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Occurrence and recurrence of diabetes in pregnancy.

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Abstract

Aims: To determine occurrence and recurrence rates of gestational diabetes (GDM) and pre-existing diabetes mellitus (PDM) among women having at least two consecutive pregnancies and to assess risk factors that contribute to GDM recurrence.

Methods: Population-based study using longitudinally linked hospital discharge and birth records (2001-2009) in NSW, Australia. Participants included women without a pre-existing diagnosis of Type 1 or Type II diabetes at time of first pregnancy and with at least a first and second birth. Factors associated with GDM recurrence were examined using multivariate log–binomial models to adjust for correlation within mothers and estimate relative risks (RR) and 95% confidence intervals.

Results: First occurrence of GDM was 3.7% (5 315/142 843) in the first pregnancy and 2.7% (3 689/137 528) in the second pregnancy. The recurrence rate of GDM in a second consecutive pregnancy was 41.2%. Risk of PDM in a pregnancy subsequent to one with first occurrence of GDM was 2.2% and 2.0% in the second or third pregnancy, respectively. Among women with a GDM diagnosis in the first pregnancy, independent predictors of GDM recurrence were maternal age ≥35 years, ethnicity (Middle East/North Africa and Asia), pregnancy hypertension, large for gestational age infant and preterm birth in the first pregnancy, longer interpregnancy birth interval and pregnancy hypertension and multiple pregnancy in the second pregnancy.

Conclusions: Women with a first pregnancy complicated by GDM have elevated recurrence rates and require screening, active management and monitoring in between and during subsequent pregnancies.

Keywords: diabetes, pregnancy, incidence, recurrence, record linkage

Abbreviations: Gestational diabetes mellitus (GDM); pre-existing diabetes mellitus (PDM)

Introduction

Gestational diabetes mellitus (GDM) is defined as a carbohydrate intolerance of varying degree of severity with an onset or first recognition during pregnancy.[1] Some women found to have raised glucose levels in pregnancy will have previously undiagnosed type 2 diabetes mellitus.[1] While estimates vary by country, recent data show that GDM prevalence has increased by 10 to 100% in the past 20 years, especially as the uptake of screening has increased.[2]

The frequency of GDM recurrence is reported to vary from 30 to 84% depending on the demographic profile and underlying risk of diabetes in the population, and the diagnostic criteria used.[3] Previous studies on GDM recurrence have been limited by small sample sizes, single study settings (i.e. one obstetric hospital) and from reporting estimates of recurrence for any two pregnancies (e.g. 2nd and 4th pregnancies) rather than restricting analysis to consecutive pregnancies and to primiparous women.[3-5] To our knowledge, there has only been one US study that has examined recurrence of GDM using population-based data.[4]

Identification of at-risk pregnancies provides a valuable opportunity for early pregnancy screening for GDM, monitoring and early intervention strategies. Discussion over changes in screening programs are currently being debated subsequent to the results of a large trial of over 23,000 women in 10 countries showing continuous associations between maternal glucose concentrations and adverse pregnancy outcomes including macrosomia, neonatal hypoglycaemia and caesarian section, even at glucose concentrations below those that are usually diagnostic of GDM.[6] The International Association of Diabetes and Pregnancy Study Group (IADPSG) Consensus Panel has proposed a new screening strategy for GDM that involves screening high risk women, including those with GDM in previous pregnancies, early in subsequent

pregnancies.[7] There is considerable debate around the cost effectiveness of these recommendations due to the increased rates of GDM likely to be detected if this new screening programme is implemented.[8, 9] In terms of early intervention strategies, The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) found that treatment of women with impaired glucose tolerance in pregnancy reduced adverse perinatal outcomes defined as death, shoulder dystocia, bone fracture, and nerve palsy[10] and a large trial by Landon and colleagues found that treatment for impaired glucose tolerance ('mild gestational diabetes') reduced the risks of fetal overgrowth, shoulder dystocia, caesarean delivery, and hypertensive disorders.[11]

The aim of the present study was to determine the occurrence and recurrence rates of GDM and PDM among women having at least two consecutive pregnancies and to assess risk factors for GDM recurrence.

Methods

The study population included all women with at least first and second births in New South Wales (NSW) between 1 Jan. 2001 to 31 Dec. 2009 (n=479, 068). NSW is the most populous state in Australia (~7.1 million), and has over one third of all Australian births (~90 000 births per annum).[12] Exclusions included women with a first birth prior to 1 Jan. 2001, with only one pregnancy during the study period, with non-consecutive pregnancies (e.g. an intervening birth occurred outside of NSW), with missing parity for any pregnancy (0.09% of excluded observations) or with a diagnosis of PDM (Type 1 or Type 2) at their first pregnancy.

Population health data were obtained from two validated NSW Ministry of Health computerised data sets: the Perinatal Data Collection (PDC) and the Admitted Patients Data Collection (APDC). The PDC (referred to as 'birth data') is a statutory population-based

surveillance system that includes information on all births at ≥20 weeks of gestation or birthweight at least 400 g. Information on maternal characteristics, pregnancy, labour and delivery, and infant outcomes are reported by the attending midwife or doctor. The APDC (referred to as 'hospital data') is a census of all NSW inpatient hospital discharges (public and private). In our dataset, diagnoses and procedures for each hospitalisation were recorded from the medical records and coded according to the International Classification of Diseases, 10th revision, Australian Modification (ICD-10-AM) and the affiliated Australian Classification of Health Interventions (ACHI).

Record linkage for the study was undertaken by an independent body, the NSW Centre for Health Record Linkage (CHeReL), in accordance with NSW privacy guidelines. Probabilistic record linkage methods were used to link birth and hospital data for each woman providing longitudinal information on the pregnancy history. Birth and hospital discharge data was available for a woman's first and subsequent pregnancies (i.e. 2nd, 3rd, 4th, etc). Only de-identified data were available to the researchers. The study was approved by the NSW Population and Health Services Research Ethics Committee.

The primary outcome of interest was GDM, including progression to pre-existing (Type 2) diabetes (PDM) in a subsequent pregnancy. Each record was searched in up to 20 ICD diagnosis fields for a GDM diagnosis code (O24.4, O24.9) or for a PDM diagnosis code (E11, E13, E14, O24.0-O24.3). Diabetes (GDM and PDM) was identified from the hospital data. Validation studies of the hospital data indicate 69%-96% ascertainment of GDM with few false positives, and 100% ascertainment of PDM with no false positives.[13, 14] These sensitivity and specificity values are in keeping with those reported by other international validation studies of birth and hospital records for identification of GDM and PDM.[15]

Maternal, pregnancy and obstetric risk factors that are well and accurately reported in birth and/or hospital data were included in the analysis.[16, 17] Explanatory variables measured during the first and second pregnancy included maternal age, mother's country of birth, multiple pregnancy, smoking during pregnancy, hypertension in pregnancy (including chronic, gestational, and preeclampsia), large for gestational age (>90th percentile birthweight for gestational age and sex), preterm birth (<37 weeks gestation), locality (urban versus rural) and type of hospital care (public versus private). The interpregnancy interval was calculated as the time between the dates of two consecutive live births minus the second infant's gestational age.

Statistical analyses

Using contingency table analysis, occurrence and recurrence rates of GDM and PDM were calculated for first, second and third pregnancies. For multivariate risk factor analyses, log–binomial models using generalized estimating equations (GEE) were used to adjust for correlation within mothers and estimate relative risks (RR) and 95% confidence intervals. In adjusted models, explanatory factors included the following first pregnancy factors: maternal age, maternal country of birth, pregnancy hypertension, large for gestational age infant, preterm birth, and the following second pregnancy factors: interpregnancy interval, smoking during pregnancy, pregnancy hypertension and multiple pregnancies.

Selection of first and/or second pregnancy factors to include in the model were based on whether the risk factor was time constant (i.e. country of birth), collinear with other variables (i.e. maternal age in first pregnancy and interpregnancy interval in second pregnancy) and whether the risk factor was identifiable during the second pregnancy (i.e. pregnancy outcomes such as preterm birth and infant size from the first pregnancy would be known; however, in a

second pregnancy only multiple birth would be known during antenatal care and GDM screening).

Adjusted relative risks were only calculated for the risk of recurrence in a second pregnancy, and not for a third pregnancy, given the small event rate and the number of adjustment factors. To determine whether timing of GDM screening during pregnancy had any impact on the association between risk factors and GDM recurrence, multivariate analysis was also performed restricting the analysis to women with infants born >28 weeks gestation. During the study period in NSW, guidelines recommended that women be screened at 26–28 weeks' gestation using a non-fasting 50-g glucose challenge test screening.[18] All analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

During the study period, there were 142,843 women with two consecutive births in NSW, of whom 20.1% (n= 28,724) had a third pregnancy. Study characteristics of women by GDM status in the first pregnancy are presented in **Table 1**. Compared to first pregnancies without GDM, women with GDM in their first pregnancy were more likely to be ≥35 years of age, to be born in countries in the Oceania or Pacific Islands, Middle East or North Africa, or Asia, to have gestational hypertension or preeclampsia, to have a multiple pregnancy and to live in an urban area (**Table 1**).

The 142,843 women in the study population had 318, 447 pregnancies and 3.9% of these were complicated by GDM. The first occurrence of a GDM diagnosis in the first, second and third pregnancy was 3.7%, 2.7% and 2.1%, respectively (**Figure 1**). Overall, the rate of GDM at the first, second and third pregnancy was 3.7%, 4.1% and 3.7%, respectively. For the 5,315 (3.7%) women with GDM in their first pregnancy, the recurrence risk for a second pregnancy

with GDM was 41.2% (adjusted RR: 21.33: 95% CI: 19.90, 22.86). The recurrence rate of GDM in a third consecutive pregnancy (after two previous GDMs) was 60.1%. Women with an intervening pregnancy with no GDM reported (i.e. GDM in the first and third pregnancies only) had a 22.9% rate of GDM in the third pregnancy. The risk of PDM in a pregnancy subsequent to one with first occurrence of GDM was similar whether the GDM was in the second or third pregnancy, 2.2% and 2.0% respectively. All women with PDM in a second pregnancy also had the diagnosis recorded in their third pregnancy.

Among women with first birth GDM, risk factors for recurrence of GDM (i.e. GDM in the first and second pregnancies) included the following first pregnancy factors: older maternal age (≥35 years), maternal country of birth (Middle East/North Africa and Asia), large for gestational age infant and preterm birth; and second pregnancy factors: increasing interpregnancy birth interval, pregnancy hypertension, and multiple pregnancy (**Table 2**). Results of the sensitivity analysis which excluded women with infants born ≤28 weeks of gestation for either the first or second pregnancy (n=28 cases excluded) found no notable difference in the multivariate results for predictors of GDM recurrence (results not shown).

Discussion

In this population-based prospective cohort study, we found that first diagnosis of GDM was highest in the first pregnancy (3.7%) compared to subsequent pregnancies (2.7% and 2.1% in the second and third pregnancy, respectively) and that women with GDM in their first pregnancy are at higher risk of GDM in their subsequent pregnancies. Forty-one percent of women with a GDM diagnosis in their first pregnancy had GDM recurrence in their second consecutive pregnancy. The risk of GDM recurrence decreased, but was not ameliorated, after an intervening non-GDM pregnancy. Risk factors for recurrent GDM included the following

first pregnancy factors: older maternal age, Middle Eastern, North African and Asian country of birth, large for gestational age infant, and preterm birth; and second pregnancy factors: increasing interpregnancy birth interval, pregnancy hypertension, and multiple pregnancy.

A comparison of GDM recurrence rates found in this study to those in the literature is hampered by the fact that most of the previous studies on GDM recurrence report estimates of GDM in any recorded subsequent pregnancy that occurred after an index pregnancy, rather than restricting their analysis to first, second and third consecutive pregnancies.[3-5, 19, 20] However, a study among Kaiser Permanente in California of women with two consecutive singleton births reported rates remarkably similar to those found in our study.[4] The rate of GDM recurrence in the second pregnancy among women with GDM in the first pregnancy was 41.3% compared to 41.2% in our study, the recurrence rate of GDM in a third consecutive pregnancy (after two previous GDMs) was 56.9% in the Getahun et al. study compared to 60.1% in our study, and the rate of GDM recurrence in a third pregnancy after an intervening unaffected pregnancy was 23.4% compared to 22.9% in our study.[4]

The risk patterns for occurrence and recurrence of GDM observed in the present study are similar to recurrence studies on other pregnancy conditions, such as postpartum haemorrhage and breech presentation.[21, 22] Common patterns observed include: highest risk of occurrence in the first pregnancy, increased risk with each subsequent pregnancy and decreased risk after an intervening unaffected pregnancy. The rate of recurrence of GDM in this study (41.2%) is much higher than recurrence rates for other pregnancy complications, including postpartum haemorrhage (14.8%),[21] placenta praevia (4.3%),[23] and pre-eclampsia (ranges from 6.8% to 65% depending on severity and complications of the initial case).[24] Thus, GDM in a previous pregnancy is a strong indicator of future risk and useful clinical marker for identifying women at

elevated risk. Strategies to improve early detection of recurrent GDM include increasing education to healthcare providers about the importance of collecting detailed pregnancy history information, following screening guidelines that include early screening or diagnostic tests for GDM, and putting systems in place that will ensure comprehensive medical information from a woman's previous pregnancy is collected, accessible and referred to, so that it can factored into antenatal care during future pregnancies.

In terms of GDM recurrence, information on first pregnancy (i.e. maternal age, ethnicity, pregnancy hypertension) and second pregnancy (i.e. previous large for gestational age infant, previous preterm birth, multiple pregnancy) risk factors that were identified in the present study are readily available and already ascertained as part of routine antenatal care. While many of the identified risk factors have previously been associated with increased risk of diabetes in general,[25, 26] pregnancy hypertension in the first and second pregnancy, previous preterm birth and long interpregnancy birth interval have not been identified in previous GDM recurrence studies. Studies on Type 2 diabetes have reported an increased prevalence of hypertension; hypertension being twice as common in individuals with diabetes as compared to those without diabetes.[27] Co-morbidity may also be related to unhealthy lifestyle factors such as obesity, poor diet and lack of exercise. Risk factors that were identified in this study which support findings from previous recurrence studies include ethnicity, older maternal age, and infant birth weight in the prior pregnancy.[4, 5, 28] Factors identified in other recurrence studies that were not available for analysis in this study are body mass index, and insulin requirement in the first pregnancy.[5, 28]

The clinical and policy implications of these study findings indicate that the high rate of GDM recurrence makes prevention and screening in this high-risk group an obvious part of antenatal care. All women with a previous history of GDM should have a follow-up glucose

tolerance test after the pregnancy, be counselled on healthy lifestyle behaviours, preferably prior to pregnancy, and be tested for GDM in any subsequent pregnancies. These findings also reinforce the importance of identifying GDM in first-time mothers. Women not appropriately screened, diagnosed and classified for GDM in their first pregnancy will not be identified as high-risk for diabetes screening in the postpartum period or in subsequent pregnancies. Well-recognized risk factors for GDM include increased body mass index, advanced maternal age, a family history of type 2 diabetes, certain ethnicities including Asian, Hispanic, and Native American, polycystic ovary disease, previous stillbirth, high blood pressure during pregnancy, and multiple pregnancies.[29] The risk factors for GDM occurrence found in the present study correlate with previous studies[29] and the clinical risk assessment criteria (such as age, ethnicity and family history) that is already part of recommendations for identifying high-risk women for earlier and more extensive blood glucose screening and testing.[7]

Importantly, in this study, women in rural areas were less likely to have a GDM diagnosis in the first pregnancy compared to women in urban localities. This finding may reflect differences in population risk profiles in urban and rural communities in terms of adiposity, ethnicity, or lifestyle behaviours such as diet and exercise. Another possibility is that women in rural areas have more limited access to health care and medical resources compared to women in urban areas and may not be screened for or diagnosed with GDM during their pregnancy. The generalisability of this finding to other countries is uncertain, but it is likely a similar situation in countries with large land masses and low-population density, such as Canada and the United States or in countries where large proportions of population live in rural areas, such as India and China. Further research examining barriers in rural communities to diabetes screening, patient

access to healthcare services and education are needed to improve detection and ensure adequate management once cases are identified.

The strengths of our study include a large sample size, inclusion of several clinically relevant and easily identifiable risk factors, use of validated risk factors and outcomes, limiting the analysis to nulliparous women and longitudinally linked population-based data, which allowed us to follow the consecutive pregnancies of individual women. Interpretation of study findings should however be made in the context of study limitations. There has been a reported increase in GDM screening from the beginning to the middle of the 1990s[30] therefore, estimates of GDM occurrence may be affected by increased screening activity. To reduce the introduction of ascertainment bias, the study period was limited to recent years and recurrence rates were analysed for women who were all diagnosed with GDM in their first pregnancy. Since, women in childbearing age are usually not screened for diabetes pre-pregnancy, it is difficult to distinguish between undiagnosed diabetes existing before pregnancy and hyperglycemia induced by pregnancy.[2] It is also possible that some women with GDM may have actually had undiagnosed PDM and that the recurrence rate of GDM may also incorporate some cases of PDM among women that were not tested for diabetes in between pregnancies. A limitation of using already existing population health databases is the lack of information on certain factors of interest. In this study, there was no information on maternal prepregnancy weight and weight gain during pregnancy or on postpartum lifestyle changes after a GDM pregnancy or diabetes treatments during pregnancy such as diet and insulin, which may reflect disease severity.

In conclusion, results of this study reveal that women are more likely to have GDM if they had GDM in a previous (immediately before) or prior (non-consecutive) pregnancy. Based on these findings, we recommend that health professionals be aware of the increased risk of

GDM in subsequent pregnancies and the risk factors that increase risk of recurrence so that they can counsel and manage high-risk patients accordingly.

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Contribution to authorship

AK, NN, JF and CR developed the concept and design of the study. AK conducted the analysis and was responsible for the overall drafting of the article. All authors revised the manuscript for important intellectual content, contributed to the interpretation of data and had final approval of the manuscript to be published.

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Table 1
Descriptive characteristics of women with and without a first pregnancy diagnosis of gestational diabetes (GDM) from Jan 2001 to Dec 2009, NSW.

	First birth, n (%)		
	GDM	**No GDM**	**p-value**
	n= 5, 315 (3.7)	n= 137, 528 (96.3)	
Maternal age			
<25 years	740 (13.9)	38894 (28.3)	<0.0001
25-34 years	3731 (70.2)	87000 (63.3)	Reference
≥35 years	844 (15.9)	11634 (8.5)	<0.0001
Country of birth			
Australia & New Zealand	3059 (58.9)	103221 (77.4)	Reference
Oceania/Pacific Islands	119 (2.3)	1471 (1.1)	<0.0001
Middle East/North Africa	268 (5.2)	4520 (3.4)	<0.0001
Asia	1313 (25.3)	13196 (9.9)	<0.0001
Others (Europe, NA, etc)	436 (8.4)	10916 (8.2)	<0.0001
Smoking during pregnancy	436 (8.2)	17361 (12.6)	<0.0001
Pregnancy hypertension[1]	781 (14.7)	14922 (10.9)	<0.0001
Multiple pregnancy	57 (1.1)	959 (0.7)	0.001
Urban residence (versus rural)	4200 (79.0)	97796 (71.1)	<0.0001
Public hospital (versus private)	1454 (27.4)	38525 (28.0)	0.30

[1]Includes gestational hypertension and preeclampsia.

Table 2
Risk of developing gestational diabetes in second consecutive pregnancy among women with a first pregnancy diagnosis of gestational diabetes from Jan 2001 to Dec 2009, NSW.

	Second birth, n (%)					
	GDM n=2192 (42.2)	**No GDM n=3005(57.8)**	**Crude RR (95% CI)**	**p-value**	**Adjusted RR (95% CI)**	**p-value**
1st pregnancy factors						
Maternal age						
<25 years	269 (12.3)	448 (14.9)	0.82 (0.70, 0.97)	0.02	0.87 (0.73, 1.03)	0.10
25-34 years	1541 (70.3)	2111 (70.3)	Reference	--	Reference	--
≥35 years	382 (17.4)	446 (14.8)	1.17 (1.01, 1.37)	0.04	1.19 (1.02, 1.39)	0.03
Country of birth						
Australia & New Zealand	1151 (53.7)	1840 (62.7)	Reference		Reference	--
Oceania/Pacific Islands	49 (2.3)	62 (2.1)	1.26 (0.86, 1.85)	0.23	1.25 (0.84, 1.84)	0.27
Middle East/North Africa	122 (5.7)	140 (4.8)	1.39 (1.08, 1.80)	0.01	1.44 (1.11, 1.86)	0.006
Asia	652 (30.4)	633 (21.6)	1.65 (1.44, 1.88)	<0.0001	1.71 (1.49, 1.96)	<0.0001
Others (Europe, NA, etc)	170 (7.9)	262 (8.9)	1.04 (0.84, 1.28)	0.73	1.01 (0.82, 1.24)	0.94
Pregnancy hypertension[1]	350 (16.0)	404 (13.4)	1.22 (1.05, 1.43)	0.01	1.16 (0.98, 1.38)	0.08
LGA 90th percentile	457 (20.9)	523 (17.4)	1.25 (1.09, 1.44)	0.002	1.36 (1.17, 1.57)	<0.0001
Preterm birth (<37 weeks)	198 (9.0)	210 (7.0)	1.32 (1.08, 1.62)	0.007	1.23 (1.00, 1.51)	0.06
2nd pregnancy factors						
Interpregnancy interval in years, mean (±SD)	2.48 (1.20)	2.35 (1.09)	1.11 (1.05, 1.16)	<0.0001	1.09 (1.03, 1.14)	0.001
Smoking during pregnancy	142 (6.5)	251 (8.4)	0.76 (0.61, 0.94)	0.01	0.92 (0.74, 1.16)	0.48
Pregnancy hypertension[1]	239 (10.9)	239 (8.0)	1.42 (1.17, 1.71)	0.0003	1.34 (1.09, 1.65)	0.006
Multiple pregnancy	47 (2.1)	30 (1.00)	2.17 (1.37, 3.45)	0.001	2.13 (1.34, 3.38)	0.001

[1]Includes gestational hypertension and preeclampsia.

Figure 1

Title: Occurrence and recurrence for gestational diabetes (GDM) and pre-existing diabetes (PDM) among women in the period 2001–2009 in New South Wales.