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Pregnancy outcomes in women with onset of type 1 diabetes mellitus less than 18 years of age

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ABSTRACT

Background Pregnancy in women with type 1 diabetes mellitus (T1DM) is associated with an increased risk of congenital malformations, obstetric complications and neonatal morbidity. This study aims to investigate maternal, perinatal and neonatal outcomes of pregnancies in women with onset of T1DM less than 18 years of age.

Methods This retrospective cohort study extracted data regarding prenatal, intrapartum and postnatal outcomes of pregnancies in women with onset of T1DM<18 years identified from the diabetes in pregnancy register at University Maternity Hospital Limerick, treated from July 1, 2007 to July 1, 2017.

Results Seventeen women with onset of T1DM <18 years gave birth to 23 live infants during the period studied. 73.9% of pregnancies were unplanned. Only 21.7% of pregnancies took preconceptual folic acid. 60.9% of infants required treatment for hypoglycemia.

Conclusion The high prevalence of unplanned pregnancy and poor uptake of prepregnancy care must be improved on in order to improve outcomes for this high-risk group.

Significance of this study

What is already known about this subject?

- Pregnancies of women with type 1 diabetes mellitus (T1DM) have increased risk of perinatal morbidity and mortality. Good prenatal and antenatal care can improve pregnancy outcomes.

What are the new findings?

- There is a high prevalence of unplanned pregnancy and poor uptake of prepregnancy care in mothers with juvenile-onset T1DM.

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

- Quality improvement initiatives and future research need to be conducted in order to improve uptake of prepregnancy care. Clinicians treating infants of mothers with juvenile-onset T1DM should have a low threshold for admission to the neonatal unit.

INTRODUCTION

Pregnancy in women with type 1 diabetes mellitus (T1DM) is associated with increased maternal and neonatal morbidity and mortality.[1–6] In order to minimize risks to both mothers and infants, good interdisciplinary care is required between diabetologists, obstetricians, neonatologists, nursing and allied health professional specialists. Women with T1DM in pregnancy in Ireland are cared for according to 'Adult Type 1 Diabetes Mellitus National Clinical Guideline No. 17'[7] which contextualizes the NICE 2015 Diabetes in Pregnancy Guideline[8] for the Irish context. Patients with T1DM in pregnancy should be cared for in a joint diabetes and antenatal clinic and should have contact every 1–2 weeks for assessment of blood glucose control throughout pregnancy.[7 8]

The largest Irish study to date of women with T1DM was a retrospective cohort study of pregnancies delivered in the three tertiary level maternity units in Dublin in 2006.[9] This study of 25 847 pregnancies found 80 (0.31%) women had either T1DM or cystic fibrosis-related diabetes (CFRD). The severity/complexity of their T1DM/CFRD when graded according to White's Classification[10] showed n=58 (72.5%) women were class B or C (<10 years of T1DM or 10–19 years T1DM with no retinopathy or nephropathy); 14 women (17.5%) were class D (>20 years with no retinopathy or nephropathy), 6 women were class R (presence of diabetic retinopathy), 1 woman was class F (diabetic nephropathy) and 1 woman had diabetes mellitus secondary to cystic fibrosis.

The largest prospective study to date on pregnancy outcomes in T1DM is a multicenter study which took place across eight Danish centers from 1993 to 1999.[4] This study of 990 women with 1218 pregnancies showed a relative risk (RR) of 4.1 (95% CI 2.9 to 5.6) for perinatal mortality, RR 4.7 (95% CI 3.2 to 7.0) for stillbirth and RR 1.7 (95% CI 1.3 to

2.2) for congenital malformation, as compared with the general population.[4]

The primary aim of our study was to define maternal, perinatal and neonatal outcomes of pregnancies in women with onset of T1DM <18 years age in Ireland, attending a university affiliated maternity and neonatal service. A secondary aim was to describe modifiable risk factors for adverse outcomes which might be used as a basis for quality improvement locally.

METHODS

This retrospective cohort study was performed at University Maternity Hospital Limerick, which delivers approximately 5000 pregnancies per year and has specialist diabetes in pregnancy services for the wider Midwest region (population approximately 380 000). Women with T1DM delivering between July 1, 2007 and July 1, 2017 were identified from the diabetes in pregnancy register. Inclusion criteria included age less than 18 years at diagnosis of T1DM which was confirmed via chart review. Exclusion criteria included stillbirth (defined as loss of pregnancy >24 weeks gestation), miscarriage (defined as loss of pregnancy ≤23 weeks gestation), termination of pregnancy, loss to follow-up or transfer of care to another center prior to delivery. All relevant data protection laws were followed. The data were analyzed with descriptive statistics using SPSS V.25.

RESULTS

Demographics

Demographics and baseline characteristics are described in table 1. One case was excluded due to fatal fetal abnormality. Six cases were excluded due to miscarriage.

Antenatal characteristics

Seventeen of 23 pregnancies (73.9%) were unplanned and 4/23 (8.7%) were smoking at the time of booking. Two of 17 women (11.7%) had a past history of illicit drug use. There was no documented evidence of active drug use during pregnancy. At the time of conception folate was being taken in only 5 of 23 pregnancies (21.7%).

Table 1 Demographics and baseline characteristics

Number of women	17
Median age at diagnosis	11 years (IQR 10–12)
Primiparous pregnancies	9 (39.1%)
Number of pregnancies	23
Multiple births	0
Median gestation at delivery	37.6 weeks (IQR 36–38.6)
Median birth weight	3.67 kg (IQR 3.1–3.8)
Gender	14 male (60.9%)

IQR, interquartile range.

Table 2 Maternal non-diabetes-related medical conditions

Non-diabetes medical problems	Diabetes-related medical problems
Asthma (n=2)	Diabetic retinopathy (n=5)
Depression (n=2)	Recurrent urinary tract infections (n=2)
Hashimoto's thyroiditis (n=1)	Diabetic nephropathy (n=2)
Carcinoid tumor of the appendix (n=1)	Hypertension (n=2)
Hypercholesterolemia (n=1)	Poor hypoglycemia awareness (n=2)
Gastroesophageal reflux (n=1)	Diabetic neuropathy (n=1)
Bicuspid aortic valve (n=1)	Cataracts (n=1)
Irritable bowel syndrome (n=1)	
Benign kidney cyst (n=1)	
History of elevated prolactin of undefined etiology (n=1)	

Maternal prepregnancy morbidity

Fifteen of 17 women (88.2%) had medical diagnoses other than T1DM, while 8/17 women (47.1%) had diabetes-related complications (table 2). When each pregnancy is considered according to White's Classification of Diabetes in Pregnancy[10] (table 3), there were 11/23 (47.8%) class C pregnancies, 6/23 (26.1%) class D pregnancies, 3/23 (13%) class RF pregnancies, 2/23 (8.7%) class R pregnancies and 1/23 (4.3%) class F pregnancy. Of the five women who had subsequent births during the 10-year study period one woman progressed from stage B to stage C and one woman progressed from

Table 3 Classification of pregnancies according to White's Classification of Diabetes in Pregnancy[10]

	Pregnancies (n=23)
Class A1: Gestational diabetes; diet controlled Class A2: Gestational diabetes; medication controlled	
Class B: Onset at age 20 years or older or with duration of less than 10 years	
Class C: Onset at age 10–19 years or duration of 10–19 years	11 (47.8%)
Class D: Onset before age 10 years or duration greater than 20 years	6 (26.1%)
Class E: Overt diabetes mellitus with calcified pelvic vessels	
Class F: Diabetic nephropathy	1 (4.3%)
Class R: Proliferative retinopathy	2 (8.7%)
Class RF: Retinopathy and nephropathy	3 (13%)
Class H: Ischemic heart disease	
Class T: Prior kidney transplant	

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stage F to stage RF. When each of these 17 women are considered according to their most severe classification, 8/17 women (47.1%) were class C, 4/17 (23.5%) class D, 3/17 (17.6%) women class RF and 2/17 (11.8%) women class R.

HbA1C values prepregnancy

The prepregnancy HbA1c (Haemoglobin A1c) value was taken as the last recorded laboratory value prior to conception. Only 4/23 pregnancies (17.4%) had HbA1c<48 mmol/mol prior to conception. Two of 23 pregnancies (8.7%) had HbA1c>86 mmol/mol prior to conception.

Antenatal obstetric screening and complications

Anomaly scans were performed in 21 of 23 pregnancies (91.3%). Twelve of 23 pregnancies (52.2%) had antenatal complications; 4/23 (17.4%) had polyhydramnios, 4/23 (17.4%) had intrauterine growth restriction, 2/23 (8.7%) had pre-eclampsia, 1/23 (4.3%) had a hypoglycemic seizure and 1/23 (4.3%) had pregnancy-induced hypertension.

Delivery and complications

Nineteen of 23 pregnancies (82.6%) were delivered by lower segment cesarean section (LSCS). Of these, 15/23 (65.2%) were born via elective LSCS and 4/23 (17.4%) via emergency LSCS. One pregnancy (4.3%) was delivered via instrumental delivery, while the remaining 3/23 (13%) pregnancies were delivered via spontaneous vaginal delivery. Of the total 4/23 neonates (17%) born via vaginal delivery, there were no cases of shoulder dystocia. Four of 23 neonates (17.4%) required free-flow O_2 at birth and 2/23 neonates (8.7%) required bag-mask ventilation. No babies required intubation or chest compressions in the delivery suite. The median APGAR[11] at 1 min was 9 (range 5–9) and at 5 min was 10 (range 4–10). Vitamin K was given to all neonates. There were no neonatal deaths during the study period.

Postnatal advice and feeding patterns

Twenty of 23 neonates (87%) were bottle-fed. Twenty of 23 pregnancies (87%) had preconception advice and contraception discussed at discharge.

Neonatal problems

Twenty-two of 23 neonates (95.7%) were admitted to the neonatal unit. Standard care during the period studied for neonates born to mothers with T1DM included; feeding within the first hour, 3 hourly feeds and glucose measurement prior to the second feed until measurements were >3 mmol/L for two consecutive feeds. Specific diagnoses of admitted neonates are outlined in box 1[12] . Thirteen of 23 neonates (56.5%) were admitted for treatment of hypoglycemia. One other neonate (4.3%) was admitted for observation following treatment of hypoglycemia on the postnatal ward. Of the 14 neonates treated for hypoglycemia, 10/14 (71.4%) required an intravenous dextrose bolus. The median point-of-care blood glucose on admission was 1.9 mmol/L (range 0.8–2.8). Of the 15 neonates treated with intravenous fluids, 1 required 15% dextrose in intravenous fluids to maintain euglycemia, all other neonates required only 10% dextrose. There was no documented use of oral glucose gel for management of hypoglycemia. Of the 10 neonates treated for jaundice, 100% received phototherapy; 2/10 (20%) were direct Coombs test positive, and none received intravenous immunoglobulin or exchange transfusion. Two of 23 neonates (8.7%) were macrosomic (birth weight >4.5 kg), however 8/23 neonates (34.8%) were large for gestational age, >90th centile. One neonate did not have any documented indication for admission and was a 'well baby admitted for monitoring' who did not develop any medical complications.

Box 1 Recorded indication for admission to the neonatal unit

Hypoglycemia (n=14)
Jaundice requiring phototherapy (n=10)
Transient tachypnea of the newborn/respiratory distress syndrome (n=10)
Prematurity (n=7)
Macrosomia (n=4)
Low birth weight (n=3)
Poor feeding (n=3)
Polycythemia (n=2)
Trisomy 21 (n=1)
Hyponatremia (n=1)

DISCUSSION

In 1989, the St. Vincent declaration stated that the outcomes of diabetic pregnancies should approximate those of non-diabetic pregnancies within 5 years.[12] Our study demonstrates that this target has not been met. Although a potentially modifiable factor, suboptimal glycemic control is not wholly responsible for adverse outcomes of infants born to mothers with T1DM.[13] The Diabetes Control and Complications Trial has shown that it is possible to reduce morbidity owing to T1DM before, during and after pregnancy, but not to eliminate it.[6 7]

Our study shows a substantial comorbidity burden in this vulnerable population. Prepregnancy care is proven to improve outcomes.[14 15] Most women in this study did not attend for prepregnancy care, presumably as most pregnancies (73.9%) were unplanned. In contrast a 2017 cohort study by Wotherspoon *et al* reported a significantly lower rate of unplanned pregnancy at 39% in a population of 747 women with T1DM.[16] Characteristics associated with unplanned pregnancy included in this study were younger age at conception (p<0.001), being a current smoker (p<0.001), lower social class (p<0.001) and higher HbA1c value prior

to and throughout pregnancy. Infants of these women were also more likely to be small for gestational age (<5th centile, p=0.004), to be admitted to the neonatal care unit (p=0.001) and have a longer stay in hospital (p=0.01).[16]

In our study, 21.7% of women were taking supplemental folic acid at the time of booking. This is lower than the rate of 41.8% in the British National Pregnancy in Diabetes Audit[2] (NPID). The current recommendation by the National Institute for Health and Care Excellence (NICE) for folic acid supplementation is 5 mg/day until 12 weeks gestation.[8]

The 2015 NICE guidelines also advise women with diabetes who are planning to become pregnant to maintain HbA1c<48 mmol/mol as this is associated with a reduction in congenital anomalies to close to background population rates.[8] Fewer than one in five pregnancies in our study population met this target. The 2015 NICE guidelines also strongly advise women with diabetes whose HbA1c is above 86 mmol/mol not to get pregnant because of the associated risks. Of the case population on our study, 8.7% (n=2/23) met this definition. In contrast the NPID found that 14.9% of pregnancies of women with T1DM had HbA1c<48 mmol/L and that 12.5% had HBA1c>86 mmol/L.[2]

While women with T1DM are known to have a significantly higher LSCS rate than the general population, the proportion in this study (82.6%) is higher than other similar studies, which reported rates varying from 46% to 64.7%.[4–6 13 17] The rate of premature delivery (30.4%) identified in this cohort is broadly similar to other studies in the literature which vary from 21% to 43.3%.[4–6 13 17 18] Fortunately there were no perinatal deaths in this study. The reported perinatal mortality rate for women with T1DM in the literature varies from 1.8% to 4.3%.[4–6 13 17 19] Of infants of mothers with T1DM in this study 95.7% were admitted to the neonatal unit, however not all infants admitted had documented pathology. The prevalence of large for gestational age in this study was 34.8%, lower than previous studies which reported rates varying from 45.1% to 59%.[17 20–23] The incidence of neonatal hypoglycemia noted by this study (60.9%) is in keeping with the incidence of hypoglycemia noted in the literature, 25.3% to 63%.[23 24]

The high prevalence of unplanned pregnancy with a poor uptake of structured prepregnancy care must be improved on in order to improve outcomes for this high-risk group. In order to address this, future quality improvement measures will need to be implemented to reinforce the issue further in pediatric clinics, at transition and on an ongoing basis into adult care. Future audits will be required to assess the impact of these measures.

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