Timing Of Diagnosis Of Gestational Diabetes And Pregnancy Outcomes: A Retrospective Cohort

Short title: Early GDM and pregnancy outcomes

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Abstract:

Background: Recent guidelines suggest screening high risk women in early pregnancy for gestational diabetes (GDM), however there is little evidence to support this.

Aims: To compare pregnancy outcomes associated with diabetes for women with risk factors for GDM according to gestation of diagnosis. Early GDM was defined as a positive test before 20 weeks gestation, late GDM as a positive test at 20 or more weeks and no GDM when both tests were negative.

Materials and methods: Retrospective analysis in an Australian tertiary hospital of women who underwent a glucose tolerance test in pregnancy prior to 20 weeks gestation, and a repeat test after 20 weeks gestation if the initial test was negative. Results were adjusted for maternal demographics.

Results: Women with early GDM (n=170) were no more likely to experience the obstetric composite outcome than women with late GDM (n=171) or no GDM (n=547) (early OR 1.16 95%CI 0.79-1.71, late OR 0.78 95%CI 0.53-1.12). Infants of women with early GDM, but not late GDM, were more likely (early OR 1.8, 95%CI 1.15- 2.92, late OR 1.4, 95%CI 0.90-

2.23) to have the neonatal composite outcome than infants of women without GDM, predominantly due to an increase in neonatal hypoglycaemia.
Conclusions: This result may be due to careful management of GDM, or because, after adjustment for maternal demographics, the early diagnosis of GDM does not substantially increase rates of adverse outcomes compared to GDM diagnosed in later pregnancy or no GDM in women with risk factors for GDM.

Introduction

Gestational diabetes mellitus (GDM) is a common obstetric complication, affecting 12.7% of Australian pregnancies [1] and has maternal and neonatal implications. [2] Treatment of GDM has been shown to reduce maternal and neonatal complications. [3,4] In many countries, GDM screening occurs at around 28 weeks gestation, but recent guidelines have suggested that screening for GDM should also be conducted in early pregnancy in high risk groups, because early detection and treatment may improve outcomes [5,6]. The Australian Diabetes in Pregnancy (ADIPS) guideline recommends early screening with a GTT or HbA1c for women with risk factors including previous hyperglycaemia in pregnancy, previously elevated blood glucose level, pre-pregnancy BMI >30kg/m^2, previous macrosomia (>4500g or >90th centile), maternal age ≥ 40 years, polycystic ovarian syndrome (PCOS), ethnicity including Asian, Indian subcontinent, Aboriginal, Torres Strait Islander, Pacific Islander, Maori, Middle Eastern, non-white African, use of corticosteroids or antipsychotics or a family history of T2 DM or GDM. [5] There is limited published data regarding obstetric and neonatal outcomes in women diagnosed with GDM in early pregnancy and so we hypothesised that, in women with increased risk factors for GDM, diagnosis of GDM in the first half of pregnancy would be associated with adverse obstetric or neonatal outcomes compared to similar women who are diagnosed with GDM at 24 to 28 weeks gestation, or those who do not have GDM.

Methods

The study was conducted at an Australian tertiary hospital. Women were included if they underwent a 75g oral GTT between 1 January 2005 and 8 January 2016, at less than 20 weeks gestation, with a singleton pregnancy, and who then completed an GTT in the second half of pregnancy if the initial test was negative. This time frame was used to ensure similar obstetric and endocrine practices. It was not possible to identify the indication for the performance of the early GTT, but was presumed that all women who had an early GTT had a risk factor, as defined by the clinician. Data was collected on region of birth, maternal age, body mass index (BMI) and parity. The gestational age at the time of the GTT was determined from the estimated due date (identified from the medical record) and the date of the GTT. Missing late GTT values were sourced from either electronic or paper records. Until 1 January 2014, GDM was diagnosed if the fasting value was ≥5.5mmol/L or the 2 hour value was ≥8.0 mmol/L. [7] From 1 January 2014, GDM was diagnosed if the fasting value was ≥ 5.1 mmol/L, 1 hour value ≥10.0 mmol/L or 2 hour value ≥ 8.5 mmol/L. [8] The diagnosis of GDM was based on the criteria in use at the time of GTT. Maternal and neonatal outcomes were obtained from the hospital's electronic birthing outcome system, which is completed by trained midwives.

Approval to conduct the research was provided by the Mercy Hospital Human Research and Ethics committee, R15-52.

Outcome measures

The primary outcomes were an obstetric composite and a neonatal composite. The obstetric composite included one or more of caesarean section, neonatal birthweight >4500g or >90th centile for gestational age, 3rd or 4th degree perineal tear and shoulder dystocia, representing consequences of macrosomia. The neonatal composite included Apgar score of <7 at 5min, neonatal intensive care unit (NICU)/special care nursery (SCN) admission, neonatal hypoglycaemia and major birth defect. Major birth defect included hypospadias, chromosomal abnormality, cardiac anomaly, gastroschisis, imperforate anus and cleft palate. The components of the neonatal composite were chosen as they represented potential consequences of GDM or underlying, but undiagnosed, type 2 diabetes mellitus. The outcomes individually assessed included gestational age at delivery, pre-eclampsia (PE) or pregnancy-induced hypertension (PIH), admission to a high-dependency unit (HDU), post-partum haemorrhage (PPH) and induction of labour. All outcomes were defined by the midwife who entered data into the hospital's online records system according to the prespecified guidelines. [9]

Statistical analysis

Statistical analysis was performed using STATA 13IC (StataCorp, College Station TX, USA). Statistical significance was defined as two tailed $p < 0.05$. No correction of multiplicity of testing was performed. Women were grouped based on their GDM status: early GDM (diagnosis prior to 20 weeks 0 days gestation), late GDM (diagnosis after 20 weeks gestation) or no GDM. Data were summarised as the medians and interquartile ranges or means and standard deviations as appropriate for continuous variables, and as counts and proportions for categorical variables. Baseline characteristics were compared between groups using the Kruskal-Wallis test for continuous outcomes and Fisher's Exact test for categorical outcomes.

The hypothesis that women who are diagnosed with early GDM are at higher risk of developing poor pregnancy outcomes was investigated using appropriate regression models depending on the nature of the outcomes: a logistic regression model for binary outcomes and median regression model with bootstrap standard error estimation for continuous outcomes due to the nature of the distribution. All models included GDM status as an independent variable and maternal age, BMI, parity and region of birth as covariates for adjustment purposes. These variables were chosen as they are known to independently influence maternal and neonatal outcomes. The no GDM group was chosen as a reference group. The effect sizes were presented as OR (odds ratio) and adjusted odds ratios with correspondent 95% confidence intervals (CIs) or adjusted median difference with corresponding 95% CI. Standard assessment of model collinearity and fit were performed. No a priori power analysis was conducted.

Results

Baseline characteristics

44,675 pregnant women underwent a GTT during the specified time period and 888 women fulfilled the inclusion criteria. The demographics of the women included in the study are detailed in Table 1. The demographics of the women who were not included were not available. Women without GDM were younger than women with early or late GDM ($p = 0.001$) and more likely to be nulliparous, however there was no difference between groups in BMI or gestational age at the first GTT between groups.

GDM diagnosis

GDM was diagnosed in 38.4% (341/888, 95% CI 35%-42%) of the women. Of the women who developed GDM, 49.9% were diagnosed before 20 weeks gestation (170/341, 95% CI 44%-55%) and 50.1% were diagnosed after 20 weeks gestation (171/341 95% CI 45%-56%). 23.8% of the women who had a negative early GTT went on to have a later positive test result. 30 women underwent an GTT ≤12 weeks gestation and 12 of these were diagnosed with early GDM.

Associations between GDM and pregnancy outcomes

No statistically significant increase was identified in the odds of the obstetric composite outcome in women who developed early or late GDM when compared to no GDM, following adjustment for maternal BMI, age, parity and region of birth (early OR 1.16 95% CI 0.79-1.71 p=0.46, late OR 0.78 95% CI 0.53-1.12 p=0.23) (Table 2). The odds of an infant demonstrating one or more components of the neonatal composite was significantly increased in women with early GDM, but not late GDM compared to no GDM (early OR 1.8, 95% CI 1.15- 2.92 p=0.01, late 1.4, 95% CI 0.90-2.23, p=0.13). Neonatal hypoglycaemia was significantly increased both in women with early and late GDM compared to no GDM, however there was no statistically significant difference identified between early and late GDM groups. Similarly, no statistically significant differences were identified in the number of women with PE/PIH, admission to HDU or PPH between groups. The odds of induction of labour was significantly higher in women with early and late GDM compared to women with no GDM, but there was no statistically significant difference identified between the women with early GDM and late GDM. Compared to women no GDM, women with early and late GDM delivered an average of one week earlier. Of women who were induced, 39% were induced because of GDM. Among women with GDM who were induced, approximately 80% in both groups were induced because of GDM. There was no excessive collinearity identified for the obstetric or neonatal composite.

Discussion

The objective of our study was to determine whether women with risk factors for GDM who were diagnosed with early GDM experienced greater adverse pregnancy outcomes compared to similar women with late GDM or women without GDM in a retrospective analysis.

Following adjustment for maternal BMI, age and region of birth, we found no evidence that women with early GDM were more likely to experience the obstetric composite outcome than women with late GDM or no GDM. There was an increase in the odds of the neonatal composite outcome, which was predominantly due to an increase in neonatal hypoglycaemia. The increased rates of neonatal hypoglycaemia may be due to a true increase in neonatal hypoglycaemia or increased testing of the infants because of the GDM diagnosis, as infants of women without GDM do not have their blood glucose level tested unless symptomatic or large for gestational age. Data on the numbers of neonatal blood sugar tests, or on negative results were not available. The rate of induction was also increased, which is consistent with hospital guidelines advising induction of labour for women with GDM.

38.4% of women in the cohort were diagnosed with GDM, a figure almost 3-fold higher than the current prevalence of GDM in Australia. [1] This is likely to be because the women had risk factors for GDM, as identified by their clinician. Of the women diagnosed with GDM, 49.9% were diagnosed in early pregnancy and 50.1% in later pregnancy. These proportions are different from other reported series, in which higher proportion of women have been diagnosed in later pregnancy, from 71 to 88%. [10-12]

Early pregnancy testing may detect either women with a false positive GDM result due to high fasting glucose in early pregnancy [13] or women with underlying type 2 diabetes. 30 women underwent a GTT ≤12 weeks gestation and 12 were diagnosed with early GDM. It is possible that these women were incorrectly diagnosed with early GDM, as increased fasting plasma glucose occurs in first trimester. [14,15] The inclusion of 12 women with a false positive diagnosis may have decreased the true association between early GDM and pregnancy outcomes. Some women who had an early positive diagnosis of GDM may have had previously undiagnosed type 2 diabetes, however we were not able to confirm postnatal diagnoses of type 2 diabetes.

The strengths of our study are that it is the largest published cohort that we are aware of which includes a relevant control group of similar women, and includes adjustment for important maternal factors which impact on pregnancy outcomes. The cohort is of mixed ethnicity, making the result more able to be generalised.

This study has some limitations, including using retrospective data over a 10 year time period in which time there were inevitably some changes in obstetric practice in the institution, and changes in the diagnostic criteria for GDM. However, the analysis of outcome was based on the diagnostic criteria in use at the time of diagnosis. We were not able to determine the risk factors for each woman that prompted clinicians to request an early GTT. It is a single institution study, which may limit generalisability.

We did not find an increase in the odds of the obstetric composite outcome, or individual components of the obstetric composite, but others have demonstrated increased rates of adverse outcomes in women with early GDM including preeclampsia, caesarean section, and macrosomia. [11,12,16,17] These differences may be due to small sample size, cohorts extending over prolonged periods and encompassing changes in diabetes management and obstetric management, and lack of an appropriate control group. Because of the independent associations between increased BMI or advanced maternal age and many important obstetric outcomes, data which are not adjusted for these covariates are more likely to show an association between early GDM and these outcomes. Other studies have not demonstrated increases in adverse outcomes when results are adjusted for maternal characteristics. [10,16,18] Conversely, some authors have found higher prevalence of polyhydramnios and preterm birth in women diagnosed in later pregnancy compared to early pregnancy which they attributed to better control of diabetes with early diagnosis. [19]

Women who were diagnosed with GDM were referred for multidisciplinary care, including diet and lifestyle management, and pharmacological intervention as required. It is possible that return to normoglycaemic values returned the risk profile to baseline, although this has not been demonstrated in other cohorts of women with GDM diagnosed as part of routine screening. [20] We do not have information on the degree of compliance with therapy or level of blood sugar control in the cohort.

Conclusion

There has been little published information to date regarding the relationship between GDM diagnosed prior to 20 weeks gestation and pregnancy outcomes. In our study, there was no significant difference in the composite obstetric outcome between the groups but an increase in the neonatal composite outcome for women with early GDM. Outcomes which are dependent on the clinicians' knowledge of the diagnosis of GDM, induction of labour and diagnosis of neonatal hypoglycaemia, were increased in women with GDM, compared to women who never developed GDM. The results of our study suggest that following adjustment for maternal confounders, early GDM does not have a significant impact on maternal outcomes but may impact on neonatal outcomes. This is consistent with the published recommendations of a number of authorities suggesting that early pregnancy screening for GDM does not provide additional maternal health benefits. [21,22] A prospective, randomised, multicentre trial would help to better understand the role of screening and treatment for early GDM and its effect on pregnancy outcomes.

Table legends

Table 1 Baseline characteristics of women with early GDM, late GDM and no GDM

Table 2 Obstetric and neonatal outcomes of women with early GDM, late GDM and no GDM

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Table 1 Baseline characteristics of women with early GDM, late GDM and no GDM

	No GDM (N = 547)	Early GDM (N = 170)	Late GDM (N = 171)	
Age (years)	31 (28-35)	33 (30-36)	32 (30-35)	p<0.001
BMI (kg/m^2)	27 (23-35)	29 (25-35)	27.5 (23-35)	p=0.15
Nulliparity	210 (38.4)	39 (22.9)	43 (25.1)	p=0.01
Gestational age at early GTT (weeks)	16 (15-18)	16 (15-18)	16 (15-18)	p=0.39
Glucose values at early GTT (mmol/L)				
Fasting	4.46 (0.36)	5.01 (5.02)	4.63 (0.37)	p<0.001
1-hour post	6.73 (1.70)	9.82 (1.82)	8.18 (1.48)	p<0.001
2-hours post	5.43 (1.16)	8.41 (1.36)	6.41 (1.02)	p<0.001
Region of birth				
Europe/Americas	31 (5.7)	13 (7.7)	6 (3.5)	
Africa/Middle East	38 (7.0)	19 (11.2)	14 (8.2)	
Australia	368 (67.3)	70 (41.2)	92 (53.8)	
Northern Asia	23 (4.2)	24 (14.1)	13 (7.6)	
Southern/Central Asia	77 (14.1)	40 (23.5)	43 (25.2)	
Other	8 (1.5)	3 (1.8)	3 (1.8)	
Unknown	2 (0.4)	1(0.6)	0 (0)	

Data is mean (SD), median (IQR) or n (%) as appropriate

BMI data was available for 158 women with early GDM, 163 women with late GDM and 517 women with no GDM.

Table 2 Obstetric and neonatal outcomes of women with early GDM, late GDM and no GDM

	No GDM (n=547)	**Early GDM (n=170)**	**OR (95% CI)**		**aOR (95% CI)**		**Late GDM (n=171)**	**OR (95% CI)**		**aOR (95% CI)**	
Obstetric composite[†]	291 (53.2)	101 (59.7)	1.3 (0.92-1.85)	p=0.14	1.16 (0.79-1.71)	p=0.46	82 (47.9)	0.81 (0.57-1.14)	p=0.23	0.78 (0.53-1.12)	p=0.19
PE/PIH	39 (7.1)	6 (3.5)	0.48 (0.20 - 1.16)	p=0.35	0.48 (0.20-1.31)	p=0.58	7 (4.1)	0.55 (0.24-1.27)	P=0.31	0.52 (0.22-1.25)	P=0.27
Admission HDC	20 (3.70)	3 (1.8)	0.48 (0.14-1.63)	p=0.24	0.43 (0.12-1.52)	p=0.19	9 (5.3)	1.46 (0.65-3.28)	p=0.35	1.2 (0.51-2.81)	p=0.69
PPH	70 (12.8)	18 (10.7)	0.81 (0.47-1.41)	p=0.46	0.87 (0.49-1.57)	p=0.66	18 (10.5)	0.80 (0.46-1.40)	p=0.43	0.84 (0.48-1.48)	p=0.55
Perineal trauma 3rd or 4th degree	17 (3.1)	3 (1.8)			0.8 (0.21-3.23)	P=0.79	2 (1.2)			0.5 (0.10-2.37)	0.38
Induction of labour	181 (41.5)	72 (60.5)	2.16 (1.43-3.26)	p<0.001	2.46 (1.55-3.93	p<0.001	78 (59.5)	2.07 (1.39-3.09)	p<0.001	2.48 (1.61-3.84)	p<0.001
Birthweight >90th centile	139 (25.4)	38 (22.5)	0.85 (0.57-1.29)	p= 0.45	0.8 (0.49-1.23)	p=0.41	31 (18.1)	0.65 (0.42 – 1.0)	p=0.053	0.6 (0.40-1.02)	p=0.18
Birthweight >4.5kg	21 (3.8)	1 (0.6)			0.15 (0.02-1.12)	p= 0.06	0 (0)				
Neonatal composite[‡]	80 (14.7)	43 (25.4)	1.9 (1.30 – 3.01)	p=0.001	1.8 (1.15-2.92)	p=0.01	36 (21.2)	1.6 (1.01-2.41)	p=0.05	1.4 (0.90-2.23)	p=0.13
Apgar <7 at 5 minutes	14 (2.6)	3 (1.8)	0.69 (0.22-2.43)	p= 0.56	0.37 (0.08-1.80)	p=0.22	4 (2.3)	0.92 (0.3-2.83)	p= 0.88	0.6 (0.17-2.30)	p=0.49
Neonatal hypoglycaemia	18 (3.3)	21(12.3)	4.18 (2.17-8.05)	p<0.001	4.2 (2.01-9.00)	p<0.001	16(9.3)	3.04 (1.51-6.1)	p= 0.002	3.3 (1.57-7.06)	p=0.002

NICU/SCN	70 (12.8)	31(18.2)	1.61 (1.01-2.57)	p=0.04	1.6 (0.95 – 2.63)	0.08	29(17.0)	1.47 (0.91-2.36)	p=0.11	1.4 (0.85-2.29)	p=0.19
Major birth defect	12 (2.2)	3 (1.8)	0.8 (0.22 2.88)	p=0.74	0.8 (0.18-4.02)	p=0.83	3 (1.8)	0.79 (0.22-2.85)	p=0.72	0.9 (0.26-3.56)	p=0.26
Gestational age at delivery	38.9 (38.0-40.0)	38.0 (38.0-39.0)		P<0.001			38.4 (38.0-39.0)		P<0.001		

Abbreviations: OR, odds ratio; aOR, adjusted odds ratio; PPH, postpartum haemorrhage; NICU, neonatal intensive care; SCN, special care nursery; HDC, high dependency care

† Obstetric composite: caesarean section, neonatal birthweight >4500g or >90th centile for gestational age, 3rd or 4th degree perineal tear or shoulder dystocia

‡ Neonatal composite: Apgar <7 at 5min, NICU/SCN admission, neonatal hypoglycaemia or major birth defect.

Induction of labour: n= 436 (no GDM), 119 (early GDM) 131 (late GDM) excluding women with elective caesarean section

Data is n (%)

Adjusted for maternal BMI, age, parity and region of birth