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Original Article

Outcomes of type 1 diabetes mellitus in pregnancy; effect of excessive gestational weight gain and hyperglycaemia on fetal growth

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ABSTRACT

Aims: To study pregnancy outcomes in patients with type 1 diabetes mellitus (T1DM) and the factors associated with poor outcomes.
Methods: A retrospective study of 110 patients with T2DM who attended our diabetes in pregnancy clinic at the Women's Wellness and Research centre, Doha, between March 2015 and December 2016 and 1419 normoglycaemic controls.
Results: There was no difference in age, weight, and BMI between the two groups. 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 T1DM than in the control group. From a multivariate regression analysis, excessive gestational weight gain was associated with increased risk of LGA (OR 4.53; 95% CI [1.42–14.25]). Last trimester HBA1c was associated with increased risk for macrosomia [OR 2.46, 95% CI [1.03–5.86)]; LGA [OR 3.25, 95% CI [1.65–6.40)]; increased risk for C-section (OR 1.96, 95% CI [1.12–3.45]), and increased risk of NICU admission (OR 2.46, 95% CI [1.04–5.86]). The changes in HBA1C between the first and last trimester HBA1c was associated with a reduction in the risk of LGA [OR 0.46, 95% CI [(0.28–0.75)]
Conclusion: T1DM in pregnancy is associated with adverse pregnancy outcomes compared to the general population. Reducing gestational weight gain and improving glycaemic control might improve pregnancy outcomes.

1. Introduction

Type 1 diabetes mellitus (T1DM) is associated with an undisputed increased risk of maternal and fetal morbidity and mortality [1]. One of the five years targets of the St. Vincent's declaration was to "achieve pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman" [2]. It has been 29 years since this declaration was signed and this target has not been achieved by many countries [3]. Achieving normal or near normal glucose levels in patients with type 1 diabetes is challenging. The continuous change in food intake and insulin sensitivity during pregnancy result in unpredictable fluctuation in glucose levels needing frequent adjustment of insulin doses. As a result the risk of moderate and severe hypoglycaemia is increased substantially in patients with T1DM [4]. Most of the guidelines recommend to adjust the glucose targets during pregnancy in patients with T1DM to avoid undue hypoglycaemia [5,6]. In addition to poor glycaemic control, pre-pregnancy BMI, excessive gestational weight gain and smoking are recognised risk factors for poor pregnancy outcomes in patients with T1DM [7].

There is evidence that pregnancy outcomes in T1DM have improved over time in some countries [8]. There are not too many studies that have reported on pregnancy outcomes in T1DM patients from the Middle-East and North Africa (MENA) region. This study aims to describe the outcomes of pregnancies complicated with T1DM and to examine the effects of maternal weight and glycaemic control on pregnancy outcomes.

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2. Methods

This was a retrospective cross-sectional study undertaken at the Women's Wellness and Research Centre (WWRC) formely known as the Women's Hospital of Hamad Medical Corporation, Doha, Qatar. The WWRC is the largest maternity hospital in the state of Qatar delivering between 16-18,000 women per year. The diabetes clinic in the WWRC is the largest provider of diabetes care during pregnancy in the state of Qatar.

We reviewed the outcomes of pregnancies in women with T1DM that were managed in our institution between March 2014 and December 2017. For controls, we identified women without diabetes based on normal oral glucose tolerance (OGTT) test screening result. Pre-pregnancy weight is recorded in the first visit based on patient self-report and is found on the electronic medical records as '' pre-pregnancy weight''. If 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 (wGWG) ((weight at delivery (kg)-weight at conception (kg))/(Gestational age at delivery (weeks)). Gestational weight gain (GWG) was also classified as excessive or adequate if it exceeds the institute of medicine (IOM) recommendations [9]. The differece between the first trimeseter and last (third) trimeseter HBA1c was calculated as (first trimeter HBA1C-last trimeseter HBA1C). 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 and mean ± standard deviation for normally distributed continuous variables. 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. Multivariate logistic regression analysis was performed to examine the independent effects of first trimester HBA1C, pre-conception BMI, GWG and last trimester HBA1c on macrosomia, LGA, Caesarean section (C-section), neonatal intensive care Unit (NICU) admission and neonatal hypoglycaemia. $P < 0.05$ was considered significant.

3. Results

A total of 110 women with T1DM (index group) and 1419 non-diabetics (control group) were included in this study. Five pregnancies (4.6%) in the index group were excluded from our analysis of outcomes because they ended as miscarriage prior to 24 weeks gestation (i.e. ended before viability).

Table 1 shows the baseline characteristics in the two groups. There was no difference between the two groups in age, pre-pregnancy weight, pre-pregnancy BMI, and the prevalence of overweight and obesity. T1DM patients were more likely to be Qatari nationals compared to the normal group.

As shown in Table 2, the average duration of diabetes mellitus at the time of booking was 13.7 ± 4.8 years. The mean first trimester HBA1C was 7.9 ± 1.5% (63 mmol/mol), and the mean third trimester HBA1C was 6.70 ± 1.4% (50 mmo/mol). The target pre-pregnancy HBA1C of ≤7.0% (53 mmol/mol) was met by 38 patients (34.6%) and the target last trimester HBA1C of ≤6.5% (48 mmol/mol) was met by 46 patients (41.8%).

Table 1
Baseline characteristics. Data are expressed as means ±SD or actual number of subjects and percentages.

	DM-1 (110)	Control (1419)	P value
Age (Years)	29.5 ± 5.0	29.6 ± 5.5	0.8189
Pre-pregnancy weight (kg)[a]	69.7 ± 14.3	72.8 ± 16.9	0.0588
Pre-pregnancy BMI*(kg/m^2)[a]	27.7 ± 5.5	28.8 ± 6.1	0.0794
BMI Categories			0.109
Normal (18–24.9)	37 (35.2%)	379 (27.7%)	
Overweight (25–29.9)	48 (36.2%)	467 (34.2%)	
Obese (≥30)	39 (28.6%)	521 (38.1%)	
Ethnicity			<0.001
Qatari	59 (53.6%)	535 (37.7%)	
Arab	41 (37.3%)	512 (36.1%)	
Asian	7 (6.4%)	305 (21.5%)	
Other	3 (2.7%)	67 (4.7%)	

[a] 3.7% are missing.

Table 2
Summary of T1DM characteristics, glycaemic control, and medications. Data are expressed as means ±SD or actual number of subjects and percentages.

	T1DM (110)
Mean Duration of diabetes (years)[a]	13.7 ± 7.8
Mean First trimester HBA1C (%)	7.9 ± 1.5
≤7.0% (53 mmol/mol)	38 (34.6%)
>7.0% (53 mmol/mol)	72 (65.4%)
Mean Last Trimester HBA1C (%)	6.7 ± 1.4
≤6.5% (48 mmol/mol)	46 (41.8%)
>6.5% (48 mmol/mol)	64 (58.2%)

[a] <1% missing.

Table 3 summarises pregnancy outcomes in the two groups. T1DM patients gained significantly more weight during pregnancy compared to the control group (wGWG 0.28 ± 0.17 kg/week vs 0.19 ± 0.17 kg/week; $p < 0.001$). T1DM group delivered earlier than the control group with a mean GA at delivery of 36.5 ± 2.22 weeks vs 38.8 ± 2.06 weeks ($p < 0.001$) respectively. There was no difference between the two groups in the incidence of pregnancy induced hypertension (PIH), macrosomia, shoulder dystocia and stillbirth. The incidence of small for gestational age was lower in the T1DM group compared to the control group (6.7% vs 14.2% $p < 0.001$). Apart from the above all other outcomes were worse in the T1DM group compared to the control group.

Multivariate regression analysis showed excessive GWG were associated with (OR4.53; 95% CI [1.42–14.45]) after correction for age, pre-pregnancy BMI, first trimester HBA1c and last trimester HBA1C (Table 4). Last trimester HBA1c was associated increased risk for macrosomia [OR 2.46, 95% CI [1.03–5.86)]; LGA [OR 3.25, 95% CI [1.65–6.40)]; an increased risk for C-section (OR 1.96, 95% CI [1.12–3.45]), and an increased risk of NICU admission (OR 2.46, 95% CI [1.04–5.86]) after correction for age, BMI, GWG and first trimester HBA1C. Furthermore, after correcting for age, BMI and gestational weight, the difference between the first and last trimester HBA1c was associated with a reduction in LGA [OR 0.46, 95% CI [(0.28–0.75)].

4. Discussion

This study showed that pregnancies in women with T1DM are at higher risk of maternal and neonatal complications compared to the background population. T1DM was associated with an increased risk of pre-eclampsia, induction of labour, pre-term

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

	T1DM (105)	Controls (1419)	P value	Adjusted OR (95% CI)
wGWG (kg/wk)‡	0.28 ± 0.17	0.19 ± 0.17	<0.001	
Excessive GWG†	28 (36.8%)	295 (24.0%)	0.012	1.85 (1.14–3.00)*ø
PIH	5 (4.8%)	35 (2.5%)	0.156	1.35 (0.97–1.78)
Pre-eclampsia	7 (6.7%)	36 (2.5%)	0.014	1.69 (1.27–2.23)*
Polyhydramnios	14 (13.7%)	26 (2.0%)	<0.001	1.92 (1.52–2.44)*
Gestational age at delivery (weeks)	36.5 ± 2.22	38.8 ± 2.06	<0.001	
Induction of labour	34 (32.7%)	149 (10.5%)	<0.001	1.60 (1.37–1.87)*
Steroids given	12 (11.4%)	53 (3.7%)	<0.001	1.44 (1.13–1.82)*
Pre-term Labour	50 (47.6%)	157 (11.1%)	<0.001	1.93 (1.67–2.23)*
Mode of Delivery			<0.001	
C-section	67 (63.8%)	496 (35%)		1.44 (1.25–1.67)
Vaginal delivery	38 (36.2%)	923 (65%)		1.0
Primary C-section	31 (29.5%)	253 (17.8%)	0.003	
Emergency C-section	45 (42.9%)	249 (17.6%)	<0.001	
Neonatal weight (grams)	3125 ± 714	3152 ± 566	0.6544	
Large for gestational age	29 (27.9%)	95 (6.7%)	<0.001	1.76 (1.49–2.07)*
Macrosomia	7 (6.8%)	59 (4.2%)	0.204	1.19 (0.91–1.57)
Small for gestational age	7 (6.7%)	202 (14.2%)	0.032	0.70 (0.51–0.95)*
Outcomes			0.272	
Life birth	103 (98.1%)	1407 (99.2%)		
Still Birth	2 (1.9%)	12 (0.8%)		
NICU admission	39 (38.2%)	114 (8.0%)	<0.001	1.89 (1.62–2.21)*
Shoulder Dystocia	1 (0.98%)	4 (0.28%)	0.234	1.46 (0.70–3.07)*
Respiratory distress	22 (21.6%)	67 (4.7%)	<0.001	1.63 (1.31–2.03)*
Neonatal Hypoglycaemia	46 (45.1%)	39 (2.8%)	<0.001	3.2 (2.65–3.76)*
Neonatal Jaundice	21 (20.6%)	137 (9.7%)	<0.001	1.30 (1.09–1.55)*

‡4.3% missing data. †14% are missing. *p < 0.05. Adjusted OR for gestational weight gain. ºCrude odds ratio.

Table 4
Multivariate Logistic Regression Analysis. Data is expressed as Odds ratio and 95% CI.

	Macrosomia	LGA	Pre-eclampsia	C-section	Neonatal hypoglycaemia	NICU
First trimester A1C[a]	0.68 (0.34–5.86)	0.83 (0.59–1.17)	0.58 (0.26–1.28)	0.86 (0.59–1.25)	1.15 (0.82–1.64)	1.11 (0.79–1.58)
Age[b]	1.06 (0.88–1.28)	1.05 (0.93–1.18)	0.94 (0.74–1.19)	1.05 (0.95–1.16)	0.95 (0.86–1.05)	0.99 (0.89–1.10)
BMI[c]	1.07 (0.34–1.36)	1.08 (0.97–1.19)	1.01 (0.82–1.23)	1.08 (0.98–1.18)	1.07 (0.98–1.16)	0.97 (0.89–1.06)
Last trimester A1C[d]	2.46 (1.03–5.86)*	3.25 (1.65–6.40)*	2.10 (0.84–5.20)	1.96 (1.12–3.45)*	1.21 (0.75–1.95)	2.46 (1.04–5.86)*
Difference A1c[e]	0.57 (0.28–1.14)	0.46 (0.28–0.75)*	0.54 (0.25–1.14)	0.79 (0.56–1.12)	1.08 (0.77–1.50_	1.02 (0.74–1.43)
Excessive GWG[f]	7.21 (0.56–96.28)	4.53 (1.42–14.45)*	13.06 (0.78–218.03)	1.59 (0.54–4.62)	1.58 (0.56–4.45)	2.50 (0.85–7.42)

*$p<0.005$.
[a] Corrected for age, pre-pregnancy BMI, gestational weight gain and last trimester HBA1C.
[b] Corrected for pre-pregnancy BMI, gestational weight gain, first trimester HBA1C and last trimester HBA1C.
[c] Corrected for age gestational weight gain, first trimester HBA1C and last trimester HBA1C.
[d] Corrected for age, pre-pregnancy BMI, gestational weight gain and first trimester HBA1C.
[e] Corrected for age, pre-pregnancy BMI and gestational weight gain.
[f] Corrected for age, pre-pregnancy BMI, first trimester HBA1C and last trimester HBA1C.

labour, C-section, emergency C-section, LGA, NICU admission, neonatal hypoglycaemia, neonatal respiratory distress, and neonatal jaundice compared to the control group. There was no difference in the incidences of PIH, macrosomia, and stillbirth between the two groups; while the incidence of SGA was reduced in T1DM compared to control group. Multivariate analysis showed that these differences persisted even after correction for known covariates; pre-pregnancy BMI, gestational weight gain and maternal age. The study also showed that T1DM gained more weight and were more likely to exceed the IOM recommendations for GWG compared the control group background population [9]. Excessive GWG was independently associated with the increased risk of LGA in T1DM patients. Third-trimester glycaemic control was independently associated with increased risks of macrosomia, LGA, C-section and neonatal hypoglycaemia. The improvement in HBA1C was associated with lower risks of LGA.

The incidences of LGA and macrosomia (27.9% and 6.8% respectively) in this study are much lower than in other large cohorts. Murphy et al. reported on 397 T1DM patients from a single region in England and showed that the incidence of LGA was 52.9% [10]. An audit from England that included 1563 T1DM patients reported an LGA incidence of 46.1% [11]. A single centre study from Sweden reported on 221 patients with T1DM; the incidence of LGA and macrosomia were 50% and 39% respectively [12]. A study from the United States reported on 358 T1DM patients from the Consortium on Safe Labour (CSL)study and showed that the incidence of LGA was 36.0% [13]. On the other hand, a study from Japan of 369 T1DM patients reported similar rates of LGA and macrosomia to our cohort; 30.2% and 4.6% respectively [14]. There was no difference in the HBA1c at early and late pregnancy between our cohort and all the above referred four cohorts. This difference in the rates of fetal overgrowth could be due to racial disparity as 90% of our cohort were Qatari and non-Qatari Arabs. One study from Saudia Arabia that included 73 patients with T1DM reported a 5.6% similar incidence of macrosomia [15]. Besides, the incidence of pre-term delivery in our cohort was 47.6% compared to 17–39% in the above cohorts, which can partially explain the lower rate of macrosomia but not LGA.

In this study, the incidence of excessive GWG was higher in T1DM patients compared to the control group (36.8% vs 24.0% respectively), and it has the strongest association with LGA. Previous studies have shown that excessive GWG is quite common in T1DM patients and is

often associated with elevated risk of LGA. Kawakita et al. showed that the prevalence of excessive GWG in a cohort of 293 T1DM patients was 53.9% and that excessive GWG was associated with higher risk of macrosomia and neonatal jaundice [16]. Morrens et al. showed that the prevalence of excessive GWG in T1DM patients ranged between 21.3-42.4% over a ten years period [17]. McWhorter et al. showed that 56.1% of the T1DM in the CSL study had excessive GWG and that high BMI and excessive GWG were associated with increased risk for LGA [13]. In a univariate analysis, Ladfors et al. showed that excessive GWG in T1DM patients was associated with a two folds increase in the odds of LGA [12].

Excessive GWG is likely to be multifactorial due increase in insulin doses, recurrent hypoglycaemia, lack of exercise and unpredictability of carbohydrates counting. Patients with T1DM during pregnancy face many hurdles and most of the care is glucose -centric. Intensive insulin treatment is implemented to achieve near-normal glucose levels. The total daily doses of insulin are often increased during pregnancy by 40–50% [18]. In the Diabetes Control and Complications Trial (DCCT), intensive insulin therapy in T1DM patients was associated with more weight gain compared to the usual care [19]. Furthermore, the tight glycaemic targets in T1DM patients during pregnancy increase the frequency of severe and non-severe hypoglycaemia; another independent risk factor for weight gain [20,21]. Besides, the fear of hypoglycaemia is a main barrier for prescribing exercise for patients with T1DM [22]. The continuous changes in insulin sensitivity during pregnancy require frequent adjustments of the insulin-carbohydrate ratio. The changes in carbohydrate ratio are difficult to predict and requires frequent interaction with trained dietitians to maintain euglycaemia, and avoid both hypoglycaemia and ketosis [23]. Thus trying to reduce the carbohydrate intake in T1DM patients during pregnancy is quite tricky.

The relationship between the third trimester HBA1C and poor pregnancy outcomes was shown in other studies [12,17]. This study is the first to show that the reduction in HBA1c between the first and third trimester reduces the risk of LGA and the higher the reduction, the more the protection. This further stresses the importance of glycaemic control during pregnancy in patients with T1DM.

As a retrospective study, ours suffers from limitations such as lack of data on trimester based- GWG rates, severe and non-severe hypoglycaemia episodes and failure to include confounding factors which were not available such as parity, smoking, and socio-economic factors in the analysis. The main strength of our study, however, is the large number of subjects, the detailed pregnancy outcomes and the low levels of missing data. Besides, care was delivered to patients through the same multidisciplinary team of endocrinologists, obstetricians, dietitian, and diabetes nurse specialists.

5. Conclusion

T1DM during pregnancy is associated with poor maternal and neonatal outcomes. Third trimesters HBA1C and excessive GWG are risk factors for fetal overgrowth and other poor pregnancy outcomes, while the improvement in HBA1c reduces the incidence of fetal overgrowth. More studies are needed to study ways to reduce of excessive GWG in T1DM without increasing the risk of severe and non-severe hypoglycaemia.

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Conflicts of interest

The authors declare no conflict of interest regarding the publication of this paper.

Data availability

Data used to support the findings of this study are included within the article.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.08.030.

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