First-trimester glycaemic markers as predictors of gestational diabetes and its associated adverse outcomes: a prospective cohort study

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RESEARCH ARTICLE

First-trimester glycaemic markers as predictors of gestational diabetes and its associated adverse outcomes: A prospective cohort study

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Abstract

Objective: Gestational diabetes mellitus (GDM) is associated with excessive fetal growth in later gestation.

Recent data suggest accelerated growth may begin before 28 weeks' gestation when GDM is typically diagnosed. The identification of pregnancies at risk of early fetal growth would enable early intervention. We assessed the use of early pregnancy HbA1c in predicting excessive fetal growth.

Research Design and Methods: Women were recruited at antenatal booking from a major maternity unit in the UK. HbA1c was measured at <14 weeks gestation in 1243 women at risk of GDM as defined by UK NICE risk factors of whom 1115 underwent OGTT. Women with previous GDM were excluded. Comprehensive fetal ultrasound was performed at 28 weeks' gestation alongside 75 g OGTT in 976 of these women. GDM was defined using WHO criteria. Pregnancy outcomes were extracted from the regional maternity care database.

Results: Two hundred and thirty-six women screened positive for GDM. At diagnosis, GDM pregnancies demonstrated higher adjusted fetal weight percentile than non-GDM pregnancies: (51.8 vs. 46.3, $p = 0.008$). This was driven by increases in the fetal abdominal circumference percentile in GDM compared with non-GDM pregnancies (55.3 vs. 46.2, $p = <0.001$). Early pregnancy HbA1c was higher in the GDM versus non-GDM group: (35.7 mmol/mol vs. 32.9 mmol/mol $p = <0.01$). A threshold for predicting excessive fetal growth was not identified in this cohort.

Conclusions: Accelerated fetal growth is evident prior to the diagnosis of GDM. There remains a need for suitable methods of early identification of pregnancies at high risk for early accelerated fetal growth due to GDM. First-trimester HbA1c was not useful in identifying these pregnancies.

KEYWORDS
fetal growth, gestational diabetes mellitus, HbA1c, large for gestational age, macrosomia, preeclampsia, pregnancy-induced hypertension

1 | INTRODUCTION

Gestational diabetes (GDM) is associated with excessive fetal growth (estimated fetal weight > 90th centile) in later gestation. It is typically diagnosed at 26–28 weeks' gestation by oral glucose tolerance testing (OGTT). Subsequent monitoring and treatment aim to limit excessive fetal growth and its associated sequelae. Recent data suggest that this acceleration in fetal growth may begin in advance of the 26–28 week window typically employed for GDM testing.[1] The identification of such pregnancies would potentially allow for more timely observation and treatment in order to prevent excessive fetal growth prior to its emergence. To date, no useful method for identifying these pregnancies has emerged. The use of first-trimester HbA1c has been demonstrated to identify high-risk cohorts for GDM development and other adverse pregnancy outcomes in a number of cohorts, most often employing thresholds from 39 to 41 mmol/mol.[2–7]

Following the onset of the COVID-19 pandemic, many centres were unable to offer OGTT testing given the attendant risks of COVID-19 transmission. In response, several authorities advocated the use of HbA1c as screening tool to identify GDM pregnancies in the first and/or second trimesters.[8–10]

We assessed the utility of first-trimester HbA1c in predicting excessive fetal growth in later pregnancy among women at risk of GDM. We employed a threshold of 39 mmol/mol (5.7%) given prior work highlighting its association with adverse outcomes of pregnancy and its adoption by the American Diabetes Association as the threshold for prediabetes.[2–7] Second, we assessed the performance of first-trimester HbA1c as a predictor of later GDM and of adverse pregnancy outcomes among women at risk of GDM.

2 | RESEARCH DESIGN AND METHODS

SHAPE was a prospective observational study conducted at a tertiary obstetric centre, the Royal Jubilee Maternity Hospital, in Belfast, UK, between October 2017 and March 2020. The study was given ethical approval by the Yorkshire and Humber Research Ethics Committee (ref 17/YH/0207) and sponsored by the Belfast Health & Social Care Trust (ref 17024UGSW). The study protocol was registered at clinicaltrials.gov (NCT04858386). Women were assessed for eligibility by research staff at their first antenatal booking visit usually around 12 weeks' gestation. Those aged over 18 years with ultrasound-confirmed gestation <14 weeks were invited to participate if they met one or more of the UK National Institute for

Novelty Statement

What is already known?:

- Recent research suggests excessive growth associated with GDM may begin prior to 28 weeks' gestation, when GDM is typically tested for

What this study has found?:

- Pregnancies affected by GDM are already subject to accelerated fetal growth in comparison to non-GDM pregnancies by way of higher estimated fetal weight and fetal abdominal circumference
- Neither first-trimester HbA1c nor plasma glucose was useful predictors of these outcomes

**What are the implications of this study?:**

- Highlights the emergence of excessive growth prior to detection of GDM
- Reinforces need for suitable methods of identifying such pregnancies in earlier gestation

Health and Care Excellence (NICE) defined risk factors for GDM and therefore merited OGTT at 27–28 weeks' gestation namely; family history of diabetes mellitus in a first-degree relative, previous incidence of a macrosomic infant (birth weight ≥4.5 kg), body mass index ≥30 kg/m^2 or ethnicity with a high prevalence of diabetes mellitus.[11] Women with previous GDM were excluded as, at the time of the study, they were instructed to commence capillary glucose monitoring at booking and it was considered that potential treatment might confound maternal/fetal outcomes. Other exclusion criteria included pre-exiting diabetes mellitus, multiple pregnancy, HbA1c returned ≥48 mmol/mol (6.5%), anaemia at (total Hb <110 g/L), corticosteroid use or metformin use within the preceding 12 weeks.

Height, weight and BMI were measured/calculated at booking by the research team. After informed consent, participants had blood drawn at their booking visit for HbA1c measurement on the BioRad Variant II Turbo analyser platform (Bio-Rad Laboratories Ltd, Watford, UK). Subjects also consented for the sampling of plasma, serum and urine for storage, for later analysis. As per routine antenatal care, women also had screening random plasma glucose (RPG) measured at their booking visit for pre-existing diabetes using the Roche Cobas GLUC3 analyser platform (Roche/Hitachi, Basel, Switzerland).

A 75 g OGTT was performed at 27–28 weeks' gestation and GDM was diagnosed using IDPSG/WHO

FIGURE 1 Recruitment and participant follow-up
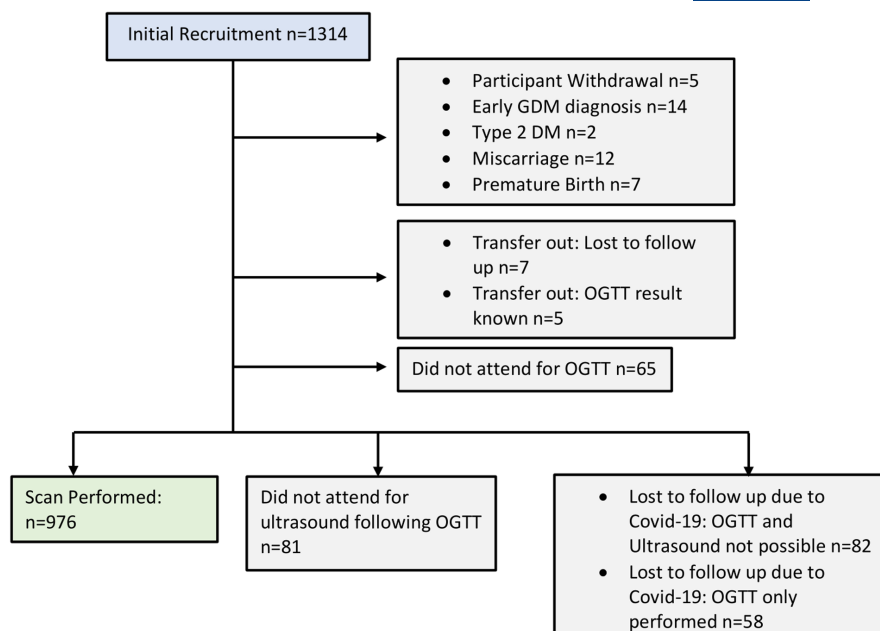
criteria: fasting glucose ≥5.1 mmoL/L, or 1-hour glucose ≥10.0 mmoL/L or 2-hour glucose ≥8.5 mmoL/L.[12] Immediately following the OGTT, and prior to any diagnosis of GDM, comprehensive fetal biometry was performed using ultrasonography to quantify fetal growth immediately. Ultrasonography was performed by trained radiographers who were competent to perform independent fetal ultrasonography and who were blinded to all participant data including first-trimester HbA1c, using a Voluson P8 Scanner with a 2-5 MHz probe in an obstetric view (GE Healthcare, USA). The following measurements were taken during this assessment: Biparietal Diameter (BPD), Occipitofrontal Diameter (OFD), Head Circumference (HC), Abdominal Circumference (AC), Femur Length (FL), Amniotic Fluid Index (AFI), Estimated Fetal Weight (EFW).

Centiles for EFW and AC were calculated using integrated software. The EFW was calculated using BPD, HC, AC and FL measurements as described by Hadlock using the formula:

Log10 EFW = 1.3596 + 0.0064(HC) + 0.0424(AC) + 0.174(FL) + 0.00061(BPD)(AC) − .0.00386(AC)(FL)[13]

Customised EFW centiles were generated for each participant, adjusted for maternal height, weight, parity and ethnicity. These customised centiles were generated using the bulk centile calculator provided on request by the UK Perinatal Institute. This customization process is identical to that provided by the GROW application in use across the UK.[14]

Following OGTT and fetal ultrasound, women resumed routine antenatal care and standard treatment depending on the outcome of their OGTT.

Relevant pregnancy outcomes were collected from the Northern Ireland Maternity Database System (NIMATS) which is used to collect data on all pregnancies from booking through to delivery and matched to SHAPE participants using unique identifiers.

Logistic regression was used to determine odds ratios for outcomes of interest. The clinical relevance of any observed effect sizes was considered alongside their significance.

Statistical analysis was performed using IBM SPSS Statistics® version 27.0 working to a.

significance level of 0.05. Additional graphing was performed using GraphPad Prism®.

Version 9.1.

3 | RESULTS

In total, 1314 women were recruited between October 2017 and February 2020 prior to the study's premature termination due to the onset of the COVID-19 pandemic in March 2020. All women were recruited between 10 and 14 weeks' gestation (mean 85 days). Participant follow-up data are summarised in Figure 1. In total, five participants withdrew (99.6% retention rate). Early GDM was diagnosed in 14 cases (all <20 weeks' gestation) by OGTT testing based on IADPSG/WHO criteria. For the purposes of analysis, these women were considered to have GDM and hence did not undergo the additional fetal ultrasound assessment at 28 weeks. Two women had a booking HbA1c ≥48 mmol/mol (6.5%) indicative of diabetes and both were confirmed by OGTT. Following the study's termination

due to COVID-19, fetal ultrasound and OGTT could no longer be performed. In total, 976/1314 women (74.3%) successfully underwent additional fetal ultrasound assessment alongside OGTT as shown in Figure 1.

3.1 | Baseline characteristics

The mean BMI among participants was 31.5 kg/m^2 (SD 6.8) and the mean age was 30.4 years (SD 5.3) One-third of women were nulliparous at recruitment. The majority of participants, 89.1%, were white British European, as reflected by the local population.[15] Table 1 outlines the relevant baseline characteristics of the cohort at the time of recruitment.

3.2 | First-Trimester HbA1c and RPG

First-trimester HbA1c was evaluated in 1251 women. Values were normally distributed with a mean of 33.5 mmol/mol (5.2%) (SD 4.10).

RPG was obtained in 1291 women. The distribution of RPG approximated normality with a slight positive skew and a mean of 4.5 mmol/L (SD 0.71).

3.3 | GDM status

Where an OGTT was incomplete, but one or more of the glucose results exceeded the diagnostic threshold for GDM, the participant was considered to have GDM.

Where a test was incomplete and none of the glucose values returned exceeded the diagnostic threshold, the result was considered incomplete and GDM status was considered unknown. A total of 1115 tests were suitable for analysis. Testing occurred at a mean gestation of 197.9 days (SD 5.8) or 28 weeks + 1 day. A total of 236 women (21.2%) exceeded the diagnostic threshold for GDM.

3.4 | Fetal growth

The mean EFW centile was higher among women with GDM compared with those women without GDM (53.0 vs. 45.4, p = <0.001). After adjustment for maternal height, weight, parity and ethnicity, the mean EFW centile remained higher among GDM women than among non-GDM women (51.8 vs. 46.3, p = 0.008). Frequency distributions for EFW before and after adjustment are shown in Figure 2.

The mean fetal AC centile was higher among GDM women than among non-GDM women (55.3 vs. 46.2, p = <0.001).

TABLE 1 Baseline maternal age, weight, height, BMI, gestational age, parity and NICE risk factor profiles. Data are mean (SD) or n (%).

	$n = 1314$
Maternal age in years (SD)	30.4 (5.3)
Height in cm (SD)	164.2 (6.6)
Weight in kg (SD)	85.0 (19.3)
BMI in kg/m^2 (SD)	31.5 (6.8)
Gestational Age at booking in days (SD)	85.7 (5.9)
BMI ≥ 30 kg/m^2 (%)	834 (63.5%)
Positive family history of diabetes (%) (first-degree relative)	549 (41.8%)
Previous macrosomia (%)	56 (4.3%)
High-risk ethnicity for GDM (%)	101 (7.7%)
1 Risk factor present	1075 (81.8%)
2 Risk factors present	229 (17.4%)
3 Risk factors present	10 (0.8%)
Parity:0	444 (33.8%)
Parity:1	488 (37.1%
Parity:2	247 (18.8%)
Parity:3+	159 (10.3%)

GDM pregnancies were at three times greater odds of having EFW >90th centile (OR 3.02, 95% CI 1.64–5.55, $p < 0.001$) and fourfold greater odds of having fetal AC >90th centile (OR 4.30, 95% CI 2.45–7.57, p = <0.001). Significance was lost for EFW >90th centile after adjustment for maternal height, weight, parity, ethnicity and fetal sex.

3.5 | First-trimester HbA1c as a predictor of excessive fetal growth and GDM

Participants were stratified on the basis of their first-trimester HbA1c into those with HbA1c ≥39 mmol/mol and those with HbA1c <39 mmol/mol (<5.7%). Participants with concomitant anaemia or missing samples were excluded from analysis. These two groups were compared with respect to their odds of relevant outcomes and are summarised in Table 2 below. There was no difference in the odds of adjusted EFW >90th centile (OR 1.18, (*95% CI 0.52–2.66*) p = 0.7), nor of fetal AC >90th centile (OR 1.93, (*95% CI 0.88–4.25*) p = 0.1) between these groups. The mean first-trimester HbA1c was higher among women with subsequent GDM than among those without (32.9 mmol/mol (5.2%) vs. 35.7 (5.4%), p = <0.001) but there was considerable overlap in the distribution of HbA1c between these groups as shown in Figure 3. Women with first-trimester HbA1c >39 mmol/mol (5.7%)

were at fivefold greater odds of developing GDM (OR 5.49, (*95% CI 3.61–8.37*) $p = <0.001$). The sensitivity of using this threshold for the prediction of later GDM was 24.2% with a specificity of 94.5%. Whilst they may be considered a high-risk group (PPV 54.37%), on a whole-population level HbA1c performs poorly as a predictor of GDM. This is confirmed on ROC analysis.

Which did not identify any alternative, more useful first-trimester HbA1c threshold for the prediction of GDM or fetal growth outcomes. Total area under the ROC curve (AUC) was 0.546 (95% CI 0.47–0.62) for predicting EFW >90th centile, AUC 0.560 (95% CI 0.47–0.65) for fetal AC >90th centile and AUC of 0.686 (95% CI 0.66–0.73) for the prediction of GDM.

Frequency distribution: EFW Centile

Frequency distribution: Adjusted EFW Centile

FIGURE 2 Frequency distributions for EFW pre and post adjustment

Similarly, taking HbA1c as a continuous variable, each mmol/mol increase in first-trimester HbA1c led to a 4.2% increase in the odds of EFW ≥90th centile but this was not significant ($p = 0.23$). This was also demonstrated for the outcome of fetal AC ≥90th centile (4.2% increase per mmol/mol increase in HbA1c $p = 0.24$). For the outcome of GDM, each mmol/mol increase in first-trimester HbA1c conferred a 21% increase in the odds of GDM, $p = <0.001$.

Likewise, ROC analysis of first-trimester RPG did not identify any threshold which offered reasonable clinical utility as predictor of fetal growth or of GDM. Total AUC was 0.548 (95% CI 0.48–0.62) for predicting EFW >90th centile, 0.599 (95% CI 0.53–0.67) for predicting fetal AC >90th centile and 0.680 (95% CI 0.64–0.72) for predicting GDM.
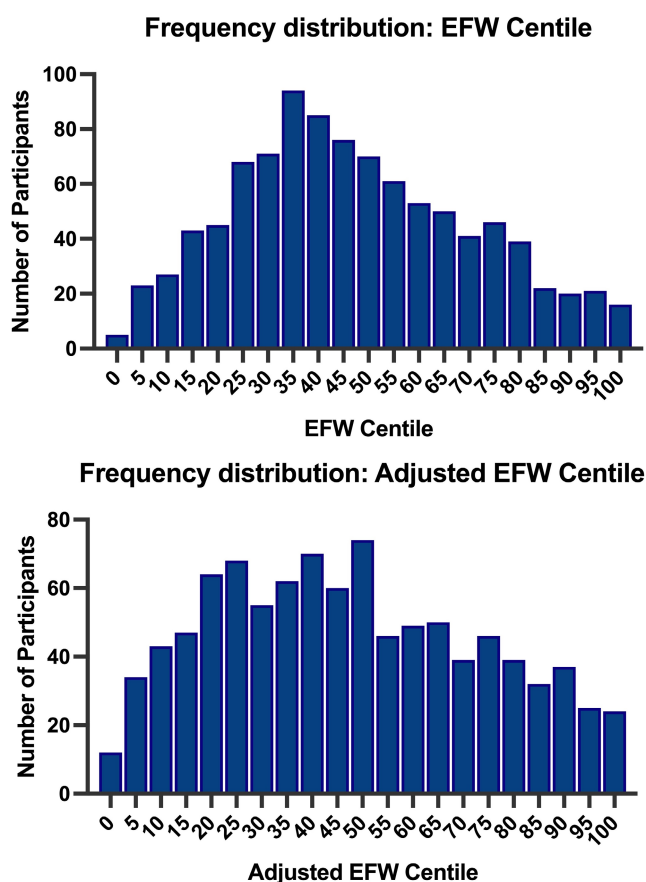
3.6 | Adverse pregnancy outcomes

Birth data (occurring ≥24 weeks' gestation) and adverse outcome data were extracted from the NIMATS database for 1277 pregnancies. Births occurred at a mean of 274.6 days (SD 12.6 days) or 39 weeks +1 day. Female sex was recorded in 597/46.75% births, male sex in 680/53.25% births.

After excluding participants lost to follow-up and those in whom first-trimester HbA1c was not available due to lost samples/processing errors, miscarriages, losses to follow-up and those diagnosed with type 2 diabetes, combined outcomes were available for 1243 participants. Women with first-trimester HbA1c ≥39 mmol/mol (≥5.7%) and < 39 mmol/mol (<5.7%) were compared with respect to the odds of each of these adverse outcomes as shown in Table 3.

When stratified by first-trimester HbA1c, there was no significant difference in the odds of macrosomia, small for gestational age (SGA), large for gestational age (LGA) nor the requirement for emergency caesarean section. A first-trimester HbA1c ≥39 mmol/mol (≥5.7%) was associated with twofold greater odds of requiring admission to neonatal intensive care (NICU) admission at birth (OR 2.19, $p = 0.008$). The reasons for NICU admission are not recorded. These pregnancies were also at more than twofold greater odds of pregnancy-induced hypertension (OR

TABLE 2 Outcomes for fetal growth and later diagnosis of GDM stratified by first-trimester HbA1c.

Outcome	First-trimester HbA1c <39 mmol/mol n/total (%)	First-trimester HbA1c ≥39 mmol/mol n/total (%)	OR (95% CI)	*p*
EFW ≥90th centile	61/861 (7.08%)	7/85 (8.24%)	1.18 (0.52–2.66)	0.70
Fetal AC ≥90th centile	44/861 (5.11%)	8/85 (9.41%)	1.93 (0.88–4.25)	0.10
GDM	175/982 (17.82%)	56/103 (54.37%)	5.49 (3.61–8.37)	<0.001

2.22, $p = 0.01$) and more than four times the odds of pre-eclampsia (OR 4.40, p-0.006). Pregnancy-induced hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg first detected after 20 weeks' gestation. Pre-eclampsia was defined as the presence of pregnancy-induced hypertension along with detectable proteinuria.

The frequency distributions for unadjusted EFW and adjusted EFW provided here (Figure 2) are novel in a contemporary cohort. The assumption that 10% of pregnancies will be subject to EFW >90th centile did not hold true in this cohort. There is pronounced clustering towards lower EFW with a peak around the 35th centile. After adjustment, the distribution flattens considerably and peaks around the 50th centile. This provides some validation for the adjustment process but there remains an unequal distribution among the centiles which is of immediate relevance for future research and service planning.
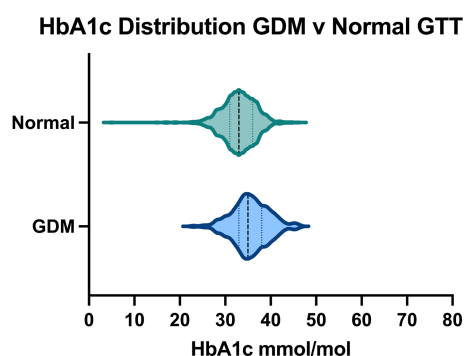

FIGURE 3 Violin plot showing HbA1c distribution among women who subsequently developed GDM versus those with normal GTT at 28 weeks. Heavy dashed line represents the median, light dashed lines represent the 1st and 3rd quartiles

4 | DISCUSSION AND CONCLUSION

First-trimester HbA1c did not predict EFW; when stratified by HbA1c ≥ 39 mmol/mol ($\geq 5.7\%$) or < 39 mmol/mol ($<5.7\%$), there was no significant difference in the proportion of pregnancies experiencing excessive fetal growth. ROC analysis did not identify an alternative threshold which would offer reasonable clinical utility for either EFW or fetal AC >90th centile. With respect to fetal AC, there was almost twice the incidence of fetal AC >90th centile among pregnancies with first-trimester HbA1c ≥ 39 mmol/mol ($\geq 5.7\%$) compared to those <39 mmol/mol ($<5.7\%$). However, this was not statistically significant ($p = 0.10$) possibly owing to sample size restrictions and the associated loss of power as a result of the study's early termination. Given that fetal adiposity is typical of GDM pregnancies, it might be expected that a difference in this parameter would emerge earlier than changes to overall EFW. Indeed, these data would suggest that an increase in fetal AC may be associated with higher first-trimester HbA1c with the OR (1.93) much closer to the effect size on which the power calculations were based, whereas there is little evidence to support an association with overall EFW (OR 1.18).

We have demonstrated that excessive fetal growth is evident prior to a diagnosis of GDM among women ultimately testing positive by OGTT. This was manifest by a higher mean centile for estimated fetal weight among GDM versus non-GDM pregnancies. This difference was underpinned by a higher fetal AC among GDM pregnancies when compared to non-GDM pregnancies. This is in keeping with growth patterns that typify GDM pregnancies and with previously published data.[1] Whilst it is clear that excessive fetal growth is evident prior to a diagnosis of GDM, further research is required to identify suitable methods for identifying such pregnancies early in gestation.

TABLE 3 Adverse pregnancy outcomes stratified by first-trimester HbA1c for 1243 participants for whom outcome data and first-trimester HbA1c were available.

Outcome	First-trimester HbA1c <39 mmol/mol n/total (%)	First-trimester HbA1c ≥39 mmol/mol n/total (%)	OR (95% CI)	p
Macrosomia (>4500 g)	20/1132 (1.77%)	1/111 (0.9%)	0.51 (0.07–3.80)	0.51
Macrosomia (>4000 g)	161/1132 (14.22%)	12/111 (10.81%)	0.73 (0.39–1.36)	0.32
Large for gestational age	117/1132 (10.34%)	18/111 (16.22%)	1.68 (0.98–2.88)	0.06
Small for gestational age	134/1132 (11.84%)	19/111 (17.12%)	1.54 (0.91–2.60)	0.11
Pregnancy-induced hypertension	69/1132 (6.10%)	14/111 (12.61%)	2.22 (1.21–4.10)	0.01*
Preeclampsia	12/1132 (1.06%)	5/111 (4.50%)	4.40 (1.52–12.73)	0.006*
NICU admission	81/1132 (7.16%)	16/111 (14.41%)	2.19 (1.23–3.89)	0.008*
Emergency caesarean section	165/1132 (14.58%)	18/111 (16.22%)	1.13 (0.67–1.93)	0.64
Elective caesarean section	207/1132 (18.29%)	25/111 (22.52%)	1.29 (0.81–2.08)	0.27

*Significant to level of $p < 0.05$.

For the prediction of GDM in later pregnancy, those with first-trimester HbA1c ≥39 mmol/mol (≥5.7%) represent a high-risk cohort, being at fivefold greater odds of GDM development compared to those pregnancies below this threshold. Although there may be clinical utility in identifying such high-risk pregnancies, routine use of HbA1c as predictor of GDM could not be supported given its lack of specificity at any reasonable level of sensitivity. There is considerable overlap in the distributions of first-trimester HbA1c among GDM and non-GDM pregnancies.

At the point of delivery, there were no differences in the rates of SGA nor macrosomia when pregnancies were stratified by first-trimester HbA1c. Although not reaching statistical significance, there was weak evidence of greater odds of LGA among women with first-trimester HbA1c ≥39 mmol/mol (≥5.7%) with an OR 1.68 (0.98–2.88) and *p*-value 0.06. Such a borderline result is potentially driven by the study's early termination and concomitant sacrifice in power and a slightly larger cohort may well demonstrate a significant relationship. Consideration must also be given for the fact that GDM pregnancies will have received treatment prior to delivery which has the potential to alter fetal growth.

Women who had a first-trimester HbA1c ≥39 mmol/mol (≥5.7%) were at twofold greater odds of developing pregnancy-induced hypertension compared to women below that threshold. This observation might have been accounted for by other risk factors for pregnancy-induced hypertension such as maternal BMI, nulliparity, age and baseline blood pressure and GDM status. Logistic regression demonstrated that even after adjustment for these factors, there remained a significant relationship between first-trimester HbA1c ≥39 mmol/mol (≥5.7%) and pregnancy-induced hypertension. Similarly, these women were at fourfold greater odds of developing preeclampsia when compared to women with first-trimester HbA1c <39 mmol/mol (5.7%) which likewise retained statistically significant after adjustment for other risk factors. There is a well-established relationship between HbA1c and the odds of preeclampsia development in the context of pre-existing diabetes.[16] There are little data concerning the relationship between HbA1c and pregnancy-induced hypertension/preeclampsia in pregnancies outside of pre-gestational diabetes. The prior study by Hughes et al in 2014 demonstrated first-trimester HbA1c ≥41 mmol/mol was associated with an elevated risk of preeclampsia (RR 2.42).[2] Similarly, another study, which included women with GDM, found that first-trimester HbA1c ≥41 mmol/mol (≥5.9%) was also associated with an elevated risk of preeclampsia (OR 3.54).[17] The mechanisms which might underpin this relationship between HbA1c and

hypertensive disorders remains unclear. Within the HAPO study, rising second-trimester HbA1c was associated with increased odds for preeclampsia but less so than direct glucose measures.[18] Given that the relationship persists after removing GDM pregnancies and after adjustment for GDM status, it remains unclear whether the relationship is mediated by hyperglycaemia, coexisting metabolic syndrome in mothers with mild dysglycaemia or by another unknown mechanism.

It is notable also that the rates of SGA were slightly higher than those of LGA in this cohort. This observation is tempered by that fact that treatments for GDM aim to limit excessive fetal growth. The role of concomitant risks, particularly PIH and preeclampsia remains uncertain as does the influence of any ethnic differences in the local population not accounted for by current birth centile adjustment models.

First-trimester HbA1c was not useful in identifying pregnancies at risk of excessive fetal growth in later gestation. There remains a requirement for ongoing research to identify suitable screening methods which might identify pregnancies at high risk for excessive fetal growth.

Although women with first-trimester HbA1c ≥39 mmol/mol represent a high-risk cohort for the later development of GDM, its use cannot be advocated given a lack of sensitivity. The use of first-trimester RPG also lacks sufficient sensitivity in identifying later GDM. The changes in screening for GDM adopted during the COVID-19 pandemic may therefore fail to identify a considerable proportion of GDM and therefore potentially culminate in an increase in macrosomia. These data provide a strong argument in favour of returning to gold-standard OGTT.

First-trimester HbA1c identifies a cohort a high risk for the later development of pregnancy-induced hypertension and pre-eclampsia. The mechanisms underlying this association remain unclear and further study is required to establish any role for HbA1c as a screening test for these outcomes.

5 | LIMITATIONS

This study is limited by its early termination in the setting of COVID-19 which naturally leads to a corresponding sacrifice in power for some outcomes. This is notable for the outcome of fetal AC ≥90th centile, as discussed above, for which a larger cohort may have demonstrated a significant result.

It also remains unclear as to why the EFW at 28 weeks' gestation did not predict birthweight in this cohort and is suggestive of a heterogenous picture whereby some

pregnancies are subject to early accelerated growth whilst others develop excessive growth in later gestation.

AUTHOR CONTRIBUTIONS

Robert D'Arcy is the primary author, conducting this research as part of a doctoral fellowship, and acts as guarantor for its content. The remaining authors have helped to design and supervise this research throughout its duration. They have also contributed to the editing and revision of this manuscript for publication.

DATA AVAILABILITY STATEMENT

Anonymised data that support the findings of this study are available on request from the corresponding author, RD.

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REFERENCES

1. Sovio U, Murphy HR, Smith GCS. Accelerated fetal growth prior to diagnosis of gestational diabetes mellitus: a prospective cohort study of nulliparous women. *Diabetes Care*. 2016;39:982-987.
2. Hughes RCE, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy HbA1c ≥5.9% (41 mmol/Mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care*. 2014;37:2953-2959.
3. Rowan JA, Budden A, Sadler LC. Women with a nondiagnostic 75 g glucose tolerance test but elevated HbA1c in pregnancy: an additional group of women with gestational diabetes. *Aust New Zeal J Obstet Gynaecol*. 2014;54:177-180.
4. McGrath NM, Baker C, Simkins A. Increased detection of gestational diabetes mellitus by using HbA$_{1c}$ screening in the first antenatal blood tests. *Diabet Med*. 2014;31:1277-1277.
5. Alunni ML, Roeder HA, Moore TR, Ramos GA. First trimester gestational diabetes screening - change in incidence and pharmacotherapy need. *Diabetes Res Clin Pract*. 2015;109:135-140.
6. Fong A, Serra AE, Gabby L, Wing DA, Berkowitz KM. Use of hemoglobin A1c as an early predictor of gestational diabetes mellitus. *Am J Obstet Gynecol*. 2014;211:641.e1-641.e7.
7. Benaiges D, Flores-le Roux JA, Marcelo I, et al. Is first-trimester HbA1c useful in the diagnosis of gestational diabetes? *Diabetes Res Clin Pract*. 2017;133:85-91.
8. Royal College of Obstetricians and Gynaecologists. *Guidance for Maternal Medicine Services in the Evolving Coronavirus (COVID-19) Pandemic*. Royal College of Obstetricians and Gynaecologists; (2020). https://www.rcog.org.uk/globalassets/documents/guidelines/2020-07-10-guidance-for-maternal-medicine.pdf
9. Yamamoto J. M. et al. Urgent Update-Temporary Alternative Screening Strategy for Gestational Diabetes Screening during the COVID-19 Pandemic A Joint Consensus Statement from the Diabetes Canada Clinical Practice Guidelines Steering Committee* and the Society of Obstetricians and Gynecologists of Canada.
10. McIntyre HD, Gibbons KS, Ma RCW, et al. Testing for gestational diabetes during the COVID-19 pandemic. An evaluation of proposed protocols for the United Kingdom, Canada and Australia. *Diabetes Res Clin Pract*. 2020;167:108353.
11. National Institute for Health and Care Excellence. N. Overview | Diabetes in pregnancy: management from preconception to the postnatal period | Guidance | NICE. https://www.nice.org.uk/guidance/ng3
12. WHO. WHO | Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy. https://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/
13. Hadlock FP, Harrist RB, Martinez-Poyer J. In utero analysis of fetal growth: a sonographic weight standard. *Radiology*. 1991;181:129-133.
14. Perinatal Institute: FetalGrowth. https://www.perinatal.org.uk/FetalGrowth/home
15. Northern Ireland Statistics and Research Agency. Northern Ireland Census STATISTICS BULLETIN. https://www.nisra.gov.uk/sites/nisra.gov.uk/files/publications/2011-census-results-detailed-characteristics-statistics-bulletin-28-june-2013.pdf (2013).
16. Holmes VA, Young IS, Patterson CC, et al. Optimal glycemic control, pre-eclampsia, and gestational hypertension in women with type 1 diabetes in the diabetes and pre-eclampsia intervention trial. *Diabetes Care*. 2011;34:1683-1688.
17. Mañé L. et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. *J Clin Endocrinol Metab* 102, jc.2016-2581 (2016).
18. Lowe LP, Metzger BE, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcome (HAPO) study: associations of maternal A1C and glucose with pregnancy outcomes. *Diabetes Care*. 2012;35:574-580.