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RESEARCH ARTICLE

The utility of plasma glycated CD59 in predicting postpartum glucose intolerance: A prospective study of women diagnosed with GDM during a period of universal GDM screening

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Abstract

Aims: Gestational diabetes (GDM) is associated with the development of postpartum (PP) glucose intolerance. Plasma glycated CD59 (pGCD59) is an emerging biomarker for the detection of hyperglycaemia. The aim of this study was to assess the ability of PP pGCD59 to predict the development of PP GI as defined by the 2 h 75 g OGTT using the ADA criteria, in a cohort of women diagnosed with prior GDM in the index pregnancy using the 2 h 75 g OGTT at 24–28 weeks of gestation according to the World Health Organization (WHO) 2013 criteria.

Methods: Of the 2017 pregnant women recruited prospectively 140 women with gestational diabetes had samples for pGCD59 taken PP at the time of the OGTT. The ability of pGCD59 to predict the results of the PP OGTT was assessed using nonparametric receiver operating characteristic (ROC) curves.

Results: Women with PP glucose intolerance had significantly higher PP pGCD59 levels compared to women with normal glucose tolerance PP (3.8 vs. 2.7 SPU). PP pGCD59 identified women who developed glucose intolerance PP with an AUC of 0.80 (95% CI: 0.70–0.91). A PP pGCD59 cut-off value of 1.9 SPU generated a sensitivity of 100% (95% CI: 83.9–100), specificity of 16.9% (95% CI: 9.8–26.3), positive predictive value of 22.1% (95% CI: 21.0–22.6), and negative predictive value of 100% (95% CI: 87.4–100). PP fasting plasma glucose generated an AUC of 0.96 (95% CI: 0.89–0.99) for the identification of PP glucose intolerance.

Conclusion: Our study found that PP pGCD9 may be a promising biomarker to identify women not requiring PP glucose intolerance screening using the traditional OGTT. While the diagnostic accuracy of pGCD59 is good, fasting plasma glucose remains a better test for the identification of PP glucose intolerance.

KEYWORDS
biomarker, CD59, gestational diabetes, postpartum glucose intolerance

1 | INTRODUCTION

It is well documented that gestational diabetes mellitus (GDM) is associated with adverse pregnancy outcomes. GDM also has lasting metabolic consequences for the mother. GDM has been associated with the long-term development of metabolic syndrome,[1] cardiovascular disease,[2] and renal disease.[3] Furthermore, women with a history of GDM have an increased risk of developing postpartum (PP) glucose intolerance (PP GI). When compared to women with normal glucose tolerance (NGT) during pregnancy, GDM is linked to a 10-fold increased risk of developing PP type 2 diabetes (T2DM) or prediabetes.[4,5] A systematic review and meta-analysis[6] of 675,455 women with up to 28 years of follow-up showed that women with GDM have a more than seven-fold increased risk of developing T2DM. Another systematic review by Dennison et al[7] involving 4,155,247 women without prior GDM and 310,214 women with prior GDM found that a third of the population analysed developed T2DM within 15 years and that women with prior GDM had an eight-fold (RR: 8.3, 95% CI: 6.5–10.6) higher risk of developing T2DM. Fu et al[8] offer a comprehensive review of the future health implications of GDM after pregnancy highlighting that GDM is a chronic cardiometabolic disease which requires long-term surveillance with the aim of early implementation of risk-modifying interventions that would lead to a reduction in the development of T2DM and cardiovascular disease.

The American Diabetes Association (ADA) recommends screening for GI in women with GDM at 6–12 weeks PP using the 2 h 75 g oral glucose tolerance test (OGTT)[9] and lifelong screening for glucose intolerance every 3 years or less depending on risk. Despite these recommendations, among women with a history of GDM, the uptake rates for the PP OGTT have remained suboptimal.[10] Critical reasons identified for this lack of compliance with PP screening include,[11,12] the responsibility for an infant, the time required for the test and physical restrictions (fasting, traveling), which combined make it difficult for the new mother to attend the PP OGTT. A single blood test, taken in the non-fasting state, ideally by the mother's family physician/general practitioner, would significantly facilitate attendance and increase compliance with PP GI screening. Plasma glycated CD59 (pGCD59) is an emerging biomarker for glucose handling in humans which requires a single sample taken in a non-fasting state and, to date, has shown good potential as a predictor of hyperglycaemia.

CD59 is a complement regulatory membrane protein that protects self-cells from complement-mediated harm by preventing formation of membrane attack complex.[13] In hyperglycaemic states, the complement regulatory function of CD59 is inhibited by the non-enzymatic glycation forming a functionally inactive plasma glycated CD59 (pGCD59). pGCD59 is a promising novel biomarker for GI. pGCD59 levels have been shown to identify subjects with T2DM with high sensitivity and specificity.[14,15] More so, pGCD59 has been shown to identify women with GDM at 24–28 weeks of gestation as well as early in pregnancy (<20 weeks of gestation), as indicated by AUC of the ROC curves of 0.92 and 0.86, respectively.[16]

The aim of this study was to assess the ability of PP pGCD59 to predict the development of PP GI as defined by the 2 h 75 g OGTT using the ADA criteria, in a cohort of women diagnosed with prior GDM in the index pregnancy using the 2 h 75 g OGTT at 24–28 weeks of gestation according to the World Health Organization (WHO) 2013 criteria.[17]

What is already known

- Gestational diabetes is associated with an increased risk of developing postpartum (PP) glucose intolerance (GI)
- pGCD59 is a promising biomarker for the detection of hyperglycaemia

What this study has found?

- Women with PP GI have higher pGCD59 levels compared to women with normal glucose tolerance
- PP pGCD59 may identify women with PP GI with good accuracy cut-off value of 1.9 SPU generated a very good sensitivity and negative predictive value
- A cut-off value of 1.9 SPU generated a very good sensitivity and negative predictive value

What are the implications of the study?

- PP pGCD9 may be a promising biomarker that might simplify the PP GI screening process.

2 | METHODS

The study protocol is available here.[18] In brief, this was a prospective study that took place between November 2018 and March 2020 and included consecutive pregnant women attending their first antenatal visit at Galway University Hospital, Galway. Only pregnant women without diabetes were eligible for the study. The patient information leaflet was distributed to women at the initial clinic appointment. If agreeable, a consent form was signed.

At their first antenatal appointment, the weight and height were measured using SECA scales model 799, and the BMI and body surface area (BSA) were calculated. To establish the gestational age, a dating ultrasound scan was performed.

In the second trimester, women were offered GDM screening utilising a 2 h 75 g OGTT (24–28 weeks of gestation). Whole blood was taken into fluoride oxalate specimen tubes and plasma glucose was subsequently measured on the Roche Cobas® 8000 analyser using the hexokinase method (Roche Diagnostics). GDM was diagnosed using the WHO 2013 criteria if the OGTT revealed one abnormal plasma glucose value fasting value >/=5.1 mmol/L (92 mg/dL), 1 h value >/=10 mmol/L (180 mg/dL), and 2 h value >/=8.5 mmol/L (154 mg/dL).

In our centre, women with GDM are advised to have a 2 h 75 g OGTT 3 months PP. Two weeks prior to the scheduled appointment, women receive an appointment for the PP OGTT. If women fail to attend their PP OGTT appointment, the diabetes service administrator contacts them to reschedule. The PP pGCD59 was taken at the time of the PP 2 h 75 g OGTT.

In accordance with the ADA criteria,[19] PP glucose intolerance was defined as: impaired fasting glucose (IFG) – fasting plasma glucose (FPG) ≥5.6–6.9 mmol/L (100–125 mg/dL); impaired glucose tolerance (IGT) – 2 h glucose levels ≥7.8–11 mmol/L (140–199 mg/dL); diabetes – FPG ≥7 mmol/L (126 mg/dL) and/or 2 h glucose levels ≥11.1 mmol/L (200 mg/dL).

All samples for pGCD59 measurement were collected into ethylenediaminetetraacetic acid (EDTA). Each EDTA plasma sample was divided into two 500 μL aliquots barcoded and stored at −80°C. On completion of the study, an aliquot of each participant's EDTA plasma sample frozen at −80°C was transferred on dry ice to the Laboratory for Translational Research, Haematology Division, Department of Medicine, Brigham and Women's Hospital, Boston, USA for pGCD59 analysis. At the latter institution, pGCD59 levels were determined using the enzyme-linked immunosorbent test (ELISA) previously published by Ghosh et al.[14] The results were expressed in standard peptide units (SPU). The intra-assay coefficient of variation (CV) was 3.0%. Test operators were blind to the women's PP glucose tolerance status.

2.1 | Data confidentiality

To ensure participant data confidentiality, all laboratory specimens were assigned a coded identity number. The barcoded samples were linked to a clinical database that was pseudo-anonymised. This information was password-protected and stored on a secure server.

2.2 | Statistical analysis

Patient characteristics are described using mean and standard deviations/median and interquartile range for continuous variables and count/percentages for categorical variables. Baseline characteristics of pregnant women who had a normal PP OGTT (PP NGT) were compared with characteristics of women who developed PP GI using cross tabulations and χ^2 test for categorical variables, Wilcoxon-Mann–Whitney test for continuous variables not normally distributed, and Student t tests for continuous variables normally distributed. The power calculation and sample size have been previously described.[18]

Logistic regression was used to evaluate the association between maternal characteristics and laboratory parameters with PP GI. Adjusted odds ratios (ORs) were derived together with their respective type of Wald 95% CIs. To describe pGCD59 distribution across levels of the study covariates means and standard deviations were used.

The ability of pGCD59 to predict the results of the PP OGTT was assessed using nonparametric receiver operating characteristic (ROC) curves and adjusted for maternal age, BMI, maternal ethnicity, and gestational weight gain and the AUC derived using 95% CI. Diagnostic accuracy measures (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV)) were estimated and presented with 95% CI. The accuracy, Youden index, likelihood ratios (LR), the number of patients needed to diagnose (NND) and the number of patients needed to misdiagnose (NNM) were also calculated.

Missing data were assumed to be completely at random and a complete case analysis was performed. In all analyses, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS for Windows, version 20 (IBM SPSS Statistics for Windows, version 20 SPSS).

2.3 | Ethics

Ethical approval for this study was granted by the Clinical Research Ethics Committee, Galway, Ireland (reference no-C.A. 2026).

3 | RESULTS

Women 2037 were recruited for this study, with 7 withdrawing consent, 11 experiencing a miscarriage, and 2 women having their pregnancies terminated (TOP). Anaemia ($n=1$), cystic fibrosis ($n=1$), and needle fear ($n=5$) were among the reasons for withdrawal (Figure 1). GDM was identified in 230 of the remaining

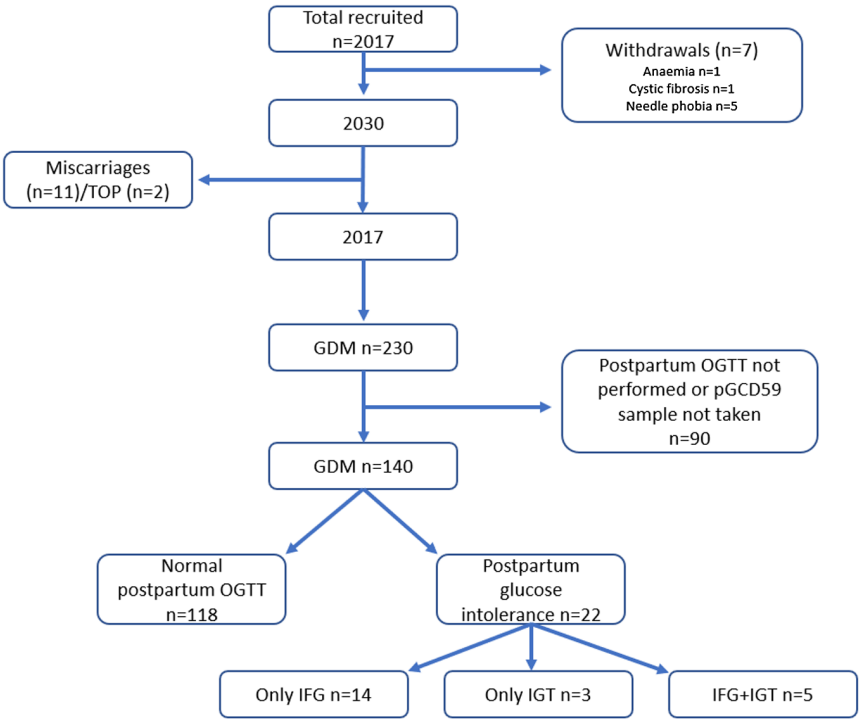

FIGURE 1 Study flowchart. GDM, gestational diabetes; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

2017 participants, resulting in a prevalence of 11.4%. Of the 230 women with GDM, 90 (39%) women did not attend their PP OGTT appointment and of the remaining 140 patients, 118 subjects had a normal PP OGTT, and 22 subjects (15.7%) were diagnosed with GI (IFG $n=19$, IGT $n=8$, IFG + IGT $n=5$) (Figure 1). None of the women in the population studied met criteria for T2DM at the time of testing.

The characteristics of women are presented in Table 1. Compared to women with PP NGT, women with PP GI had a higher pre-pregnancy weight (73.7 vs. 87.5 kg, $p<0.01$), higher pre-pregnancy BMI (27.4 vs. 32.9 kg/m^2, $p<0.01$), and higher BSA (1.8 vs. 1.9 m^2, $p<0.01$). Women with PP NGT were more likely to be non-smokers (60.1 vs. 36.3%, $p=0.03$) and to gain more weight during pregnancy (7 vs. 3.3 kg, $p<0.001$). The laboratory values for study participants are presented in Table 1. There was a significant difference between the PP NGT and PP GI groups for PP pGCD59 levels (2.7 vs. 3.8 SPU, $p=0.01$). Women with PP GI had significantly higher glucose values at all time points on the OGTT performed at 24–28 weeks of gestation and at both time points at the PP OGTT.

Table 2 shows the results from the multivariable logistic model revealing that pre-pregnancy BMI was associated with a slight increase in the odds of developing PP GI (OR: 1.1, 95% CI: 1.03–1.19, $p=0.005$). Conversely, gestational weight gain was associated with a reduction in the odds of developing PP GI (OR: 0.8, 95% CI: 0.77–0.94, $p=0.004$), supporting the findings from our descriptive analysis. PP pGCD59 levels were associated with almost a twofold increase in the odds of developing PP GI (OR: 1.9, 95% CI: 1.18–3.17, $p=0.008$).

We assessed pGCD59 levels by maternal characterisitcs in the PP NGT and PP GI groups (Table 3). Mean PP pGCD59 values were higher in the PP GI group compared to the PP NGT subjects across most categories; however, the analysis did not reach statistical significance.

PP pGCD59 identified women who developed PP GI with an AUC of 0.80 (95% CI: 0.70–0.91) (Figure 2). The optimal threshold for diagnosis was identified for a PP pGCD59 cut-off value of 3.27 SPU (Youden index 37.72). This generated a sensitivity of 71.4% (95% CI: 47.8%–88.7%), specificity of 66.3% (95% CI: 55.5%–76.0%), PPV of 33.3% (95% CI: 33.1%–34.4%), NPV of 90.8% (95% CI: 85.4%–95.1%), positive LR (LR+) of 2.12 and negative LR (LR−) of 0.43(Table 4). A PP pGCD59 cut-off value of 1.9 SPU, however, generated a sensitivity of 100% (95% CI: 83.9–100), specificity of 16.9% (95% CI: 9.8–26.3), PPV of 22.1% (95% CI: 21.0–22.6), NPV of 100% (95% CI: 87.4–100), a LR+ of 1.20 and LR− of 0.00.

TABLE 1 Baseline characteristics of women and their laboratory values $n = 140$.

Parameter	PP-NGT ($n = 118$)	PP-GI ($n = 22$)	p-value
Age (years)	35 (31.6–37.5)	35 (31.7–37.2)	0.600
Weeks of gestation at booking	13.1 (12.2–14.0)	12.7 (12–13.5)	0.900
Height (cm)	164 (159–168)	164.7 (159.7–170.3)	0.300
Weight (kg)	73.7 (64.1–85.8)	87.5 (73.6–104.4)	**0.002**
BMI (kg/m^2)	27.4 (23.8–31.4)	32.9 (27.8–35.8)	**0.003**
BSA (m^2)	1.8 (1.7–1.9)	1.9 (1.7–2.2)	**0.003**
SBP (mm Hg)	120 (113.7–128.2)	122.5 (111.7–132.7)	0.400
DBP (mm Hg)	68 (60.7–72.2)	70 (65.5–79.2)	0.200
Gravida	2 (1–3)	2.5 (2–3)	0.500
Parity	1 (0–1)	1 (1–2)	0.100
Ethnicity (white)	95/118 (80.5%)	18/22 (81.8%)	0.600
Alcohol before pregnancy	86/118 (72.8%)	19/22 (86.3%)	0.400
Non-smoker	71/118 (60.1%)	8/22 (36.3%)	**0.030**
GDM on insulin	41/118 (34.7%)	7/22 (31.8%)	0.400
Weight gain in pregnancy (kg)	7 (3.5–10)	3.3 (−1.2–6.8)	**<0.001**
Weeks of gestation at delivery	39.5 (38.7–40.5)	39.9 (39.1–40.4)	0.100
Weeks pospartum OGTT	14.3 (12.0–17.9)	15 (13–20.7)	**0.020**
PP pGCD59 (SPU)	2.7 (2.2–3.7)	3.8 (2.8–4.2)	**0.010**
Fasting glucose at pregnancy OGTT (mmol/L)	5 (4.5–5.2)	5.3 (5.1–5.8)	**<0.001**
1 h glucose at pregnancy OGTT (mmol/L)	9.6 (8.2–10.5)	10.8 (9.5–12.2)	**<0.001**
2 h glucose at pregnancy OGTT (mmol/L)	7.1 (6.0–8.5)	8.4 (6–9.6)	**0.020**
Fasting glucose at PP OGTT (mmol/L)	4.9 (4.5–5.1)	5.7 (5.6–6)	**<0.001**
2 h glucose at PP OGTT (mmol/L)	5.1 (4.6–6.1)	6.9 (5.1–7.8)	**<0.001**

Bold value indicates p values <0.05.

Abbreviations: BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure; GI, glucose intolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PP, postpartum; SBP, systolic blood pressure.

TABLE 2 Postpartum glucose intolerance univariate risk factors, $n = 140$.

Parameter	OR	95% CI	p-value
Age	0.9	0.89–1.05	0.600
BMI	1.1	1.03–1.19	**0.005**
Gestational weight gain	0.8	0.77–0.94	**0.004**
Family history	0.9	0.51–1.95	0.900
GDM treatment	0.8	0.33–2.10	0.700
PP pGCD59	1.9	1.18–3.17	**0.008**

Abbreviations: BMI, body mass index; GDM, gestational diabetes; PP, postpartum.

We assessed the ability of PP FPG to identify PP GI (Figure 3). This generated an AUC of 0.96 (95% CI: 0.89–0.99). While there was no PP HbA1c data available, HbA1c levels were collected in the first trimester of pregnancy in 96 study participants (PP GI $n = 15$). This generated an AUC of 0.68 (95% CI: 0.54–0.82) for the early prediction of PP GI (data not shown).

4 | DISCUSSION

Our study found that PP pGCD59 might have the potential to identify women with PP GI with good accuracy (AUC: 0.80). Moreso, PP pGCD59 may be used for screening to out rule women in need of a PP OGTT.

pGCD59 is an emerging biomarker that has shown great potential in identifying glucose intolerance in pregnancy. Ma et al[20] found that early pregnancy pGCD59 (<20 weeks of gestation) can identify early pregnancy GDM (<20 weeks of gestation) with an AUC of 0.86 (95% CI: 0.83–0.90) in a high risk population (BMI: ≥29 kg/m^2).

TABLE 3 PP pGCD59 by maternal characteristics in the PP NGT and PP GI groups. Values are mean pGCD59 in SPU, $n = 140$.

Parameter	PP NGT values ± SD (SPU)	*p*-value	PP GI values ± SD (SPU)	*p*-value
BMI < 25	2.8 ± 1.0	0.70	3.8 ± 0.8	0.80
BMI ≥ 25–29.9	2.8 ± 1.0		3.7 ± 0.8	
BMI ≥ 30	3.0 ± 1.0		3.5 ± 0.9	
Age < 30	2.7 ± 0.7	0.70	4.0 ± 0.1	0.40
Age 30–39.9	2.9 ± 1.0		3.5 ± 1.0	
Age > 40	3.0 ± 1.2		–	
Ethnicity white	2.9 ± 1.0	0.70	3.6 ± 0.7	0.90
Ethnicity non-white	2.9 ± 1.0		3.6 ± 1.0	
Adequate GWG[a]	2.5 ± 0.9	0.10	3.6 ± 1.1	0.10
Excessive GWG[a]	3.0 ± 1.0		2.7 ± 0.9	
Insufficient GWG[a]	3.0 ± 1.0		3.8 ± 1.0	

Abbreviations: BMI, body mass index; GI, glucose intolerance; GWG, gestational weight gain; NGT, normal glucose tolerance; PP, postpartum.
[a]IOM recommandations.

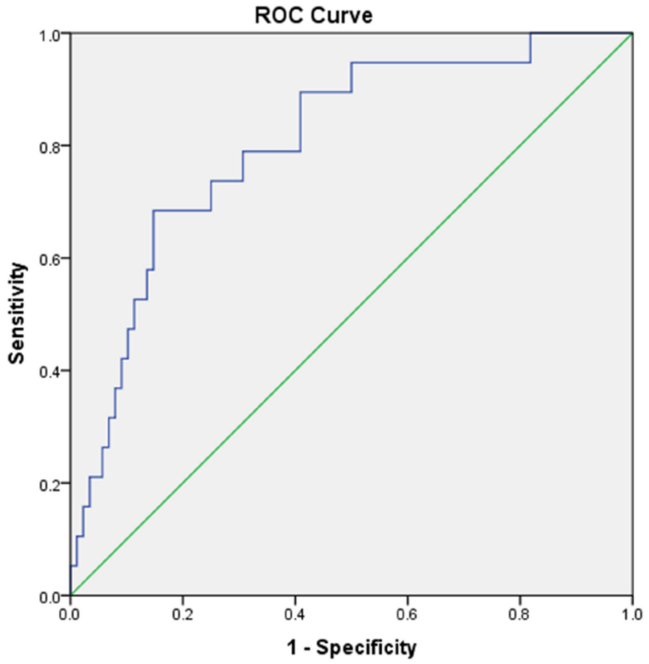

FIGURE 2 PP pGCD59 – ROC curve for PP GI prediction adjusted for maternal age, BMI, maternal ethnicity, and pregnancy weight gain. Postpartum (PP) pGCD59 AUC: 0.80; 95% CI: 0.70–0.91.

Ghosh et al[16] found that pGCD59 taken at the time of second trimester OGTT can identify GDM cases with an AUC of 0.92 (95% CI: 0.87–0.96). Bogdanet et al[21] found that pGCD59 can identify GDM cases with good accuracy in women with a high BMI.

A study by Benhalima et al[22] explored the accuracy of PP pGCD59 sampled at the time of the PP OGTT in 210 subjects (GDM $n = 105$; PP glucose intolerance $n = 35$; 16.6%). They found that PP pGCD59 can predict PP glucose intolerance with an AUC of 0.72 (95% CI: 0.62–0.83). A possible explanation for the higher AUC identified by our study is that our cohort was older and had a higher pre-pregnancy BMI.[23] Our cohort also had higher FPG values at the diagnostic OGTT at 24–28 weeks of gestation and higher PP FPG values in both the PP NGT and PP GI groups. This suggests that our cohort had a higher degree of dysglycaemia and more adverse risk factors and this perhaps led to a better pGCD59 performance. This is further emphasised by the higher mean PP pGCD59 levels found in our study in both the PP NGT and PP GI groups compared to the study by Benhalima et al. This is further reflected in the AUC generated by FPG for the detection of PP GI. Our study identified an AUC of 0.96 while the study by Benhalima et al[24] identified an AUC of 0.76 (95% CI: 0.65–0.87) further reflecting the higher metabolic profile of our population. The pGCD59 samples in our study and the study by Benhalima et al. have been analysed in the same laboratory using the same assay.

Testing that requires the patient to be fasting (OGTT, FPG) is generally viewed as onerous; this is particularly true in the early PP period, when women are focused on their newborn and lack time for a 2 h test undertaken in the hospital setting. Battarbee et al[25] found that 51.1% of OGTT non-completion was due to the lack of patient's adherence. In a qualitative study that involved 22 patients, Bennett et al[26] identified several factors impairing the woman's attendance for the PP OGTT including: baby health needs, adjustment to the baby, baby's schedule, emotional stress/anxiety, availability of childcare, dissatisfaction with care, logistics of accessing care, concerns about future health and fear of receiving bad news. Our study has found that, in our cohort, FPG has a very good ability to identify women with PP GI. However, in the early PP period the baby's sleep patterns might impair the woman's ability to adequately fast overnight (the WHO recommends a period of fasting of minimum 8 h and no longer than 14).[27] A single non-fasting sample taken in a non-hospital setting might improve compliance with PP screening. Women with a history of GDM are at increased risk of long-term adverse outcomes such as T2DM[28] and cardiovascular disease[29] and the identification of women with PP GI would facilitate the implementation of lifestyle modifications, initiate treatment and organise adequate long term follow-up. PP pGCD59 levels were associated with almost a twofold increased risk of developing GI and pGCD59 identified PP GI with good accuracy. Furthermore, our data show that a pGCD59 cut-off value of 1.9 SPU has an excellent sensitivity, NPV and LR− at the expense of a low specificity and low PPV. This has important clinical implications as post-partum screening

TABLE 4 An overview of diagnostic accuracy of PP pGCD59 by different cut-offs to predict PP GDM.

PP pGCD59 cut-off level	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic accuracy	Youden index	PPV (95% CI)	NPV (95% CI)	LR+	LR−	NND	NNM
1.90 SPU	100 (83.9–100)	16.85 (9.8–26.3)	29.90	16.85	22.10 (21.0–22.6)	100 (87.4–100)	1.20	0.00	5.93	1.43
2.38 SPU	90.48 (69.6–98.8)	30.34 (21.0–41.0)	39.78	20.82	23.45 (21.6–23.6)	93.10 (85.1–98.6)	1.30	0.31	4.80	1.66
2.73 SPU	80.95 (58.1–94.6)	51.69 (40.8–62.4)	56.28	30.64	28.33 (26.6–28.6)	92.00 (86.3–96.9	1.68	0.37	3.26	2.29
3.27 SPU	71.43 (47.8–88.7)	66.29 (55.5–76.0)	67.10	37.72	33.33 (33.1–34.4)	90.76 (85.4–95.1)	2.12	0.43	2.65	3.04
3.81 SPU	57.14 (34.0–78.2)	78.65 (68.7–86.6)	75.27	35.79	38.70 (38.6–39.9)	88.60 (84.0–92.2)	2.68	0.54	2.79	4.04
4.07 SPU	33.33 (14.6–57.0)	86.52 (77.6–92.8)	78.17	19.85	36.84 (35.0–40.3)	84.61 (80.3–87.1)	2.47	0.77	5.04	4.58

Abbreviations: LR, likelihood ratio; NPV, negative predictive value; NND, numbers needed to diagnose; NNM, numbers needed to misdiagnose; PPV, positive predictive value.

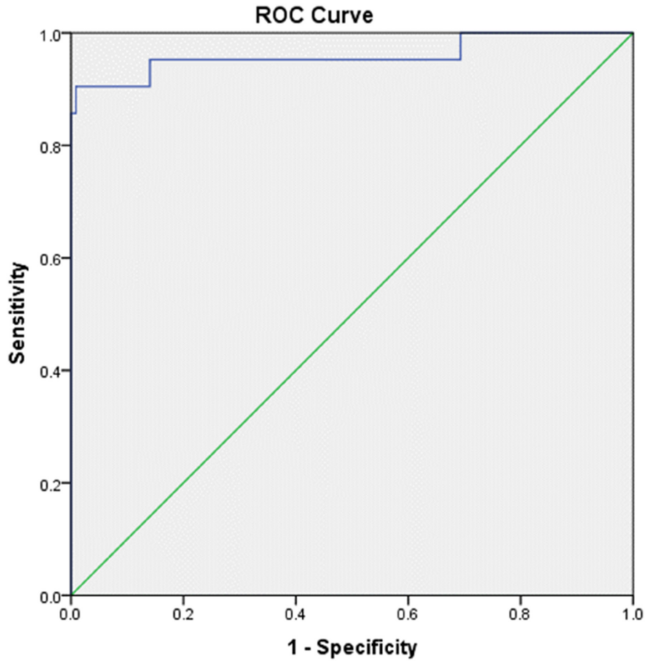

FIGURE 3 PP fasting plasma glucose – ROC curve for PP GI prediction adjusted for maternal age, BMI, maternal ethnicity, and pregnancy weight gain. Postpartum (PP) FPG AUC: 0.96 95%; CI: 0.89–0.99.

with a 2-h 75 g OGTT could be limited to women with a pGCD59 > 1.9 SPU. These findings must be taken in the context of a generated Youden index of 16.85 which suggests suboptimal diagnostic accuracy. Accounting for all the indicators presented in Table 4, however, the proposed cut-off is of good clinical utility particularly in out ruling women in need of a PP OGTT. Moreover, due to its ease of application and utilisation (one non-fasting blood sample), it can be considered a more patient-friendly approach to evaluate PP GI and necessitating less utilisation of resources. The difference observed in the pGCD59 cut-offs between this study and that of Benhalima et al., while substantiating the utility of pGCD59 to identify women with PP GI, it also highlights the pressing need for larger studies to confirm the optimum decision threshold for use in this clinical context.

The study has several limitations. The sample size is relatively small. However, the numbers with dysglycaemia PP (15.7%) are consistent with the previously reported GDM prevalence and PP GI prevalence in an Irish population.[30,31] We could only assess the development of GI as none of the study participants developed T2DM PP. We did not assess the ability of pGCD59 to identify IFG and IGT separately due to the low number of IGT cases (IGT without IFG $n = 3$). Breastfeeding has been shown to play a role in reducing PP GI,[32] however, we did not have data on the PP breastfeeding rates. The COVID-19 pandemic has had a significant impact on the scientific world, including this study. The restrictions and lockdowns have led to a delay in the PP OGTT appointment (usually performed at 12 weeks postdelivery). More so, in our cohort, 60.8% of women underwent the PP OGTT, lower than the expected rates[33] which also reflects the impact of the pandemic. A study by Gosh et al[14] which found that pGCD59 can identify subjects with T2DM with a very high accuracy. The PP testing in this study has been done in the early PP period. As the risk of progression to GI or T2DM following GDM increases over time, the ability of pGCD59 to predict dysglycaemia and pGCD59 diagnostic accuracy parameters may also improve with longer follow-up data. Lastly, we did not have data on HbA1c levels at the time of the PP OGTT. However, previous studies have identified a prediction accuracy of PP HbA1c to identify PP GI ranging from AUC: 0.54 (95% CI: 0.43–0.65) to 0.70 (95% CI: 0.62–0.79).[24,34]

While further research is required, our study found that PP pGCD9 might be a promising biomarker in the screening for PP GI. Furthermore, pGCD59 may be a useful alternative to the OGTT for PP screening that may simplify

the process and result in increased patient test uptake. A single non-fasting sample able to identify women not at risk of developing PP GI and therefore do not have to undergo the PP 2 h 75 g OGTT would significantly increase compliance with the test and simplify the PP screening practice. To further investigate pGCD59's clinical value as a biomarker to test for PP GI, larger studies in a more ethnically diverse cohort, with extended follow-up and longitudinal monitoring are needed.

AUTHOR CONTRIBUTIONS

Delia Bogdanet, Michelle Toth-Castillo, Miguel A. Luque-Fernandez and Jose Halperin analysed the data. Delia Bogdanet, Helen Doheny, Paula M. O'Shea and, Fidelma P. Dunne, contributed to the study design, data analysis and writing of the manuscript. All authors (Delia Bogdanet, Michelle Toth-Castillo, Helen Doheny, Louise Dervan, Miguel A. Luque-Fernandez, Jose Halperin, Paula M. O'Shea, Fidelma P. Dunne) made substantial contributions to the interpretation of data, revised the manuscript critically for important intellectual content and approved the final version to be published. DB is responsible for the integrity of the work as a whole.

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CONFLICT OF INTEREST STATEMENT

JAH has a financial interest in Mellitus LLC. Mellitus has licensed intellectual property for the technology used in this research and in developing diagnostic tools for diabetes. The interests of J.A.H. are reviewed and are managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. Reagents and laboratory analysis for pGCD59 were provided by Prof Jose Halperin.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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