

Periconception glycemic control and congenital anomalies in women with pregestational diabetes

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ABSTRACT

Introduction To assess the relationship between periconception glycemic control and congenital anomalies in a contemporary, diverse population of women with pregestational diabetes.

Research design and methods This is a retrospective cohort study of all pregnant women with pregestational diabetes at a single institution (2003–2017) in the USA. The primary outcome was frequency of major or minor congenital anomalies. Glycemic control was assessed by periconception glycosylated hemoglobin (HbA1c). The association of periconception HbA1c with pregnancy outcomes was assessed using bivariable and multivariable analyses.

Results Our sample included 351 women, of which 63.8% had type 2 diabetes. Our study cohort is racially and ethnically diverse, with approximately equal numbers of women identifying as white non-Hispanic, black non-Hispanic and Hispanic, with 3.4% identifying as Asian. Of these 351 women, 52 (14.8%) had a fetus with a congenital anomaly, of whom the majority (n=43) had a major anomaly. Over half (51.1%) of all major anomalies were cardiovascular. Compared with the group with the best glycemic control (HbA1c ≤7.4%), which had an anomaly frequency of 10.2%, the frequency of congenital anomalies increased significantly with each category of worsening glycemic control (HbA1c 7.5%–9.4%: 20.6%, adjusted OR (aOR) 2.35, 95% confidence interval (CI) 1.08 to 5.13; HbA1c 9.5% to 11.4%: 25.8%, aOR 2.86, 95% CI 1.08 to 7.59; HbA1c ≥11.5%: 37.5%, aOR 7.66, 95% CI 2.27 to 25.9).

Conclusion In a diverse cohort of women with pregestational diabetes, higher periconception HbA1c, especially HbA1c >9.5, was significantly associated with major congenital fetal anomalies. Our study sample is reflective of the current population of pregnant women with diabetes, including women with type 2 diabetes and from racial and ethnic minorities.

INTRODUCTION

Pregestational diabetes affects approximately 1% of pregnancies in the USA,¹ and its prevalence is increasing.² Women with pregestational diabetes are at greater risk of spontaneous abortion,³ stillbirth,⁴ macrosomia⁵ and congenital anomalies.⁶ Past research indicates that the risk of these outcomes increases with worsening maternal glycemic control.⁷

Significance of this study

What is already known about this subject?

► Congenital anomalies are more common among pregnant women with diabetes who have poor periconceptional glycemic control. Much of the original data on this topic, however, focuses on white women with type 1 diabetes, although more recent literature incorporates more women with type 2 diabetes. The characteristics of pregnant women with pregestational diabetes have changed significantly over time, with non-white women with type 2 diabetes now comprising the majority.

What are the new findings?

► In a diverse cohort of women with pregestational diabetes that is more reflective of the contemporary population of women with diabetes in pregnancy, higher periconception glycosylated hemoglobin (HbA1c), especially HbA1c >9.5%, was significantly associated with major and minor congenital fetal anomalies.

How might these results change the focus of research or clinical practice?

► These results emphasize the importance of periconceptional glycemic control among women with diabetes of reproductive age.

Congenital anomalies are especially known to be associated with poor glycemic control in women with diabetes.⁸ Numerous studies have demonstrated rates of fetal anomalies ranging from 4.5% among women with well-controlled diabetes to as high as 30%–40% among women with poor glycemic control.^{7 9 10} The background risk of congenital anomalies in the general population, in contrast, is 2%–4%.^{7 9 11} Cardiac and neural tube anomalies, which often require surgical correction and cause significant neonatal morbidity and mortality, are especially common among women with diabetes.^{12 13}

Much of the original literature, however, regarding the increased risk of congenital anomalies in women with diabetes comes from the 1980s to 1990s.^{7 9} These older studies disproportionately included non-Hispanic

white women with type 1 diabetes, as these women comprised the majority of those entering pregnancy with diabetes during that era. The majority of women currently entering pregnancy with diabetes, however, have type 2 diabetes,¹⁴ which disproportionately affects individuals from racial and ethnic minorities in the US population.¹⁵ Although previous research indicates that women with type 2, as opposed to type 1, diabetes have similar risks of congenital anomalies, these largely used administrative rather than clinical data and were mainly performed outside the USA.^{10 16–21} Individuals with diabetes in the USA are also more likely to be obese, which may compound the risks incurred by hyperglycemia alone. In this paper, we quantify the risks of congenital anomalies among women with pregestational diabetes in a diverse cohort that is more reflective of the contemporary pregnant population in the USA.

MATERIALS AND METHODS

This is a retrospective cohort study of all pregnant patients with pregestational diabetes who received care at Northwestern Memorial Hospital between 1 January 2003 and 1 January 2017. At this institution, located in Chicago, Illinois, over 11 000 individuals give birth each year, and a long-standing diabetes and pregnancy program has provided comprehensive care to a large referral population of individuals with pregestational or gestational diabetes. For this study, pregnant women with any type of pregestational diabetes were identified by querying the institutional electronic medical record. Records queried included those from deliveries, ultrasound, pathology and any other interaction with this healthcare system, and thus women whose pregnancies did not end in a live birth were able to be captured. Women were excluded if, on further review, they were found to have gestational diabetes, multifetal gestation or a known fetal chromosomal abnormality on diagnostic testing. Women were also excluded if they had incomplete data on periconception glycosylated hemoglobin (HbA1c), defined as no HbA1c value measured during the 3 months before or after the estimated time of conception. Pregnancy outcomes were identified and classified as either first trimester induced abortion, spontaneous pregnancy loss prior to 20 weeks' gestation, intrauterine fetal demise at 20 weeks' gestation or greater or live birth. Women were ultimately included if they had a pregnancy that lasted beyond 20 weeks' gestation regardless of pregnancy outcome. For women who had more than one pregnancy that lasted beyond 20 weeks' duration, only data from the first pregnancy during the study time period were used.

Information regarding congenital anomalies was collected through review of ultrasound reports, autopsy records and neonatal physical examinations. Major and minor anomalies were defined in concordance with the European Surveillance of Congenital Anomalies (EUROCAT) classifications.²² Major anomalies were defined as those that have medical and/or social

implications, many of which often require surgical repair or are life threatening, such as complex cardiac defects or neural tube defects. Minor anomalies were defined as those having only cosmetic significance or that presented only minor functional issues, such as extra digits or mild pelviectasis. These definitions were in accordance with previous studies.²³ Anomalies were then further classified according to affected organ system. Fetuses were categorized as having multiple anomalies if more than one organ system was affected. When available, information regarding diagnostic genetic testing was obtained from results of amniocentesis or chorionic villi sampling, or in the case of intrauterine fetal demise (IUID) or pregnancy termination from placental chromosomal analysis or fetal chromosomes.

Glycemic control, as measured by HbA1c, was modeled two ways. First, glycemic control was modeled as a continuous variable. Second, HbA1c was modeled as a categorical variable. We assigned women to one of four glycemic control groups: $\leq 7.4\%$ (≤ 57 millimoles/mole (mmol/mol)), 7.5%–9.4% (58–79 mmol/mol), 9.5%–11.4% (80–101 mmol/mol) and $\geq 11.5\%$ (≥ 102 mmol/mol). These values are similar to those used in prior studies.^{7 24} This latter method may be less sensitive to violations of assumed linearity between HbA1c and outcome. For multivariable models, we decided a priori to include several potential confounders known to be associated with increased risk of congenital anomalies, including age, body mass index (BMI), parity (nulliparous vs multiparous), insurance status (public vs private) and smoking status (any vs none). As the sample size was fixed, no power calculations were performed.

Student's *t*-tests, analysis of variance or Wilcoxon rank-sum tests were used for bivariable analyses with continuous variables, and χ^2 and Fisher's exact tests were used for bivariable analyses with categorical variables. Multivariable logistic regression was used to control for potential confounders. All hypothesis tests were two tailed, and a probability value of 0.05 was used to determine statistical significance. All analyses were carried out in STATA (V.15.0, StataCorp, College Station, Texas, USA).

RESULTS

A total of 443 pregnant women with pregestational diabetes and an HbA1c within 3 months (either before or after) of the start of the observed pregnancy were initially identified. We excluded 20 women with a multifetal gestation and 5 women with a diagnosis of fetal chromosomal abnormalities. A further 66 women either underwent pregnancy termination ($n=19$) or had a spontaneous pregnancy loss prior to 20 weeks' gestation ($n=47$). Women with a higher HbA1c were more likely to undergo pregnancy termination ($p=0.04$). The final sample size for analysis included 351 women.

This study population was racially and ethnically diverse, with 29.3% of women identifying as white non-Hispanic,

Table 1 Maternal characteristics by periconception glycosylated hemoglobin

Variable	Overall sample (N=351)	≤7.4% ≤57 mmol/mol (n=236)	7.5%–9.4% 58–79 mmol/mol (n=68)	9.5%–11.4% 80–101 mmol/mol (n=31)	≥11.5% ≥102 mmol/mol (n=16)	P value*
Maternal age (years)	32.3±5.7†	32.3±5.9	32.0±5.7	32.3±5.5	33.4±4.1	0.84
Nulliparous	175 (49.9)	119 (50.4)	33 (48.5)	15 (48.4)	8 (50.0)	0.99
Body mass index (kg/m ²)	34.7±9.1	34.3±9.4	36.1±8.6	34.6±8.0	35.5±9.4	0.57
Race/ethnicity						0.01
White non-Hispanic	103 (29.3)	73 (30.9)	12 (17.7)	10 (32.3)	8 (50.0)	
Black non-Hispanic	98 (27.9)	54 (22.8)	34 (50.0)	8 (25.8)	2 (12.5)	
Hispanic	98 (27.9)	71 (30.1)	14 (20.6)	8 (25.8)	5 (31.3)	
Asian	12 (3.4)	10 (4.2)	1 (1.5)	1 (3.2)	0 (0.0)	
Other	40 (11.4)	28 (11.9)	7 (10.3)	4 (12.9)	1 (6.3)	
Public insurance	211 (70.1)	151 (75.9)	36 (58.1)	18 (66.7)	6 (46.2)	0.01
Smoking	89 (26.0)	58 (25.2)	15 (22.4)	10 (34.5)	6 (37.5)	0.44
Diabetes type						0.34
Type 1	127 (36.2)	92 (39.0)	22 (32.4)	10 (32.3)	3 (18.8)	
Type 2	224 (63.8)	144 (61.0)	46 (67.7)	21 (67.7)	13 (81.3)	

*P value is for analysis of variance, χ^2 or Fisher's exact tests.

†Data presented as mean±SD for continuous variables and n (%) for categorical variables.

27.9% identifying as black non-Hispanic, 27.9% identifying as Hispanic and 3.4% identifying as Asian. Seventy per cent of women were publicly insured. Women with type 2 diabetes comprised the majority (63.8%) of the cohort (table 1). Demographic characteristics largely did not differ by HbA1c, with the exception of race and insurance status (table 1). There were no differences in proportion of type 1 versus type 2 diabetes by HbA1c (p=0.34).

Overall, 14.8% of women had any fetal anomaly (n=52), and 12.3% (n=43) had a major fetal anomaly (table 2). Of the anomalies identified, 43 were classified as major and 13 as minor; four fetuses had both major and minor anomalies. Anomalies were predominantly cardiac, with 22 major (51.2%) and 2 minor (15.4%) cardiac anomalies. On bivariable analysis, higher periconception HbA1c was significantly associated with any anomaly (p=0.002), as well as major (p=0.002), but not minor (p=0.38), anomalies. The median HbA1c was greater for those with anomalies than those without (8.4% (68 mmol/mol) vs 7.1% (54 mmol/mol), p<0.001).

When controlling for potential confounding factors (table 3), increasing HbA1c remained associated with both any anomaly (adjusted OR (aOR)=2.35, 95% CI 1.08 to 5.13 for HbA1c 7.5–9.4 (58–79 mmol/mol); aOR=2.86, 95% CI 1.08 to 7.59 for HbA1c 9.5–11.4 (80–101 mmol/mol); aOR 7.66, 95% CI 2.27 to 25.9 for HbA1c ≥11.5 (≥102 mmol/mol)) and major anomalies (aOR 2.35, 95% CI 1.02 to 5.44 for HbA1c 7.5–9.4 (58–79 mmol/mol); aOR 3.17, 95% CI 1.11 to 9.06 for HbA1c 9.5–11.4 (80–101 mmol/mol); aOR 7.75, 95% CI 2.17 to 27.7 for HbA1c ≥11.5 (≥102 mmol/mol)). There

was no significant association between HbA1c group and minor anomalies.

DISCUSSION

Pregestational diabetes is increasingly a comorbidity of pregnancy.²⁵ This study provides further evidence for a strong association between poor glycemic control and increased risk of congenital anomalies among women with pregestational diabetes, using a cohort of racially and ethnically diverse women more representative of the current obstetric population in the USA than seen in prior studies, which largely focus on women with type 1 diabetes^{7 26–28} or were performed elsewhere,^{10 16–21} mostly in European countries. Odds of an anomaly were especially high among the groups with the worst glycemic control (HbA1c ≥11.5% or ≥102 mmol/mol), a finding consistent with prior studies.^{24 27} Among the group with the worst glycemic control, over one-third of women had at least a minor anomaly, although this is a small group. Similar to the findings of Tinker *et al*,¹² the most common class of defects we found were cardiac defects. Similarly to Eriksen *et al*,¹⁰ however, we found a higher rate of congenital anomalies than the background rate even among women with the best glucose control.

One important implication of this finding is that care for women with pregestational diabetes must occur prior to conception. The American Diabetes Association (ADA) recommends that all women of childbearing age with diabetes receive developmentally appropriate preconception education from the onset of puberty about the risks of malformations associated with unplanned pregnancies during times of poor glycemic control, that preconception

Table 2 Fetal anomalies by periconception HbA1c

Variable	Overall sample (N=351)	≤7.4% ≤57 mmol/mol (n=236)	7.5%–9.4% 58–79 mmol/mol (n=68)	9.5%–11.4% 80–101 mmol/mol (n=31)	≥11.5% ≥102 mmol/mol (n=16)	P value*
Any anomaly	52 (14.8)†	24 (10.2)	14 (20.6)	8 (25.8)	6 (37.5)	0.002
Minor anomaly	13 (3.8)	7 (2.6)	3 (7.6)	2 (6.7)	1 (16.7)	0.38
Cardiovascular	2	1	1	0	0	
Musculoskeletal	3	1	1	1	0	
GU	4	2	1	1	0	
ENT	2	2	0	0	0	
Multiple	1	1	0	0	0	
Dermatologic	1	0	0	0	1	
Major anomaly	43 (12.3)	19 (8.1)	12 (17.7)	7 (22.6)	5 (31.3)	0.002
Cardiovascular	22	8	8	2	4	
Musculoskeletal/limb	3	1	1	1	0	
GU/renal	4	2	1	0	1	
CNS	4	3	0	1	0	
GI	0	0	0	0	0	
ENT/face	1	0	1	0	0	
Multiple	8	5	1	2	0	
Dermatologic	1	0	0	1	0	

*P values are for χ^2 or Fisher's exact tests.

†Data presented as n (%), except for specific organ subgroups of anomalies, which are presented as n only.

CNS, central nervous system; ENT, ear, nose and throat; GI, gastrointestinal; GU, genitourinary; HbA1c, glycosylated hemoglobin.

HbA1c should ideally be <6.5% (<48 mmol/mol) and also be advised on the use of contraception.²⁹ Adequate preconception care in conjunction with counseling has been proven to reduce birth defects among women with diabetes.³⁰ Yet, in recent studies, as few as 4% of women with pregestational diabetes received this preconception counseling.⁶

Similarly, despite the ADA recommendation that all women with diabetes receive counseling regarding contraception, women with diabetes are often more likely to have an unintended pregnancy and less likely to receive contraception counseling and prescriptions than women without chronic disease.^{31 32} Women with diabetes who experience unintended pregnancies are

less likely to have optimal glucose control,³³ are less likely to recognize that they are pregnant or to initiate prenatal care until at least the second trimester,³⁴ well past the point in pregnancy after which most birth defects have developed. Improving counseling about reproductive planning and access to contraception for women with diabetes may help reduce congenital anomalies among this group.

More generally, preconception care for all women could improve outcomes for women with diabetes, as approximately 0.5% of all US women of reproductive age are estimated to have undiagnosed diabetes,³⁵ especially women from racial and ethnic minorities.³⁶ One particularly important population of women with pregestational

Table 3 Periconception HbA1c and fetal anomalies

Hba1c category	Any fetal anomaly		Minor anomaly		Major anomaly	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
≤7.4% ≤57 mmol/mol	(ref)	(ref)	(ref)	(ref)	(ref)	(ref)
7.5%–9.4% 58–79 mmol/mol	2.28 (1.04 to 5.00)	2.35 (1.08 to 5.13)	1.47 (0.37 to 5.87)	2.08 (0.48 to 9.02)	2.50 (1.06 to 5.9)	2.35 (1.02 to 5.44)
9.5%–11.4% 80–101 mmol/mol	3.26 (1.23 to 8.64)	2.86 (1.08 to 7.59)	2.27 (0.45 to 11.6)	2.22 (0.42 to 11.6)	3.64 (1.28 to 10.4)	3.17 (1.11 to 9.06)
≥11.5% ≥102 mmol/mol	5.58 (1.83 to 17.0)	7.66 (2.27 to 25.9)	1.90 (0.22 to 16.4)	1.76 (0.18 to 17.0)	5.79 (1.78 to 18.9)	7.75 (2.17 to 27.7)

*Adjusted for insurance and maternal race. HbA1c, glycosylated hemoglobin.

diabetes that is often missed are women who experienced gestational diabetes in prior pregnancies,³⁷ approximately 25%–50% of whom will develop type 2 diabetes over 10 years.^{38,39} Identifying women with undiagnosed diabetes prior to pregnancy might further decrease the incidence of congenital anomalies due to diabetes.

Major strengths of this study include the availability of 14 years of data from high-volume (over 11 000 births per year) tertiary care center with a specialized diabetes in pregnancy program. The availability of multiple types of medical records allowed ascertainment of all women with pregestational diabetes regardless of pregnancy outcome and allowed for triangulation of outcomes from multiple sources, rather than relying on International Classification of Disease (ICD) 9 or ICD-10 codes found in administrative data, as used in most prior studies.

However, this study has several limitations. Only those anomalies detected antenatally or shortly after birth were identified, as there were no follow-up data for neonates after initial discharge from the delivery hospitalization, and many anomalies, particularly cardiac, are diagnosed later in childhood. Additionally, minor anomalies may not have been apparent in the initial newborn exams, limiting their ability to be captured. Even in the group with the best glycemic control (HbA1c $\leq 7.4\%$, ≤ 57 mmol/mol), we found a higher rate of anomalies in than in prior studies. The overall anomaly rate in our cohort was nearly 10%, compared with rates of 3%–4% in prior studies.^{7,26} This higher prevalence may reflect improved detection of anomalies with more advanced screening ultrasound technology and use of fetal echocardiograms. We may therefore be identifying more anomalies that may have negligible significance on a neonates' future health, such as a small ventricular septal defect. Alternatively, this higher rate may reflect a higher baseline rate of anomalies in this population. Despite the high birth volume of our institution, the sample size is relatively small, especially in the groups with the worst glycemic control, reflected by our large CIs.

In addition, as this study covers a long time period, there may have been changes to the management of diabetes in both pregnant and non-pregnant adults that may affect periconceptional HbA1c, including technologies such as insulin analogs, insulin pumps, continuous glucose monitors and other treatment practices such as the increased use of telehealth. However, the purpose of this study was not to describe temporal changes in diabetes management or the impact of such changes on glycemic control, but rather to evaluate the relationship of glycemic control on risk for congenital malformation. We are unable to control for all aspects of prenatal care and patient characteristics that may affect the likelihood of congenital malformations, such as folic acid intake, substance use, type of diabetes therapy and use of other medications such as ACE inhibitors. Thus, residual confounding may remain. As this is a retrospective study using existing data, HbA1c was not measured at a uniform point in time and is subject to inherent variability that

would not occur in a prospective study with standardized timing. Finally, there may be selection bias in terms of which women with diabetes had periconception HbA1c testing; future work on expanding periconception care will be important for improving the health of pregnant women with diabetes and in order to reduce potential selection bias in this investigation.

CONCLUSIONS

In a diverse cohort of women with pregestational diabetes in the USA, higher periconception HbA1c was significantly associated with major and minor congenital fetal anomalies. The prevalence of anomalies was overall very high and supports the ongoing need for attention to reproductive life planning and glycemic control even in a changing population of individuals with pregestational diabetes. These findings have important clinical and public health implications in the counseling of pregnant women with diabetes, and most importantly, those women with diabetes presenting for care in the preconception period.

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Competing interests None declared.

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Data availability statement No data are available. This study uses clinical data from Northwestern University. Per our Institutional Review Board approval, we cannot share data with individuals not listed on the protocol.

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