studies in Table 2, nor in international cohorts of more than >2,500 women since 2003 [2 21 51 63 70]. Despite frequent mention of aspirin in guidelines [10 15 87-90], its use was not reported in studies about diabetes which included pre-eclampsia as a pregnancy outcome.

3.2.3. **Caesarean section, induction of labour and shoulder dystocia**

Twenty-nine studies report Caesarean section (CS) rates among women with PPDM: see Table 1. Many report between 51% [66] and 77% [28] of women were delivered by caesarean section [2 8 19 23 24 26 28 31-33 42 43 46 47 57 60-62 66 91], most of whom (71%) had type 1 DM. Fewer papers [22 28 42 51 52 57 64 68 70 72 79 92] report lower CS rates: between 36% [28 42] (both studies of women with T2DM) and 49% [92] where the latter paper and one other did not specify diabetes type [51 92]. Among study settings with lower CS rate (36 to 49%), type 1 DM accounted for the majority (93%) of specified type of PPDM. Where reported separately, emergency CS make up between 31.7% and 55.8% of all CS [2 8 19 22-24 26 62 72]

As for other women, repeat Caesarean section is a significant contributor to the CS rate for women with PPDM [93]. The modified Robson classification of CS according to labour onset , gestational age, fetal presentation and maternal parity and prior Caesarean section [94], has not been applied to cohorts of women with PPDM.

Large Canadian, UK and Australian studies report labour induction rates between 30 and 40% among women with PPDM [2 8 19 57]. Some Nordic countries have rates closer to 20% [68]. See also Table 1 and Table 2.

Shoulder dystocia is most often defined by being a vaginal birth requiring additional manoeuvres to deliver the shoulders [17]. Clinicians' behaviour and documentation of shoulder dystocia may be altered by knowing that the woman has PPDM. Province-wide birth statistics in Alberta, Canada report shoulder dystocia in 6.4% of women with pre-pregnancy diabetes who have a vaginal birth [51]. This is comparable with 4.5% from New South Wales [19] and 8.1% from a multi-centre study in 3 Australian states [65]. Some studies of women with type 1 diabetes note rates of 13.7% and 17.0% [33 70]. Small sample size limits interpretation of more extreme findings [23 43 57 72].

3.2.4. **Breastfeeding**

Breastfeeding is important for many reasons including optimising both maternal and neonatal metabolism when a woman has diabetes [90 95], yet it is often underreported. IADPSG recommends reporting breastfeeding in a standardised manner in future research into diabetes in pregnancy [17].

More than 55% of new mothers with PPDM intended to breastfeed their infants to some degree in the CEMACH prospective survey [2]. By 4 weeks of age 23.8% of infants were exclusively breastfed and a further 16.4% of infants received some breastmilk [2]. Trends to improved breastfeeding rates among mothers with diabetes have been noted in Australia [96] and elsewhere [36].

3.3. **Infant outcomes**

3.3.1. **Perinatal Death**

The definitions of perinatal loss, stillbirth and neonatal death vary internationally which makes comparisons difficult. Delineating miscarriage or pregnancy loss from registered birth and death can affect ascertainment of perinatal death. Varying gestational age thresholds (between 20 and 28 weeks) or birthweight thresholds (between 350 and 1000g) exist in different health jurisdictions.

Within these limits, among 14 studies, including over 10,000 women with type 1 DM, three studies report low perinatal mortality (PNM) rates (1.0% and 2.0%)[31 33 65]. Three studies from tertiary or quaternary obstetric-endocrine services in Australia report high rates (6 to 7%) which may have been affected by referrals of pregnancies complicated by congenital anomaly or extreme preterm birth [29 33 65]. The remaining studies report rates intermediate to these [26 44 47 54 71 76] or present no perinatal losses in very small samples [28 72].

Trends indicate some progress towards the St Vincent Declaration goals [1]. PNM for women with type 1 DM was reported as 3.2%% in the CEMACH 2002 survey [71] and 2.7% in a systematic review of European studies a decade later [48]. The 2015 UK re-audit reported a further reduction in stillbirth [78] and the Atlantic-DIP Irish network recently reported equivalent PNM for women without diabetes [23].

Among 11 studies including more than 1,500 women with type 2 DM, lower PNM rates of 2.2% were reported from an Australian quaternary obstetric-endocrine service [32], similar to that found in an Australian population study [19] and United Kingdom [47]. Much higher rates of 12.0% [29] or 6 to 7% [42 44 65] may reflect previous under-recognition of perinatal risks of type 2

diabetes, barriers to women with type 2 DM receiving care or other factors. The only prospective study reported 3.2% PNM for women with type 2 DM [71].

Four large studies grouped pre-pregnancy type 1 and type 2 diabetes and reported PNM rates of 1.4%[63], 2.5%[92], 2.9% [51] and 6.2% [21]. The authors who reported the highest PNM rate were careful to distinguish PPDM from GDM [21]. Outcomes from GDM are substantially better than for PPDM [19] and stillbirth rates for women with GDM are even lower than for women with normal glucose tolerance [8] so inadvertently including the latter skews results towards lower perinatal mortality.

3.3.2. **Macrosomia**

Different population or customised birthweight charts, various threshold centiles (90th or higher) and threshold birthweights (between 4000g and 5000g) make comparison of newborn overgrowth challenging: see Table 1 for a list of international studies. IADPSG endorses reporting Large for Gestational Age (LGA) as greater than 90th centile by population or customised criteria and macrosomia defined as birthweight >4000g [17].

The rate of LGA infants born to women with PPDM is higher than the expected rate of 10%. A study from a tertiary hospital in New Zealand showed that Asian mothers had only slightly more than expected chance of having a macrosomic infant compared with the background rate (11.6% versus 10%) whereas women in two other ethnic groups had 30 to 40% or more chance of giving birth to macrosomic infants [27]. Rates of birthweight > 90th centile for women with T1DM were 54.2% in a European systematic review[48], 52.3% from an Australian [29] and 52.3% from two European studies [24 46]. Birthweight > 90th centile occurred for 68.5% of a series of pregnancies to Australian women with T2DM[43]

High maternal BMI and/or gestational weight gain confer additional risks for macrosomia for infants of women with PPDM [33 53 97]. A Canadian study found that First Nation ethnicity increased the risk for mothers with pre-pregnancy diabetes giving birth to macrosomic infants [98].

3.3.3. **Small for Gestational Age**

Fetal growth restriction (FGR) in women with PPDM is conventionally attributed to maternal vasculopathy [99] although the variation in birthweight attributable to maternal microvascular complications is small, between 0.2% and 2.4% [56]. Small for gestational age (SGA), defined as birthweight less than 10th centile overlaps to a moderate degree with FGR [100]. SGA is

uncommon among pregnancies to women with PPDM. Only two studies report greater than the expected 10% of infants have birthweight < 10th centile (SGA): 15.9% [32] and 12.9% [47]. Eighteen other studies showed SGA at expected or lower than population rates [19 22 23 29 31 33 42-44 46 51 55 56 62 70 71 91 92].

3.3.4. **Congenital anomaly**

Rates of congenital anomaly are increased with poor periconception diabetic control and lack of pre-pregnancy care [62].

The reliability of data is limited by ascertainment, particularly where studies variably exclude miscarriage and pregnancy termination, especially at early gestation. Other limitations relate to definitions and inclusion of minor or major anomalies.

IADPSG recommends reporting "Malformations that include ICD 10 codes: Q00–Q99.(*Eurocat Guide) In addition, a congenital abnormality that requires medical or surgical treatment, has a serious adverse effect on health and development, or has significant cosmetic impact."[17]. The non-EuroCAT criteria used in the Australian studies in Table 2 are described in the footnote.

Internationally, 37 individual studies and a systematic review [48] report congenital abnormalities in offspring of women with pre-pregnancy diabetes. (See Table 1 for included studies). Congenital anomaly rates of 4 to 5% were reported for women with type 1 and type 2 DM in the CEMACH survey [2 71]. The EUROCAT registry information reported 4.2% congenital malformations among women with PGDM [62] compared with 2.2.% in Europe generally [101]. Within the limits of comparing studies, lower rates than those calculated in CEMACH 2002 to 2003 were reported over the following 10 years in Australia [32 33 43] and elsewhere [26 44 48 70]. A multi-centre UK study from 2015 showed that the anomaly rate had declined to 3.5% [78].

3.3.5. Neonatal hypoglycaemia and jaundice

Neonatal hypoglycaemia is a common complication that may require intervention and separation of mother and baby. The definition of hypoglycaemia is variable which partly explains the wide range in reported incidence from 10% [28] to 80% [60] with other studies reporting incidences between these [19 22 28 32 33 65 91]. IADPSG recommends that future research report hypoglycaemia as 2.2 mmol/L, which is the 10th percentile of the Hyperglycemia and Adverse Pregnancy Outcome study values [17]. In contrast, reported cut-off

levels ranged from ranged from 1.5 mmol/l [60], 1.7 mmol/ l [91] or 2.6 mmol/L [24 32 33], with or without intravenous treatment [60 91], any neonatal admission [22 23], intensive care admission [28] or undefined logistic or clinical grounds [19 65].

Neonatal jaundice or hyperbilirubinaemia is also infrequently defined and reported. Three studies reported jaundice in about 20% of infants of women with pre-pregnancy diabetes [27 33 42]. A higher rate (37.0%) among infants born in a quaternary centre to women with type 1 diabetes may be compounded by high rates of preterm birth [33]. A lower rate of 5% has also been reported [22].

3.3.6. **Prematurity**

Thirty-six percent of infants in the 2002 to 2003 CEMACH study were born preterm, that is before 37 weeks [2]. This is much higher than 6.2% of infants who were born preterm in 2005 in Europe [102]. Of infants for mothers with PPDM, 73.4% of preterm births were iatrogenic, resulting from labour induction or preterm Caesarean section [2]. The remainder followed spontaneous preterm labour or ruptured membranes. A decade later in Europe, the rate of preterm birth had reduced to 25.2% for women with type 1 diabetes as summarised in systematic review [48] but was little altered in UK [78]. Similar rates - 27.7% [92]and 23.5%[51]- were reported in Canadian studies of the same era. Two other European studies report less than 20% preterm birth [52 63].

The Australian experience is summarised in Table 2 with 19.5% [19] and 25.2% [8] preterm birth reported in population studies and variable rates from smaller single centre studies.

3.3.7. **Admission to a neonatal unit**

The CEMACH surveyors opined that up to 2/3 neonatal unit admissions were potentially avoidable [2].

Hospital policies and different definitions of what constitutes neonatal care accounts for some variation in admission rates. Neonatal intensive care admission was close to 10% in recent moderately sized Australian cohorts [19 32 33]. When including special care admission, the rate was 58% in Australia [8], and close to 50% in other parts of the world [22 46 55 67 79 91].

3.4. **Clinical guidelines**

International clinical guidance [11 12 14-16 87 88] largely matches Australian guidance documents about PCC, pregnancy, intrapartum, postnatal and neonatal care when women have PPDM [9]

[10 87]: guidance differs slightly in advising types of fetal monitoring and the threshold estimated fetal weight at which elective Caesarean section without labour is offered to reduce shoulder dystocia risk. International guidelines do not address challenges for rural-dwelling women.

Australian clinical guidelines are notable for supporting general practitioners with obstetric qualifications to lead local maternity care for women with diabetes [11], advising midwives to refer women with PPDM for secondary and tertiary care [103], suggesting telehealth multi-disciplinary consultations [11] or telephone review of glycaemic control for women living in isolated communities [9] and addressing the cultural needs of Indigenous Australian women [10] [11].

NICE (UK) clinical guidelines [87] are extremely comprehensive and appear partly transferrable to an Australian setting. Of 103 auditable standards relevant to women with PPDM, the majority seem equally applicable to rural as metropolitan setting. Eighteen standards may differ between rural and metropolitan settings: only audit can determine if this is so. The standards of interest (with associated NICE numbering [87]) are : Structured education (1.1.29), access to ophthalmological (1.1.31, 1.3.24, 1.3.26) and renal (1.1.34, 1.3.28) expertise, access to new technology such as continuous subcutaneous insulin infusion 1.3.16), continuous glucose monitoring (1.3.18) and associated technological and clinical support (1.3.19), pregnancy care booking before 10 weeks (1.3.34), pre-eclampsia prevention (1.3.29), sufficiently detailed fetal cardiac views at the 20-week fetal anatomy scan(1.3.30), anaesthetic assessment if comorbidities exist (1.4.8), frequency of multi-disciplinary review (1.3.35) and place of birth with capacity for maternal (1.3.23) and neonatal (1.5.1, 1.5.5, 1.5.6) critical care.

4. Conclusions

Pre-pregnancy diabetes is changing. On average, women are older, more overweight, of lower parity, less likely to smoke, more likely to have coexisting hypertension, type 2 rather than type 1 diabetes and shorter duration of pre-pregnancy diabetes. A significant minority live in rural locations and/or are indigenous or have cultural and linguistic backgrounds which are different from their healthcare workers. Happily, maternal mortality is rare but significant morbidity still occurs. Although perinatal mortality and the incidence of congenital anomalies seems to be improving, it is unclear if rural women are benefiting to the same extent as metropolitan based women due to lack of recent, Australian large studies.

Some plausible constraints on rural based care for women with PPDM might be overcome by technology-enhanced pre-pregnancy education [104], networking [105] and enhancing primary care [106]. Alongside listening to individual rural women's experiences [107], audit and feedback for health services of all sizes is necessary to achieve excellence everywhere for women with PPDM and their infants [36 108].

Table/figure legends

Table 1: Included studies

Table 2: Australian cohort and population studies about infant and maternal outcomes for women with pre-pregnancy diabetes

Figure 1: Trends in body mass index (BMI) and age for women with PPDM

Figure 2: Proportions of women with PPDM who are 1. nulliparous 2. smokers

Figure 3: Pre-pregnancy health for women with PPDM 1. Hypertension prevalence (%) 2. Eye and/or renal disease prevalence (%) 3. Duration of DM (years)

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Table 1: Included studies

Maternal characteristic, exposure or outcome	Number of included studies	References
Age	29	19 21 23 24 26-29 32 33 46 47 50-52 54 55 63-72 74 76
Body Mass Index	21	23 24 26-29 32 33 46 47 50 52 55 56 58-60 62 63 70 72 74
Parity	27	19 24 27 31-33 36 38 46 50 51 54 56-62 66-71 74 76
Smoking	19	19 23 24 27-29 32 33 46 50 56 57 60-63 67 70 74
Diabetes type - women giving birth 2007 to 2017	27	8 21-24 29 31-33 38 43 46-48 50-56 60 62 63 78 79
Diabetes type - women giving birth before 2007	31	2 19 20 26-28 36 42 44 57-59 61 64-76 81 91 92 109 110
Duration of pre-pregnancy diabetes	21	26 29 31 46 52 54 56 58-62 64 65 67 68 71 72 74 76
Co-existing hypertension	15	8 19 22 24 26 27 31-33 46 51 54 60 70 92
Eye and/or renal disease	19	22 26-29 31-33 42 46 52 56 58 60-62 73 91 92
Pre-pregnancy counselling	27	2 22 23 26-29 31 36 44 46 52 55 56 58-62 65 67 69 72-74 78 79
Immigration, cultural and linguistic diversity including Indigenous identification	12	2 8 27 51 81-86 108 111
Rurality	4	19-22
Maternal mortality or severe morbidity	4	2 19 42 60
Pre-eclampsia	23	8 19 22-24 26 29 31-33 42 43 46 51 57 60 62 64 68 70 72 79 92
Caesarean section	29	2 8 19 22-24 26 28 31-33 42 43 46 47 51 52 57 60-62 64 66 68 70 72 79 91 92
Induction of labour	10	2 8 19 28 32 33 43 51 57 68
Shoulder dystocia	12	19 23 32 33 43 51 57 60 65 70-72

Breastfeeding	3	2 36 96
Perinatal mortality	34	19 21-23 26 28 29 31-33 36 42-44 47 51 54 55 59 61-66 68-71 76 79 91 92 109
Large for gestational age > 90th centile	30	19 23 24 26 28 29 31-33 42-44 46 47 51 54-56 60-63 70-72 78 79 91 92 109
Small for gestational age < 10th centile	20	19 22 23 29 31-33 42-44 46 47 51 55 56 62 70 71 91 92
Congenital anomaly	37	21-23 26 28 29 32 33 36 42-44 46 47 51 54 55 57 59-67 69-72 76 78 91 92 109 112
Neonatal hypoglycaemia	10	19 22 24 28 33 60 6523 32 91
Neonatal jaundice	6	22 26 32 33 42 60
Prematurity	33	8 19 22-24 26 28 29 32 33 42 43 47 51 52 54 55 57 59-64 66 68 70-72 78 91 92 109
Admission to neonatal services	21	8 19 22-24 28 29 32 33 36 46 47 51 55 62 66 67 71 72 79 91

Table 2: Australian cohort and population studies about infant and maternal outcomes for women with pre-pregnancy diabetes

Author	Study era	Pregnancies :women	DM Duration (years) [a]	Age (years)[a]	BMI (kg/m^2) [a]	Smok-ing	% PCC	PNM[b]	LGA[c]	Shoulder dystocia	Preterm %	Fetal Anom-aly % [d]	Pre-eclamp sia	IOL	CS
Type 1 diabetes															
Abell [33]	2010 -2013	107: 94	NR	29.3 (5.3)	27.3 (5.0)	22.0%	NR	7.0%	44.0%	17.0%	39.0%	4.0%	5%	48.0%	62.0%
Kothari [43]	2006 -2011	44: 30	NR	NR	NR	NR	NR	4.5%	28.4%	31.2%	38.2%	4.5%	26.8%	47.0%	52.0%
Wong [29]	2007 - 2011	28:28	15.7 (9.0)	31.0 (4.1)	25.0 (4.8)	17.9%	78.6%	6.8%	52.3%	NR	22.7%	6.8%	9.1%	NR	NR
McElduff [e 65]	2003 -2004	81:81	13.3(8.2)	30.9 (5.1)	NR	NR	56.6%	3.4% [g]	NR	8.1% [g]	NR	8.1% [g]	NR	NR	63% [g]
Gunton [72]	1998 - 2001	24:20	13 (6)	31.9 (4.9)	24.3 (2.6)	NR	62.5%	NR	22.2%	0/24	12.5%	2.9%	10.5%	NR	47.6%
Gunton [28]	1989 -1998	74:49	12.8	28.0 (8.9)	24.8 (8.5)	28.4%	18.9%	0/74	30.0%	NR	6.8%	13.0%	NR	5.7%	77.4%
Type 2 diabetes															
Abell [32]	2010 -2013	138:124	NR	33.6 (5.3)	32.9 (26.2,36.9)	12.3%	NR	2.2%	20.3%	7.8%	22.5%	4.4%	8.7%	53.6%	53.6%
Wong [29]	2007 -2011	24:24	4.9(3.9)	34.0 (5.3)	31.8 (5.6)	4.2%	54.0%	12.0%	30.8%	NR	9.4%	6.8%	9.4%	NR	NR
Kothari [43]	2006 -2011	19: 14	NR	NR	NR	NR	NR	5.3%	68.4 %	16.5%	42.0%	0/19	21.1%	37.0%	68.0%
McElduff [e 65]	2003 -2004	99:99	4.4(3.3)	32.8 (5.4)	NR	NR	36.4%	3.4% [g]	NR	8.1% [g]	NR	8.1% [g]	NR	NR	63% [g]
Gunton [72]	1998 -2001	11:11	3 (2)	32.2 (5.4)	24.9 (4.7)	NR	36.4%	NR	33.3%	0/11	0/11	0/11	10.5%	NR	44.4%
Gunton [28]	1989 -1998	19:12	6.8	35.1 (8.6)	31.7 (25.8)	0.0%	52.6%	5.3%	39.6%	NR	15.8%	0/19	NR	45.5%	36.4%
Type of DM mixed or incompletely specified															
Shand [e,f 19]	1998 - 2002	1248 :711 T1;250 T2 unspecified 287	NR	22.6% aged 35 years+	NR	19.2%	NR	2.0%	35.0%	4.5%	19.5%	NR	13.8%	32.4%	33.3%

Templeton [8]	2005 – 2008	4603: 2119 T1; 2219 T2; Unspecified 265	NR	65% aged 30+ years	NR	NR	NR	NR (1.9% SB)	19.4% > 4.0 kg	NR	25.2%	NR	17%[h]	34.9%	59%

BMI: body mass index; CS: Caesarean section; DM: diabetes mellitus; IOL: induction of labour; LGA: large for gestational age; NR: not reported; PCC: preconception care; PNM: perinatal mortality; SB: stillbirth; T1: type 1, T2: type 2

[a]Data are %, mean (SD) or median (25th centile, 75th centile).

[b] PNM: perinatal mortality due to all causes, including terminations of pregnancy within specified gestational age.

- Abell [33], Abell [32] and Shand [19] report on pregnancies ending at 20 or more weeks, or with birthweight 400g minimum if gestational age is not known. McElduff's Research Letter [65] does not define perinatal mortality but compares findings with NSW Midwives Database 2002 which uses the same criteria as the previous 3 studies [19 32 33]. Wong [29], Gunton [28 72] and Kothari [43] do not define perinatal mortality by gestational age or birthweight.
- No studies define the greatest infant age up to which death contributes to perinatal mortality, but most imply that data collection is limited to neonatal inpatient death.
- In addition to reporting all-cause perinatal mortality as tabulated above, Abell [32 33] and Kothari [43] report perinatal mortality in the absence of detected congenital malformation.

[c]LGA: large for gestational age, defined as > 90th centile birth weight for age, except Templeton [8] who reports birthweight > 4000g. The most common reference range is Dobbin [113]

[d]Fetal anomaly:

- Kothari [43] and Gunton [28 72] did not pre-specify what anomalies would be reported and simply list diagnoses in the text : webbed thumb described as minor and complex cardiac lesion described as major [72], trisomy 13, retrognathia and encephalocoele [43].

- Three authors indicate that they report on both minor and major malformations, but do not define or report separately [29 32 65].
- Abell's report on outcomes for women with type 1 diabetes specify the outcome "major congenital malformation" but this is not defined in the paper [33].

[e] Multi-centre studies:

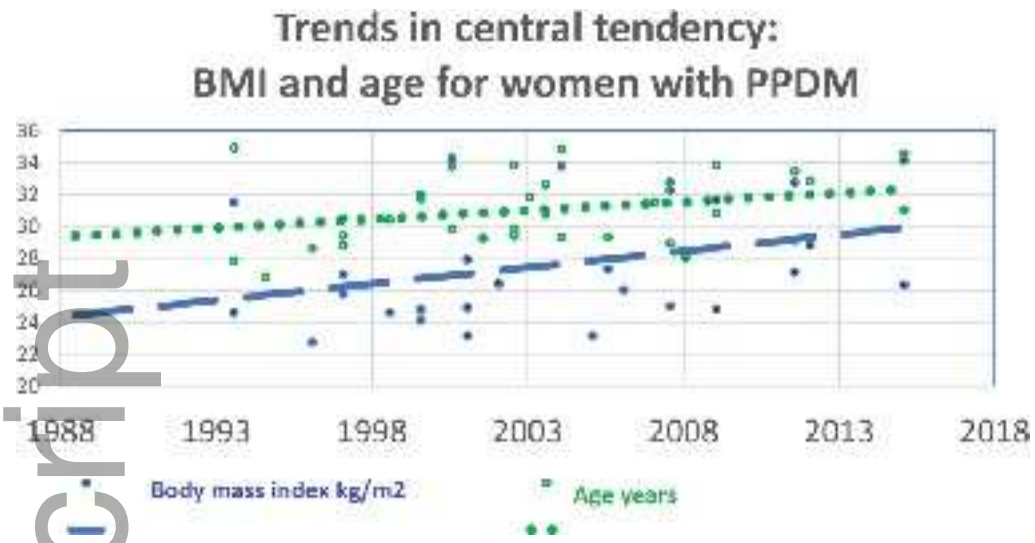
- McElduff's research letter [65] draws on a cross-section of 10 teaching hospitals in three Australian states.
- Shand's [19] setting is state-wide New South Wales.
- Templeton summarises Australian perinatal reports and hospital discharge data [8].
- All others are single centre studies. All studies are retrospective.

[f] Rurality:

- Shand's [19] study reports birth in rural hospitals for 6.5% of women.
- Templeton does not distinguish rural-dwelling from other mothers and babies [8].
- All other studies are metropolitan based.

[g] McElduff [65] reported some distinct maternal characteristics according to diabetes type. Pooled infant outcomes, not distinguished according to maternal diabetes type, are indicated by the superscript [g].

[h] Templeton [8] groups pregnancy-induced hypertension with pre-eclampsia and eclampsia.



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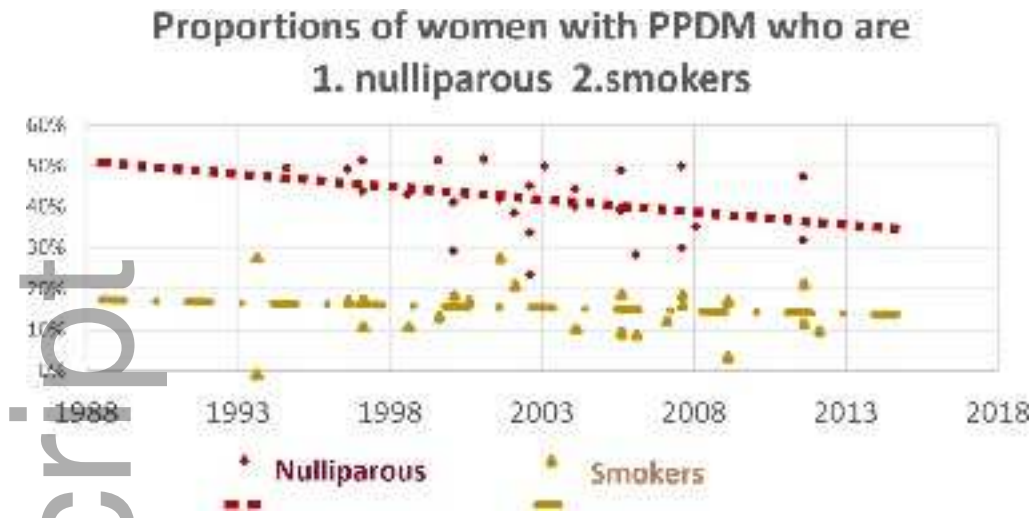

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