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Type 2 diabetes mellitus in pregnancy: The impact of maternal weight and early glycaemic control on outcomes

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ABSTRACT

Objectives: To study the pregnancy outcomes in women with type 2 diabetes mellitus (T2DM) and to relate these to maternal risk factors.
Methods: We conducted a retrospective study of 419 women with T2DM (index group)- who attended our diabetes in pregnancy clinic at the Hamad Women's Hospital, Doha, between March 2015 and December 2016 -and 1419 normoglycaemic women (control group).
Results: Compared with the controls, T2DM women were older (mean age 34.7 ± 6.9 vs 29.6 ± 5.5 years; $p < 0.001$) and had a higher BMI (34.5 ± 6.7 vs 28.8 ± 6.1 kg/m2; $p < 0.001$). The incidence of macrosomia, shoulder dystocia and stillbirth were similar in the two groups, while that of pre-term labour, pre-eclampsia, caesarean section (CS), large for gestational age (LGA), neonatal ICU (NICU) admission, and neonatal hypoglycaemia were significantly higher in the T2DM compared to the control group ($p < 0.05$). Multivariate regression analysis showed that first trimester HbA1C was associated with an increased risk of LGA (OR 1.17; 95% CI [1.01–1.36]), pre-eclampsia (OR 1.26; 95% CI [1.02–1.54]), neonatal hypoglycaemia (OR 1.32; 95% CI 1.10–1.60) and NICU admission (OR 1.32; 95% CI 1.10–1.60). Pre-pregnancy BMI was associated with increased risk of LGA (OR 1.04; 95%CI [1.00–1.08]), macrosomia (OR 1.06; 95%CI [1.00–1.12]) and CS (OR 1.05; 95% CI [1.01–1.09]). Last trimester HbA1c was associated with an increased risk of LGA [OR 1.53, 95% CI [1.13–2.10)] and CS (OR 1.37, 95% CI [1.01–1.87]).
Conclusion: T2DM is associated with adverse pregnancy outcomes compared to the normal control in Qatar. Maternal obesity and glycaemic control before and during pregnancy are the main determinants of pregnancy outcomes in women with T2DM.

Introduction

The St. Vincent's declaration for diabetes care in Europe called for normalisation of pregnancy outcomes in mothers with diabetes [1]. At the time of the declaration- 1989- the emphasis was on pre-existing type 1 diabetes and little was known about the pregnancy outcomes in women with type 2 diabetes mellitus (T2DM). There is some evidence suggesting improvement in the pregnancy outcomes in women with T1DM over the last decade, nevertheless pre-existing T1DM is still associated with poor pregnancy outcomes including higher frequencies of pre-term labour, macrosomia, caesarean-section, neonatal hypoglycaemia and stillbirth compared to the background population [2–4]. Furthermore, the prevalence of both T1DM and T2DM during pregnancy is increasing [5,6]. In Qatar, the prevalence of pre-existing diabetes among women in childbearing age is 11.4% ; hence more pregnancies are expected to be complicated by T2DM [7].

A systematic review showed that pregnancy outcomes in T2DM women were as poor as those reported in women with T1DM [8]. However, most of the studies included a small number of participants. Furthermore, little is known about the effects of glycaemic control on pregnancy outcomes in women with T2DM.

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This study aims to describe the outcomes of pregnancies complicated with T2DM in comparison with the background population. It also aims to relate maternal risk factors with pregnancy outcomes.

Methods

This was a retrospective cohort study undertaken at the Women's Hospital of Hamad Medical Corporation, Doha, Qatar. Qatar has a universal screening protocol for diabetes in pregnancy. All pregnant females – who are not known to have pre-existing diabetes-are screened for diabetes in pregnancy in the first trimester using fasting blood glucose and HBA1c, and then after 24 weeks gestation using 75 g oral glucose tolerance test. The diabetes clinic in the Women's Hospital is the largest provider of diabetes care during pregnancy in the state of Qatar.

We reviewed the pregnancy outcomes of women with T2DM who were managed in the diabetes clinic in the Women's Hospital between March 2015 and December 2016. For comparison, we identified women in whom diabetes was excluded based on normal oral glucose tolerance (OGTT) screening test results that were done between January 2016 and April 2016 as reported in a previous study [9]. Gestational Diabetes Mellitus (GDM) was defined based on the WHO criteria (fasting blood glucose $\geq$ 5.1 mmol/l; 1-hour post 75 g OGTT $\geq$ 10.0 mmol/ l; and 2-hours post 75 g OGTT $\geq$ 8.5 mmol/l). Pre-pregnancy weight was recorded in the first visit based on patient self-report and was found on the electronic medical records as '' pre-pregnancy weight''. Where this was not recorded, we used the last recorded weight before conception (provided this was within the last 6 months) as pre-pregnancy weight otherwise weight was considered as a"missing" variable. We took the last height measured before conception or the height recorded in the first trimester as a variable for calculating the BMI. Maternal age was taken as the age of the mother at conception. Macrosomia was defined as birth weight > 4000 g; large for gestational age (LGA) was birth weight >90th percentile; small for gestational age (SGA) as birth weight <10th percentile, and pre-term delivery as delivery < 37 weeks of gestation. We calculated the average weekly gestational weight gain ((weight at delivery(kg)-weight at conception(kg))/(Gestational age at delivery(weeks)). The study was approved by the Institutional Review Board (IRB) of Hamad Medical Corporation. Only pregnancies that continued after 24 weeks gestation were included in the outcome analysis.

Statistical analysis was performed using STATA 15 software (College Station, TX: Stata Corp LP). Variables are expressed as a percentage (%) for frequencies, mean $\pm$ standard deviation for normally distributed continuous variables, and median (Interquartile range) in non-normally distributed variable. Student *t*-test was used to compare continuous variables between the two groups. Univariate Chi-square test and multivariate analysis were used to compare categorical data. Logistic regression analyses was used to model the odds or likelihood of each maternal or neonatal outcomes. Purposeful selection method was used to build the models. Crude logistic regression analyses were performed as initial steps of qualifying variables to be included in the multivariable logistic regression analyses. Variables with p-values < 0.25 were considered to develop an initial reduced model [10]. Using adjusted Wald tests, variables that tested insignificant (with p-values > 0.05) were then eliminated from this model. Insignificant variables were assessed for confounding effects using a 20 percent change in the coefficients. Likelihood ratio tests were used to compare models. Variance inflation factors were used to assess multicollinearity among variables. Hosmer and Lemeshow goodness-of-fit tests were used to assess any evidence to lack of fit of the final models. Odds ratios (OR), adjusted odds ratios (AOR) and their 95% confidence intervals from logistic regression analyses were reported [11].

Results

A total of 417 women with T2DM (index group) and 1419 women without diabetes (control group) were included in this study. Thirty-four pregnancies (8.15%) in the index group were excluded from our analysis of outcomes because they ended before 24 weeks gestation (i.e. ended before viability).

Table 1 shows the baseline characteristics of the two groups. T2DM women were older (mean age was 34.7 $\pm$ 6.9 years vs 29.6 $\pm$ 5.5 years; $p < 0.001$), had higher BMI (34.5 $\pm$ 6.7 kg/m^2 vs BMI 28.8 $\pm$ 6.1 kg/m^2; $p < 0.001$) and more likely to be Qatari (46.7% vs 37.7%; $p < 0.001$) compared to controls.

The median duration of diabetes mellitus at the time of booking was 3.3 (0.5–7.7) years, the mean first trimester HbA1C was 7.2 $\pm$ 1.5%, and the mean third trimester HbA1C was 6.05 $\pm$ 0.83% (Table 2). The target pre-pregnancy HbA1C of $\leq$7.0% was met by 228 of the 416 (54.8%) women while the target third trimester HbA1C of $\leq$6.5% (47.5%) was met by 290 of 361 (80.3%) women. Most of the women were treated with Metformin, with or without insulin.

Table 3 summarises pregnancy outcomes in the two groups. The incidence rates of macrosomia, shoulder dystocia and stillbirth were similar in the two groups. The incidence of SGA was lower in the T2DM compared to the control group (7.3% vs 14.3% $p < 0.001$). Apart from these, the incidences of all other maternal and neonatal outcomes were worse in the T2DM group compared to the normal group.

Table 4 shows the crude and multivariable regression analysis. As shown in the table, multivariable regression analysis showed that first trimester HbA1C (%) was associated with an increased risk of LGA (OR 1.17; 95% CI [1.01–1.36]), an increased risk of pre-eclampsia (OR 1.26; 95% CI {1.02–1.54]), an increased risk of neonatal ICU admission (OR 1.32; 95% CI [1.10–1.60]); and an increased risk of neonatal hypoglycaemia (OR 1.32; 95% CI [1.10–1.60]), after adjustment for maternal age, pre-pregnancy BMI and gestational weight gain. After adjusting for first trimester HbA1C (%), maternal age, gestational weight gain and last trimester HbA1C (%); pre-pregnancy BMI was associated with an increased risk of macrosomia (OR 1.06; 95%CI [1.00–1.12]); an increased risk of LGA (OR 1.04; 95%CI [1.00–1.08]); and an increased risk of caesarean-section (OR 1.05; 95% CI [1.01–1.09]). The third trimester HbA1C (%) was associated with an increased risk for LGA [OR 1.54, 95% CI [1.12–2.10)]; and an increased risk for Caesarean -section (OR 1.37, 95% CI [1.01–1.87]) after adjusting for age, pre-pregnancy BMI, gestational weight gain and first trimester HbA1C (%).

Table 1
Baseline characteristics. Data are expressed as means $\pm$ SD or actual number of participants and percentages.

	T2DM (417)	Control (1419)	P value
Age (Years)	34.7 ± 6.9	29.6 ± 5.5	<0.001
Pre-pregnancy weight (kg)	85.0 ± 17.5	72.8 ± 16.9	<0.001
Pre-pregnancy BMI*(kg/m [2])	34.5 ± 6.7	28.8 ± 6.1	<0.001
BMI Categories			<0.001
Normal	15 (3.6%)	379(27.7%)	
Overweight (25-29.9)	101 (24.3%)	467(34.2%)	
Obese (≥30)	299 (72.1%)	521(38.1%)	
Ethnicity			<0.001
Qatari	194 (46.5%)	535 (37.7%)	
Arab	122 (29.3%)	512 (36.1%)	
Asian	95 (22.8%)	305 (21.5%)	
Other	6(1.4%)	67(4.7%)	

*3.6% of the data are missing

Table 2
Summary of T2DM characteristics, glycaemic control, and medications. Data are expressed as means ± SD, Median (IQR) and actual number of participants and percentages.

	T2DM (417)
Median Duration of diabetes (years)*	3.3 (0.7-5.5)
Mean First trimester HbA1C (%)	7.20 ± 1.50
≤7.0 %	228/416 (54.8%)
>7.0%	188/416 (45.2%)
Mean Last Trimester HbA1C (%)†	6.05 ± 0.83
≤6.5%	290/361 (80.3%)
>6.5%	71/361 (19.7%)
Treatment	
Metformin only	(56/ 376) (14.8%)
Metformin + Insulin	260/379 (68.6%)
Insulin only	56/370 (16.6%)

* 2.4% and.
† 5.7% of the data are missing.

Discussion

This study showed that women with T2DM during pregnancy are at higher risk of maternal and neonatal complications compared to the background population. T2DM was associated with an increased risk of hypertensive disorders in pregnancy, genitourinary infections, polyhydramnios, induction of labour, pre-term labour and caesarean-section. The neonates of women with T2DM had higher incidences of LGA, hypoglycaemia, NICU admission, jaundice, and respiratory distress. There was no difference in the incidence of macrosomia between the two groups. Multivariate analysis showed that these differences persisted even after correction for known covariates; pre-pregnancy BMI, gestational weight gain and maternal age. Besides, these differences were still present despite a reasonably good glycaemic control; 54.8% of the women with T2DM were within the HbA1C target of ≤7.0% in the first trimester, and 80.3% were within the HbA1C target of ≤6.5% in the third trimester. First trimester HbA1C, pre-pregnancy BMI, and last trimester HbA1C were the main critical factors related maternal and fetal outcomes in women with T2DM.

This study is not only one of the largest to report on pregnancy outcomes in women with T2DM but also the largest from the Middle East and North Africa (MENA) region. Two studies from Saudia Arabia (KSA) and one study from Oman reported on pregnancy outcomes in 14 and 66 (KSA) and 58 (Oman) women with T2DM respectively [12–14]. The largest study by Wahabi et al. reported a macrosomia incidence of 6.0% and a Caesarean-section incidence of 24.1% (13). Our cohort was similar at baseline to two cohorts from the United Kingdom that included 680 and 1330 women with T2DM in pregnancy [15,3]. The incidence of LGA (≥ 90th percentile) in both studies was 23.4%; similar to the 23.2% reported here. In comparison to another study from the UK on 240 pregnancies with T2DM, the incidences of pre-term delivery, pre-eclampsia, and Caesarean-section in our cohort were higher (27.1% vs 17.7%; 8.4% vs 5.2% ; and 61.9% vs 51.4%) while that of LGA was lower (23.2% vs 37.6%), respectively [16]. Studies from Ireland, Sweden and Korea, reported an incidence of macrosomia in T2DM of 23%, 22% and 15% respectively compared to that of 5.2% incidence in our cohort [2,17,18].

This is the first study to show that early and late glycaemic control, and maternal obesity are risk factors for poor pregnancy outcomes in T2DM women, properly due to the small number of subjects in the previous studies. First trimester HbA1C, pre-pregnancy BMI and third trimester HbA1C were independent risk factors for LGA, macrosomia, pre-eclampsia, Caesarean-section, neonatal hypoglycaemia, and neonatal ICU admission in our study. Murphy et al. showed that in T2DM pregnancies only maternal obesity was associated with an increased risk for LGA [16]. In a univariate analysis, Ladfors et al. showed that HbA1C in all trimesters were associated with an increased risk for LGA in T1DM but not in T2DM, and found no influence of pre-pregnancy BMI on

Table 3
Pregnancy outcomes. Data are expressed as means ± SD or actual number of participants and percentages.

	T2DM (383)	Controls (1419)	P value	†Adjusted OR (95% CI)
Weekly gestational weight gain (kg/wk)	0.15 ± 0.17	0.19 ± 0.17	<0.001	
Pregnancy Induced Hypertension	37 (9.7%)	35(2.5%)	<0.001	1.66(1.26-2.18)*
Pre-eclampsia	32(8.4%)	36(2.5%)	<0.001	1.69(1.27-2.23)*
Polyhydramnios	46(12.6%)	26(2.0%)	<0.001	2.55(1.93-3.37)*
Recurrent UTI	45(11.8%)	65(4.5%)	<0.001	1.54(1.22-1.94)*
Recurrent Vaginal Infection	21(5.5%)	23(1.6%)	<0.001	1.94(1.37-2.74)*
Gestational age at delivery (weeks)	37.3 ± 2.23	38.8 ± 2.06	<0.001	
Induction of labour	93(25.5%)	149(10.5%)	<0.001	1.74(1.47-2.05)*
Steroids given	24 (6.3%)	53(3.7%)	0.024	1.30(0.98-1.72)
Pre-term Labour	67 (27.7%)	76(11.1%)	<0.001	1.74(1.48-2.05)*
Mode of Delivery			<0.001	
C-section	239 (62.9%)	496 (35%)		1.52(1.34-1.74)*
Vaginal delivery	141(37.1%)	923 (65%)		1.0
Primary C-section	90/383 (23.5%)	253/1419 (17.8%)	<0.001	
Emergency C-section	113/383(29.5%)	248/1419(17.5%)	<0.001	
Neonatal weight	3168 ± 666	3152 ± 566	0.6384	
Large for gestational age	89(23.2%)	95(6.7%)	<0.001	1.99(1.66-2.39)*
Macrosomia	20(5.2%)	59(4.2%)	0.367	1.02(0.76-1.38)
Small for gestational age	28(7.3%)	202(14.2%)	<0.001	0.76(0.60-0.94)*
Outcomes			0.409	
Life birth	378 (98.7%)	1407(99.2%)		
Still Birth	5 (1.3%)	12(0.8%)		
NICU admission	91(23.8%)	114(8.0%)	<0.001	1.86(1.56-2.21)*
Shoulder dystocia	3(0.8%)	4(0.3%)	0.160	2.39(1.04-5.5)*
Respiratory distress	52(13.8%)	67(4.7%)	<0.001	1.63(1.31-2.03)*
Neonatal Hypoglycaemia	39(10.2%)	39(2.8%)	<0.001	2.29(1.75-2.99) *
Neonatal Jaundice	62(16.2%)	137(9.7%)	<0.001	1.33(1.13-1.64)*

†Odds ration corrected for age, BMI and gestational weight gain.
*$p < 0.05$.

Table 4
Crude regression analysis and multivariable regression analysis.

Crude Logistic Regression						
	Macrosomia	LGA	Pre-eclampsia	C-section	NICU admission	Neonatal Hypoglycaemia
Age	0.95 [0.87,1.03]	0.96 [0.92,1.01]	1.03 [0.99,1.07]	1.02 [0.99,1.06]	1.02 [0.98,1.05]	0.97 [0.92,1.03]
Pre-pregnancy BMI	1.05 [0.99,1.11]	1.02 [0.99,1.06]	1.02 [0.97,1.07]	1.05 [1.01,1.08]*	0.99 [0.96,1.03]	0.97 [0.92,1.03]
Weekly GWG	3.17 [0.25,40.31]	3.05 [0.76,12.19]	3.24 [0.42,25.19]	0.89 [0.26,3.02]	4.84 [1.21,19.36]*	6.52 [1.01,42.15]*
First Trimester A1C	1.25 [0.98,1.60]	1.19 [1.03,1.37]*	1.26 [1.03,1.55]*	1.04 [0.91,1.19]	1.19 [1.03,1.38]*	1.37 [1.14,1.64]*
Last Trimester A1C	1.69 [1.09,2.62]*	1.67 [1.26,2.23]*	1.26 [0.85,1.87]	1.36 [1.02,1.81]*	1.40 [1.06,1.85]*	1.68 [1.19,2.36]*

Multivariable Logistic Regression Analysis Model 1						
	Macrosomia	LGA	Pre-eclampsia	C-section	NICU admission	Neonatal Hypoglycaemia
Age	0.94 [0.86,1.02]	0.96 [0.92,1.01]	1.03 [0.99,1.07]	1.02 [0.99,1.06]	1.03 [0.99,1.06]	0.98 [0.93,1.05]
Pre-pregnancy BMI	1.06 [1.00,1.12]*	1.04 [1.00,1.08]*	1.02 [0.97,1.08]	1.05 [1.01,1.09]*	1.00 [0.96,1.04]	0.99 [0.94,1.05]
Weekly GWG	2.42 [0.16,37.20]	2.61 [0.60,11.42]	3.21 [0.35,29.54]	1.43 [0.39,5.24]	4.45 [1.02,19.36]*	3.14 [0.41,23.98]
First Trimester A1C	1.24 [0.96,1.61]	1.17 [1.01,1.36]*	1.26 [1.02,1.55]*	1.06 [0.92,1.22]	1.17 [1.01,1.35]*	1.32 [1.09,1.59]*

Multivariable Logistic Regression Analysis Model 2						
	Macrosomia	LGA	Pre-eclampsia	C-section	NICU admission	Neonatal Hypoglycaemia
Age	0.93 [0.85,1.02]	0.96 [0.92,1.01]	1.04 [1.00,1.08]	1.02 [0.99,1.06]	1.03 [0.99,1.06]	0.99 [0.93,1.05]
Pre-pregnancy BMI	1.06 [1.00,1.13]*	1.04 [1.00,1.08]*	1.02 [0.97,1.08]	1.05 [1.01,1.09]*	1.00 [0.96,1.04]	0.98 [0.93,1.04]
Weekly GWG	2.80 [0.14,56.32]	2.25 [0.47,10.71]	2.59 [0.26,25.35]	1.57 [0.41,6.04]	4.29 [0.93,19.82]	2.99 [0.35,25.79]
First Trimester A1C	1.22 [0.91,1.64]	1.07 [0.91,1.27]	1.26 [1.01,1.58]*	0.99 [0.85,1.15]	1.10 [0.94,1.30]	1.25 [1.01,1.53]*
Last Trimester A1C	1.42 [0.87,2.31]	1.54 [1.12,2.10]*	1.09 [0.69,1.74]	1.37 [1.01,1.87]*	1.32 [0.97,1.79]	1.44 [0.99,2.09]

* $p < 0.05$.

LGA in both types of diabetes [17]. Tennant et al. showed that pre-conception HbA1C > 6.6% is associated with an increased risk of fetal mortality [19]. Gestational weight gain did not influence pregnancy outcomes in our cohort contrary to other studies [20–22]. Metformin was widely used in our cohort and could have reduced the rate of gestational weight gain in T2DM but did not affect other outcomes. Indeed, gestational weight gain was significantly lower in the T2DM group compared to the control group.

Our findings further emphasise the impact of pre-pregnancy obesity and poor glycaemic control on pregnancy outcomes. The optimisation of weight and glycaemic control might reduce the risk of maternal and fetal complications. Murphy et al. showed that lack of pre-pregnancy care was an independent risk factor for adverse pregnancy outcomes in women with pre-gestational diabetes [23]. At booking, women who received pre-pregnancy care were leaner, had better glycaemic control and less adverse pregnancy outcomes compared to those who did not [23]. Owens et al. showed that pre-pregnancy care had improved glycaemic control, reduced incidence of obesity at conception and reduced perinatal mortality [24]. A meta-analysis of cohort studies showed that pre-pregnancy care lowered HbA1C at conception by 1.92% and was associated with reduced congenital malformations and perinatal mortality [25]. Our findings also support the importance of tighter glycaemic control during pregnancy in women with T2DM. Most of the studies have reported on the harmful impact of elevated third trimester HbA1C (>6.5%) on pregnancy outcomes in women with T1DM but not in T2DM [26,27].

As a retrospective study, ours has many limitations such as failure to include confounding factors which were not available for example, parity, smoking, lipids, micro-albuminuria, history of PCOS, and socio-economic factors in the analysis. The main strength of the study, however, is the large number of participants, the detailed pregnancy outcomes and the low levels of missing data. Besides, care was delivered to women through the same multidisciplinary team of endocrinologists, obstetricians, dietitian, and diabetes nurse specialists.

In conclusion, T2DM in pregnancy is associated with poor pregnancy outcomes compared to the background population. Maternal obesity and glycaemic control before and during pregnancy are the main determinants of outcomes. Dedicated pre-pregnancy care is needed to optimise weight and glycaemic control and reduce adverse pregnancy outcomes in women with T2DM. Future studies should include other factors that might influence pregnancy outcomes such as lipids and microalbuminuria.

Funds

The study did not receive any funds.

Conflict of interest

The authors report no competing conflict of interest.

Novelty

Type 2 diabetes mellitus during pregnancy is associated with poor pregnancy outcomes compared to the background population. This is one of the largest single centre studies to report on pregnancy outcomes in women with type 2 diabetes mellitus. The study shows that the risk of poor pregnancy outcomes is already pre-determined by the pre-pregnancy BMI and glycaemic control in women with type 2 diabetes. In addition to improving glycaemic control, future research should focus on improving maternal BMI before conception

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