The relationship between falling insulin requirements and serial ultrasound measurements in women with preexisting diabetes: a prospective cohort study

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ABSTRACT

Introduction: A large fall in insulin requirements (FIR) in women with diabetes is associated with adverse clinical outcomes but previous studies have not examined its relation with serial ultrasound parameters.

Objective: To determine whether FIR is associated with alteration in umbilical artery Doppler parameters and fetal growth restriction (FGR) in women with preexisting diabetes.

Methods: Serial obstetric Doppler ultrasounds were conducted 2 weekly from 28 weeks gestation in women with Type 1 and Type 2 diabetes who were being treated with insulin. Estimated fetal weight (EFW), head circumference:abdominal circumference (HC:AC) ratio and umbilical artery doppler parameters (SD ratio) and pulsatility index (PI) were measured. Information on insulin dose was collected prospectively throughout pregnancy and women with FIR ≥ 15% were considered cases. Linear mixed effect models were used to assess the association between FIR and ultrasound parameters.

Results: One hundred and forty two women were included in the study (type 1 diabetes n = 41, type 2 diabetes n = 101). Thirty women demonstrated FIR ≥ 15%. There was no significant difference in the change of S/D ratio or PI over the third trimester in cases with FIR ≥ 15%, compared to the rest of the cohort, before or after adjusting for type of diabetes. Likewise there was no difference in EFW and HC:AC ratio with advancing gestation before or after adjusting for variables known to influence fetal growth. FGR rates (3.3 vs 8% p = 0.298) and high S/D ratio > 95% (13.3 vs 8%, p = 0.296) were similar between the two groups.

Conclusions: FIR ≥ 15% was not associated with changes in placental flow or FGR however larger studies are needed to evaluate this further.

Introduction

The International Diabetes Federation estimated 4.16 million live births in women with preexisting diabetes in 2021, accounting for 20% of hyperglycemia in pregnancy worldwide [1]. Women entering pregnancy with preexisting Type 1 or Type 2 diabetes experience worse obstetric outcomes compared to the general population. Women typically have an increase in insulin requirements throughout second and third trimester due to the insulin-antagonistic action of placental hormones, however up to 25% have a significant fall in insulin requirements (FIR) [2,3]. FIR has long been considered a marker of fetoplacental compromise, prompting admission to hospital for increased monitoring and early delivery in some cases. We have previously shown that FIR in the third trimester is an important clinical marker associated with pre-eclampsia and altered expression of antiangiogenic factors in women with Type 1 or Type 2 diabetes [2]. However, antiangiogenic markers such as PlGF and sFlt1 are not yet in widespread clinical use and another modality for investigation of placental function in women with diabetes is needed. Ultrasound measures associated with placental dysfunction,
including umbilical artery Doppler flow and impaired intrauterine fetal growth have been well described in women who develop preeclampsia and fetal growth restriction (FGR) however few studies have looked at their significance in women with preexisting diabetes [4,5]. Considering this, we investigated the relationship between FIR and serial ultrasound parameters of placental function in women with diabetes, as part of the Falling Insulin Requirements Study (FIRST). We hypothesized that women with FIR would have increased umbilical artery Doppler resistance and reduced growth trajectories on serial ultrasound compared to those without FIR.

**Materials and methods**

The FIRST study is a prospective multicentre cohort study conducted between June 2013 and May 2016 at three tertiary referral hospitals (in Western Sydney, Australia), with dedicated diabetes in pregnancy services [2,6]. The study was approved by the Western Sydney Local Health District Ethics Committee (HREC2013/2/4.5(3649) and all participants provided written informed consent. Recruitment occurred prior to 20 weeks gestation and included women over the age of 16 with singleton pregnancies and a diagnosis of preexisting Type 1 or Type 2 diabetes, or a new diagnosis of overt diabetes on a 75g oral glucose tolerance test (fasting plasma glucose/21 mmol/L), 2 h postprandial 7 mmol/L (126 mg/dL) and/or HbA1c ≥ 6.5% (48 mmol/mol), as per the 2013 World Health Organization criteria [7]. For the purpose of analysis women with overt diabetes in pregnancy were reclassified as type 1 diabetes if positive for GAD anti-bodies or type 2 diabetes if negative [8]. Pregnancies that did not progress beyond 20 weeks gestation, or patients not requiring insulin or non-compliant with regular review for insulin dose titration were excluded. Baseline demographics and history were obtained through a structured questionnaire, data including dose of insulin was collected prospectively. Blood glucose targets of <5.5 mmol (100 mg/dL) fasting and <7 mmol (126 mg/dL) 2 h postprandial were used at all sites. FIR was calculated as the percentage fall from the highest total insulin dose (HTID) in the second half of pregnancy, to the lowest total insulin dose (LTID) following the peak; 

\[
\text{FIR} = \left( \frac{\text{HTID} - \text{LTID}}{\text{HTID}} \right) \times 100\%
\]

**Ultrasound**

Obstetric Doppler ultrasound studies were conducted fortnightly from 28 weeks gestation until 36 weeks, by experienced obstetricians or sonographers on a GE Voluson E8 ultrasound machine (GE Medical Systems, Piscataway, NJ) at three pre-specified study sites. Three dimensional curvilinear probes with a band width of 5–10 MHz were used throughout. Women were included in this analysis if they had two or more ultrasounds performed. Parameters associated with placental dysfunction in the literature, including umbilical artery doppler resistance and FGR were measured as outlined below. The ultrasound parameters presented here were prespecified secondary outcomes of the FIRST study.

**Fetal biometry**

Fetal Biometry measurements were obtained according to Hadlock’s criteria for fetal head circumference (HC), biparietal diameter (BPD), abdominal circumference (AC) and femur length (FL). Estimated fetal weight (EFW) was determined via Hadlock’s formula and were converted to percentiles via Hadlock’s in utero weight model [9,10]. HC:AC ratio was calculated, as previous studies have shown that elevation in this ratio is a more sensitive marker of asymmetric FGR due to placental insufficiency compared to either parameter alone [11]. The outcome of interest was declining fetal growth rate and HC:AC ratio during the third trimester. In-utero fetal weight of ≤ 5th percentile was attributed to FGR and recorded as an abnormal outcome if present on at least one ultrasound during the study period.

**Umbilical artery doppler resistance**

The umbilical artery peak systolic (S) and end diastolic (D) flow velocities were obtained by recording the lowest of three measurements from a free floating loop of the umbilical cord in the absence of fetal breathing or movement, and the S/D ratio, pulsatility index (PI) and the resistance index (RI) were derived. Our main outcome of interest was the rate of change (per week) in umbilical artery Doppler flow trajectories in third trimester. Furthermore a value ≥95th percentile of the reference range (using data by Kofinas et al. for S/D ratio and Acharya et al. for PI derived from low risk, non-diabetic singleton pregnancies [12,13]) in at least one of the ultrasounds conducted during the study period was considered an abnormal outcome.

**Statistical analysis**

For the purpose of analysis women with FIR were dichotomized into those with ≥ 15% FIR (defined as cases) and those without (defined as controls). A fall
of 15% was chosen as this has previously been described as clinically significant in the literature [3]. Many of the continuous variables were not normally distributed; therefore, the median and lower to upper quartile M(IQR) were used to summarize these distributions, whereas categorical variables were summarized using frequencies and percentages n (%). The Mann-Whitney U and Kruskal-Wallis tests were used to determine differences in the distribution of continuous variables, and Pearson X² or Fisher exact tests were used to test for association between categorical variables. Linear mixed effects models (LMEs) were used to investigate the joint effects of FIR status (Case versus Controls) and time (after 28 weeks gestation) for each ultrasound parameter and to estimate the rate of change in these parameters per week. All ultrasound models were adjusted for type of diabetes. Additionally, EFW and HC:AC ratio models were adjusted for third trimester HbA1c, pre-pregnancy BMI, sex of the fetus and smoking status.

The association between FIR ≥ 15% and FGR (EFW ≤ 5th percentile) and umbilical artery S/D ratio and PI ≥ 95th percentile were examined categorically with Pearson X² or Fisher exact tests. The statistical software packages SPSS Version 23 and S-PLUS 8.2 were used to analyze the data. Two-tailed tests with a significance level of 5% were used throughout.

Results

One hundred and forty two women had two or more ultrasounds available for analysis at the pre-specified study centers (type 1 diabetes n = 41, type 2 diabetes n = 101). Thirty women experienced FIR ≥15% (cases). The remaining 112 women were considered to be the control group. On average cases had a 25.4% fall in insulin requirements with a similar fall in the basal and bolus requirements (29.3% vs 25.8%). While all women in the case group had episodes of mild hypoglycemia < 4.0 mmol/L leading to reduction in insulin requirements no one in the study had severe hypoglycemia requiring external assistance. Table 1 summarizes the baseline characteristics of cases and controls. A greater proportion of cases had type 1 diabetes compared to type 2 or newly diagnosed overt diabetes, p = 0.011. While there was no difference in pre-pregnancy BMI between the groups a greater proportion were overweight or obese in the control group. However, this was largely driven by the higher number of women with Type 2 diabetes in this group and indeed after correction for type of diabetes, there was no significant difference in BMI category or other baseline characteristics. The incidence of preeclampsia was significantly higher in cases compared to controls (43.3% vs. 10.7%, p < 0.001). Data on other maternal and neonatal outcomes have been published previously [2].

Falling insulin requirements and placental blood flow

Figure 1(A,B) and supplementary Table 1 summarize the differences in umbilical artery S/D ratio and PI at 28 weeks and the change in these parameters per week until delivery. As expected the umbilical artery S/D ratio and PI decreased with advancing gestation, however there was no significant difference in the rate of change of either placental flow parameter over the third trimester between cases and controls before and after adjusting for type of diabetes. Of note, there was a very wide inter-subject variation in umbilical artery flow parameters. Overall the incidence of abnormal S/D ratio and PI (≥95th percentile) in the entire cohort (all women) was 13 (9.2%) and 22 (15.5%) respectively. While there was no significant difference between groups there was a trend for more women with abnormal parameters in the FIR group (Table 2).

Falling insulin requirements and fetal growth

There was no difference in EFW and HC:AC ratio with advancing gestation between women with and without FIR ≥15% before or after adjusting for variables known to influence fetal growth. The results are summarized in Figure 1(C,D) and supplementary Table 1. Categorical analysis was also conducted after dichotomizing the data into FGR ≤5th percentile and normal. Only 10 women (7%) had evidence of FGR on antenatal ultrasound and there was no difference in incidence of FGR between women with and without FIR ≥15% (Table 2).

Discussion

In contrast to our hypothesis, umbilical artery placental flow and incidence of FGR were not increased in women with FIR ≥15%. The clinical significance of FIR remains unclear and while we have previously reported an association between clinical and biochemical markers of placental dysfunction and FIR [2,3] other retrospective studies have reported conflicting results and most obstetric bodies still recommend that delivery timing be guided by antenatal testing [14,15]. To our knowledge this is the first study to prospectively examine the association between FIR and
ultrasound parameters which measure placental dysfunction.

Doppler ultrasound allows for the study of blood flow velocities through the feto-placental unit determined by the pressure gradient within the vessel and the surrounding vascular bed. Consequently, a placenta with impaired blood flow will result in high vascular resistance detected by high S/D ratio and PI [16]. Numerous studies have validated the role of high S/D ratio (≥95th percentile) in monitoring placental insufficiency predominantly in the setting of FGR and pre-eclampsia [4,5,17]. Furthermore, in this high-risk group of women, randomized control trials and a systematic review have confirmed that there is a role for the routine use of Doppler ultrasound in improving perinatal outcomes and mortality [16,18]. Of note however, most adverse events due to placental insufficiency in late pregnancy occur in the presence of normal umbilical artery flow [19]. Further, the role of umbilical artery Doppler amongst women with preexisting diabetes in the absence of FGR and pre-eclampsia is unclear, with studies showing conflicting results [20–22]. There are a number of possibilities for these discordant results.

First, normal reference values are only available for the low-risk population without diabetes [12,13]. These reference curves indicate significant inter subject variability and thus only very high Doppler parameters are considered clinically relevant. It is unclear whether the calculated percentiles derived from low-risk subjects can be extrapolated to women with diabetes, although they are widely used in clinical practice. Development of umbilical artery Doppler charts specific to women with diabetes would be ideal and a potential area for future research.

Furthermore, studies in women with diabetes, particularly those with vasculopathy have higher umbilical artery S/D ratios compared to the non-diabetic

| Baseline characteristic | (Case subjects n = 30) | (Control subjects n = 112) | p Value | p Value § |
|-------------------------|------------------------|---------------------------|---------|---------|
| Age (years) | 31.5 (28.0–35.0) | 33 (28.5–36.0) | .132 | .588 |
| Pre pregnancy BMI (kg/m²) | 27.7 (25.1–32.9) | 30.2 (26.2–38.1) | .709 | .704 |
| Pre pregnancy BMI Category* | | | | |
| Underweight | 3 (10.3) | 0 (0) | | |
| Normal | 4 (13.8) | 13 (11.6) | | |
| Overweight | 6 (20.7) | 34 (30.4) | | |
| Obese | 16 (55.2) | 65 (58) | | |
| Ethnicity | | | | |
| Caucasian | 16 (53.3) | 38 (33.9) | .066 | .132 |
| Asian/South Asian | 11 (36.7) | 43 (38.4) | | |
| Other | 3 (10) | 31 (27.7) | | |
| Diabetes | | | | |
| Type 1 | 15 (50) | 25 (22.3) | | |
| Type 2 | 12 (40) | 70 (62.5) | | |
| Overt | 3 (10) | 17 (15.2) | | |
| Duration of Diabetes (years) | 5 (1–15) | 4 (1–8) | .704 | .774 |
| Preconception HbA1c (%) | 7.30 (6.7–8.9) | 7.40 (6.1–9.8) | .956 | .941‡ |
| (mmol/mol) | 57 (50–79) | 56 (43–84) | | |
| Preconception Treatment | | | | |
| No treatment | 2 (6.2) | 26 (23.2) | | |
| Diet Control | 1 (3.3) | 9 (8.2) | | |
| Insulin (MDI) | 12 (40.0) | 27 (24.1) | | |
| Insulin (CSII) | 5 (16.7) | 8 (7.1) | | |
| Other Agents | 10 (33.3) | 42 (37.5) | | |
| Microvascular Complications | 5 (18.5) | 17 (17.9) | 1.0 | .583‡ |
| Retinopathy | 3 (11.1) | 9 (9.5) | .727 | .464‡ |
| Nephropathy | 2 (7.4) | 11 (11.6) | .731 | .374‡ |
| Neuropathy | 3 (11.1) | 2 (2.1) | .071 | .116‡ |
| Nulliparity | 13 (43.3) | 33 (29.5) | .188 | .287 |
| Un-planned pregnancy | 17 (56.7) | 67 (59.8) | .835 | .471 |
| Chronic Hypertension | 5 (16.7) | 12 (10.7) | .357 | .346 |
| Hypertensive disorder in Previous Pregnancy† | 5 (29.4) | 20 (25.3) | .764 | .575 |
| Smoking | | | | |
| Current Smoker | 3 (10.0) | 10 (8.9) | 1.0 | .932 |

Data represents median [IQR] or n (%) as applicable.

MDI: multiple daily injections; CSII: Continuous Subcutaneous Insulin Infusion.

*BMI Categories are specific for ethnicity as per WHO criteria (13).

*p Value after correcting for type of diabetes with logistic regression. For this analysis women with overt diabetes were reclassified as type 1 diabetes if positive for GAD antibodies or type 2 diabetes if negative for GAD antibodies and/or the participant had clinical factors consistent with type 2 diabetes.

†Women with overt diabetes excluded from this regression analysis as the variable relied on the diagnosis of diabetes to be known pre-pregnancy (n = 122).

‡Only women with parity ≥ 1 were included in this analysis (n = 96).
population [23]. This is consistent with our findings of 10–15% of the cohort having abnormal Doppler parameters, while only 5% of the normal population would be expected to be in this part of the reference curve. Due to the wide inter-subject variation, small differences in Doppler parameters amongst women with diabetes are unlikely to be detected, particularly as our study was not powered for this secondary outcome. Our study design attempted to overcome this by analyzing the rate of change in Doppler parameters, for each woman during the third trimester and the incidence of umbilical artery Doppler /C2195th percentile. Indeed, there was a trend for more women having /C2195th percentile S/D ratio in the FIR /C2115% group, with a more modest rate of decline during third trimester, however, larger studies are needed to evaluate whether this is a true signal of impaired placental flow.

The sensitivity of Doppler ultrasound for adverse outcomes outside the setting of pre-eclampsia and FGR is unclear. Wong et al. examined 104 pregnancies retrospectively in an Australian cohort of preexisting diabetes and found that an elevated umbilical artery PI (>95th percentile) had poor sensitivity (35%) and was only useful in predicting adverse neonatal outcomes if conducted within 2 weeks of delivery (positive predictive value 80%). However, those with preexisting microvascular complications or pre-eclampsia were significantly more likely to have an abnormal Doppler study suggesting greater predictive value in

Figure 1. Estimated umbilical artery S/D Ratio (A) and PI (B) EFW (C) and HC/AC Ratio (D) from 28 weeks onwards in women with and without falling insulin requirements ≥15%. Error bars represent standard error at 28 weeks. FIR: falling insulin requirements; S/D: systolic/diastolic; PI: Pulsatility Index. p Value for comparison of the rate of change in third trimester using linear mixed effects models. Figure A and B adjusted for type of diabetes, C and D adjusted for type of diabetes, pre-pregnancy BMI, third trimester HbA1c, smoking status and fetus sex.

Table 2. Incidence of fetal growth restriction and abnormal umbilical artery Dopplers in women with and without falling insulin requirements ≥15%.

| Ultrasound Parameter | (Cases, n = 30) | Controls, n = 112 | p Value | p Value § |
|----------------------|----------------|------------------|---------|-----------|
| IUGR (EFW < 5th %)   | 1 (3.3)        | 9 (8)            | .689    | .298      |
| Umbilical artery     |                |                  |         |           |
| S/D Ratio ≥ 95th %   | 4 (13.3)       | 9 (8)            | .474    | .296      |
| PI ≥ 95th %          | 6 (20)         | 16 (14.3)        | .411    | .403      |

Data presented as n (%).
FIR: falling insulin requirements; S/D: systolic/diastolic; PI: pulsatility index.
§p Value after correcting for type of diabetes with logistic regression.
this subgroup [21]. The relationship between maternal vasculopathy and abnormal umbilical artery Doppler indices has been supported by a number of other studies and probably reflects worse vascular development of the placenta [23–26]. In our cohort, only 15% of women had preexisting microvascular complications and 18% had pre-eclampsia which could explain why we found no correlation between abnormal ultrasound parameters and FIR ≥ 15%. As such, FIR may represent an earlier, more subtle clinical marker of placental dysfunction which is not detected by ultrasound measurement until placental disease has progressed. Larger studies are needed to assess this further.

Finally, we did not detect any significant difference in fetal growth trajectories, HCA:AC ratio or presence of FGR (EFW ≤ 5th percentile) between women with and without FIR ≥ 15%. It is well documented that FGR is a manifestation of chronic placental insufficiency and in turn is a major determinant of stillbirth, perinatal mortality and neonatal hypoxic brain damage [27,28]. However, the diagnosis of FGR is challenging as there is no universal definition used by clinicians or researchers alike. Small for gestational age < 10th percentile is commonly used as a proxy for FGR but this will include a proportion of babies who are constitutionally small but healthy, while high risk FGR < 3rd percentile will miss cases. Therefore EFW ≤ 5th percentile was predefined as an abnormal outcome attributed to placental dysfunction. Few studies have evaluated FGR amongst women with diabetes in whom the most common growth abnormality is LGA due to maternal hyperglycemia. Studies on fetal macrosomia have shown that preconception and first-trimester glucose control has the greatest effect on fetal size [29,30] and subsequent glucose control may not be sufficient to reverse the process of macrosomia [31,32]. Although we did adjust for glycaemic control in third trimester, earlier establishment of fetal hyperinsulinemia may have contributed to excess fetal growth. Thus, opposing growth stimulating and growth restricting forces, may negate subtle or acute reductions in growth trajectories associated with FIR.

Strengths of our study included the use of prospective longitudinal data and logistic regression models to correct for factors that could have confounded results of fetal growth. However, this was a prespecified secondary outcome of the FIRST study, which was not powered to detect subtle differences in Doppler parameters or fetal size due to wide inter-subject variation and inclusion of only a small proportion of women with known microvascular complications at baseline. As a result only a small number of women had the outcome of interest, FGR and elevated Dopplers. Future studies, should focus on this higher risk group of women. We also acknowledge that FIR are a surrogate marker of hypoglycemia and it is possible that hypoglycemia itself could contribute to placental dysfunction. However, it is unlikely that transient mild hypoglycemia < 4.0 which can occur in normal pregnancy would cause the degree of placental insult required to cause FGR or increase in doppler resistance.

Conclusion
In conclusion, we did not find any ultrasound evidence of changes in placental flow or fetal growth restriction amongst women with FIR ≥ 15%. However, the poor sensitivity of Doppler flow parameters for adverse outcomes and absence of normal reference ranges for the diabetic population may miss subtle abnormalities. In view of growth promoting factors present amongst women with preexisting diabetes, in utero growth restriction is likely to manifest only in severe cases of placental dysfunction. Further studies are needed to confirm the utility of FIR as an early clinical marker of placental dysfunction.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
The author(s) reported there is no funding associated with the work featured in this article.

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