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ATLANTIC DIP-Simplifying the follow-up of women with previous gestational diabetes (GDM)

Short running title

Simplifying follow-up post GDM

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Abbreviations

Gestational diabetes (GDM); fasting plasma glucose (FPG); oral glucose tolerance test (OGTT); American Diabetes Association (ADA); positive predictive value (PPV); negative predictive value (NPV); normal glucose tolerance (NGT); American Congress of Obstetricians and Gynaecologists (ACOG); International Association of Diabetes in Pregnancy Study Groups (IADPSG); International Federation of Clinical Chemistry (IFCC); National Glycohaemoglobin Standardisation Program (NGSP); Receiver-operator characteristic (ROC)

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Abstract

Objective

Previous gestational diabetes (GDM) is associated with a significant lifetime risk of type 2 diabetes. We assessed the performance of HbA1c and fasting plasma glucose (FPG) against 75g oral glucose tolerance testing (OGTT) for follow-up screening of these women.

Methods

266 women with previous GDM underwent follow-up testing (mean of 2.6 years [SD 1.0] post index pregnancy) using HbA1c (100%), and 75g OGTT (89%) or FPG (11%). American Diabetes Association (ADA) criteria for abnormal glucose tolerance were used.

Design

Cohort study

Results

The ADA HbA1c high-risk cut-off of 39 mmol/mol yielded sensitivity of 45% (95%CI 32,59), specificity of 84% (95%CI 78,88), NPV of 87% (95%CI 82,91), and PPV of 39% (95%CI 27,52) for detecting abnormal glucose tolerance. ADA high-risk criterion for FPG of 5.6 mmol/L showed sensitivity of 80% (95%CI 66,89), specificity 100% (95%CI 98,100), NPV 96% (95%CI 92,98), and PPV 100% (95%CI 91,100). Combining HbA1c ≥ 39 mmol/mol with FPG ≥ 5.6 mmol/L yielded sensitivity of 90% (95%CI 78,96), specificity 84% (95%CI 78,88), NPV 97% (95%CI 94,99) and PPV 56% (95%CI 45,66).

Conclusions

Combining test cut-offs of 5.6 mmol/L and HbA1c 39 mmol/mol identifies 90% of women with abnormal glucose tolerance post GDM (mean 2.6 years [SD1.0] post index pregnancy). Applying this follow-up strategy will reduce the number of OGTT tests required by 69%, will be more convenient for women and their practitioners, and is likely to lead to increased

uptake of long-term retesting by these women whose risk of type 2 diabetes is substantially increased.

Introduction

Gestational diabetes mellitus (GDM) is associated with a significant lifetime risk of progression to type 2 diabetes. A recent meta-analysis drawing on studies conducted over the last 40 years showed a relative risk of 7.7 for the future development of type 2 diabetes in women with a history of GDM versus women with normal glucose tolerance (NGT) in pregnancy [1]. Regular, effective follow-up is therefore essential. The benefits of this are twofold; firstly, re-testing allows early detection of those women who have progressed to diabetes, or who have blood glucose concentrations in the pre-diabetic range. This enables the timely commencement of appropriate treatment to prevent diabetes related complications, or ideally, intervention to prevent progression to overt diabetes. The potential for both intensive lifestyle intervention and metformin treatment to delay or prevent the onset of type 2 diabetes in these women has been previously demonstrated by the Diabetes Prevention Program study [2]. Both interventions were shown to help prevent or delay the onset of type 2 diabetes in women with previous GDM (risk reduction of 53% for intensive lifestyle intervention and 50% for metformin treatment). Secondly, regular effective follow-up reduces the risk of undiagnosed type 2 diabetes predating a subsequent pregnancy, and the increased

risk to mother and foetus associated with such an event [3].

Despite this, post partum retesting is haphazard and uptake remains low [4-11], with FPG or OGTT performed in only 33-58% of women with previous GDM. Guidelines on how best to follow women with GDM in the post-partum period and beyond vary significantly. The American Diabetes Association (ADA)[12], American Congress of Obstetricians and Gynaecologists (ACOG)[13], and the Fifth International Workshop Conference on Gestational Diabetes[14] all recommend post-partum follow-up with a 75g oral glucose tolerance test (OGTT) at 6-12 weeks, while the British National Institute for Clinical Excellence (NICE) guidelines[15] recommend follow-up with fasting plasma glucose (FPG) alone 6-12 weeks post-partum. Beyond the immediate post partum period, even more variation is evident. NICE guidelines recommend yearly FPG, while ADA guidelines recommend follow up with either fasting plasma glucose (FPG), haemoglobin A1c (HbA1c), or OGTT on a 1-3 yearly basis after the initial post partum OGTT. ACOG guidelines recommend follow up with either OGTT or FPG at 3 yearly intervals. The 75g OGTT is the current 'gold standard' for diagnosis of abnormal glucose tolerance, and is the only method by which impaired glucose tolerance (IGT), which is associated with progression to type 2 diabetes [16], and, independently, increased cardiovascular disease risk[17, 18] can be diagnosed. However, for the patient, a minimum two-hour time commitment is required, while for the healthcare provider, there are increased costs incurred due to the use of a glucose load, additional

phlebotomy services, clinic time and laboratory analyses. Using FPG alone, however, misses up to 60% of women with abnormal 2-hour glucose values [19]. A previous study from our research group has shown that the prevalence of GDM by International Association of Diabetes in Pregnancy Study Groups (IADPSG) criteria during a period of universal screening was 12.4%[20]. The total number of births for the region encompassed in this study is approximately 10,000 per annum[21], meaning over 1200 women each year in this region alone would meet IADPSG criteria for GDM. Although not all of these will be new diagnoses, a yearly OGTT for each woman with a history of GDM, as is our current policy, clearly represents a significant clinical and economic burden. Given that retesting using the 75g OGTT in clinical practice has been shown to be suboptimal [4-11], we set out to design a pragmatic and cost-effective recall and retesting program using FPG, HbA1c, or a combination of both, to detect progression to abnormal glucose tolerance in women with previous gestational diabetes.

Materials and Methods

We recruited women across four centres in the ATLANTIC DIP collaborative who had undergone a 75g OGTT during pregnancy in the preceding five years (2006-2010), and who had values diagnostic of GDM, using IADPSG criteria. This 5-year period included an 18-month period of universal screening for women attending for antenatal care. Otherwise, risk factor based screening was employed. World Health Organisation criteria for diagnosis of GDM were used prior to 2010. These women were identified using our clinical database

(DIAMOND, Hicom, Woking) and were invited to attend their closest study centre for retesting. All women were sent a letter, with a follow-up telephone call to arrange an appointment. Of 468 women invited for testing, 342 accepted, and 270 (78%) attended. Of these, 4 did not have valid HbA1c measurements, leaving a cohort of 266 women entered into this study. All participants gave informed consent for participation in this prospective cohort study, and institutional research ethics committee approval was obtained prior to the commencement of the study. Women who met IADPSG criteria only (n=92; 35%), but not WHO criteria, which were in use at the time of the index pregnancy, were informed that a change in diagnostic criteria and clinical practice had occurred since the index pregnancy. All women had clinical and laboratory parameters from their index pregnancy entered into our clinical database. Of these 266 women, 41 women (15%) were known to have abnormal glucose tolerance on 75g OGTT at their first postpartum visit, 156 women (59%) were known to have normal glucose tolerance on a 12 week postpartum 75g OGTT, while 69 (26%) had not undergone OGTT in the early postpartum period. A 75g OGTT was performed in 89% (n=237), while FPG alone was performed on the remaining 11% (n=29). All women had HbA1c levels drawn and participated in a structured standardised interview. Participants underwent an overnight fast, after which blood was drawn into a fluoride oxalate tube for FPG, and into an ethylenediaminetetraacetic acid (EDTA) tube for HbA1c. A 75g glucose load was given (Polycal®), and a 2-hour post-load plasma glucose drawn. All assays were carried out in the same laboratory (University Hospital Galway) by persons unaware of the participant's clinical history. Plasma glucose was measured using the hexokinase assay on the Roche Modular <P> Analytics system. The between run analytical coefficient of variation (CV_a%) at a mean plasma glucose of 2.97 mmol/L (53.5 mg/dl) and 18.88 mmol/L (340.2

mg/dl) was 1.9% and 1.5% respectively.

HbA1c was measured by reverse phase cation exchange chromatography using the Menarini HA8160 automated haemoglobin analyser. The method was calibrated according to International Federation of Clinical Chemistry (IFCC) standardisation[22]. Diabetes Control and Complications Trial (DCCT) units (%) were derived from the IFCC (mmol/mol) measurement using the IFCC-DCCT/NGSP (National Glycohaemoglobin Standardisation Program) master equation. The between run CV_a% at a mean HbA_{1c} of 41.6 mmol/mol (Derived DCCT 6%) and 100.5 mmol/mol (Derived DCCT 11.4%) was 2.0 and 1.3% respectively. ADA criteria were employed for the diagnosis of impaired fasting glucose (IFG), IGT, and diabetes mellitus.

Statistical analysis was carried out using PASW Statistics (formerly known as SPSS) version 18 (IBM, New York), and Minitab 15 (Minitab Inc, Pennsylvania). Diagnostic accuracy was calculated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver-operator characteristic (ROC) curves were constructed for FPG and HbA_{1c}, using the OGTT as the 'gold standard' for diagnosis of abnormal glucose tolerance, and the area under the curve (AuROC) calculated.

Differences between mean values of normally distributed continuous variables were compared using Student's t-test. Differences between the medians of non-parametrically distributed variables were compared using the Mann-Whitney U test.

Results

Of 266 women attending for retesting, 89% (n=237) had a 75g OGTT, while the remaining 11% (n=29: 19 of whom were known to have abnormal glucose tolerance at their first postpartum visit) had FPG only. Baseline characteristics are shown in table 1. Of the 266 women tested, 15.4% (n=41) were known to have abnormal glucose tolerance at their first post partum visit (6.8% IFG, 2.6% IGT, 4.5% combined IFG/IGT, 1.5% diabetes mellitus). At retesting, 81.6% (n=217) had normal glucose tolerance, while 18.4% (n=49; 95% CI 14.2 to 23.5) had abnormal glucose tolerance (IFG, n=30; 11.3%; IGT, n=8; 3%, combined IFG/IGT, n=5, 1.9%; diabetes mellitus, n=6, 2.3%). Of those women meeting IADPSG criteria, but not WHO criteria (n=95), 12% (n=11) had abnormal glucose tolerance. Baseline characteristics and results at rescreening are summarised in table 1.

HbA1c

Table 2 shows the test accuracy of HbA1c at defined thresholds for predicting abnormal glucose tolerance by ADA criteria. Using the recommended ADA HbA1c cut-off for high-risk individuals of 39 mmol/mol (5.7%) yielded a sensitivity of 45% (95% CI 32 to 59), specificity of 84% (95% CI 78 to 88), NPV of 87% (95% CI 82 to 91), and PPV of 39% (95% CI 27 to 52). ROC curve analysis for HbA1c to predict any abnormal glucose tolerance gave an AuROC of 0.742 (95% CI 0.663 to 0.821). AuROC for 2-hour glucose ≥ 7.8 mmol/L was 0.714 (95% CI 0.591 to 0.836).

FPG

Using the ADA high-risk criterion for FPG ≥ 5.6 mmol/L to identify any degree of abnormal glucose tolerance, sensitivity was 80% (95% CI 66 to 89), specificity was 100% (95% CI 98

to 100), NPV was 96% (95% CI 92 to 98), and PPV was 100% (95% CI 91 to 100). The characteristics for different cut-offs of FPG when used to screen for abnormal glucose tolerance are summarised in table 3. ROC curve analysis examining the ability of FPG alone to predict IGT (i.e. to predict a 2 hr plasma glucose of ≥ 7.8 mmol/l showed an AuROC of 0.609 (95% CI 0.438 to 0.779).

HbA1c and FPG combined

The above results show suboptimal performance using HbA1c or FPG alone to detect abnormal glucose tolerance in this cohort. We therefore used defined cut-offs of a combination of HbA1c and FPG to identify higher-risk women who should proceed to confirmatory glucose testing with a 75g OGTT. Women were classified as meeting the criteria if they met either the specified HbA1c or the FPG value. We calculated the negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity for each defined cut-off of a combination of HbA1c and FPG values. Results are shown in table 4.

Discussion

The objective of this study was to evaluate the potential of a new follow-up testing regimen using a combination of FPG and HbA1c to predict progression to abnormal glucose tolerance post-partum, following initial post-partum assessment with a 75g OGTT. Our data suggest that, by combining the decision threshold for HbA1c ≥ 39 mmol/mol (5.7%) and/or an FPG of ≥ 5.6 mmol/L, 90% (95% CI 78 to 96) of patients with any degree of glucose abnormality on a 75g OGTT are identified, with a specificity of 84% (95% CI 78 to 88). Employing this

new approach (requiring only a single blood draw) to identify those higher risk women who should proceed to a 75g OGTT would reduce the number of OGTTs performed by almost seventy percent. At an estimated cost of Euro 35,200 per 1000 women tested [23] using 75g OGTT, this new screening regime would reduce the cost of OGTT screening to Euro 10,560 although this would of course by offset by the cost of measuring HbA1c and FPG in each patient.

In our cohort, employing this new screening approach (HbA1c ≥ 39 mmol/mol or FPG of ≥ 5.6 mmol/L]), identified a total of 79 women who met the criteria, 44 of whom (56%) demonstrate abnormal glucose tolerance using either the OGTT or FPG. In addition, we now identify a further subgroup of women (44%, n=35) who have normal glucose tolerance on OGTT, but meet our criteria by virtue of their HbA1c value alone. As the HbA1c cut-off of 39 mmol/mol is the ADA criterion value at which measures to delay or prevent progression to type 2 diabetes should be instituted[12], we would suggest that a 75g oral glucose tolerance test adds little to the clinical course of these women.

Therefore, those women with a history of gestational diabetes, meeting either the HbA1c cut-off of 39 mmol/mol, or FPG of 5.6 mmol/L, should undergo at least three-yearly, and ideally annual[12-15], follow-up for assessment of progression to diabetes with HbA1c and FPG. At a minimum, individualised dietary and exercise advice should be offered to these high-risk women. However, given the proven efficacy of a structured lifestyle intervention program [2], this should be offered where possible, and a randomised controlled trial is underway at our

centre to examine the clinical impact and cost-effectiveness of such a program in women with previous GDM [24]. Of course, if further pregnancy is desired, closer clinical follow-up is needed.

The results of this study, interestingly, are similar to those in recent papers by Megia et al [25] and Picon et al[26], who employ similar approaches to predict abnormal postpartum glucose tolerance, albeit describing a lower cut off; HbA1c of 37mmol/mol (5.5%; Megia). There are several important differences between the studies, however. Our study shows a sensitivity of 90% versus 82% (Megia) and 83% (Picon), while we demonstrate a higher NPV (97%) versus Picon et al (85%). This is a key difference when designing a pragmatic retesting program for women with previous GDM. For these purposes, a higher sensitivity and NPV are desirable, and in this cohort, do not result in an unacceptable increase in confirmatory testing; the proportion of women meeting HbA1c/ FPG criteria, and therefore requiring confirmatory testing, is 31% as compared to 29% in Megia et al and 47% in Picon et al. Both Megia and Picon's studies involve higher risk cohorts, using the National Diabetes Data Group criteria for GDM as opposed to the newer, more stringent, IADPSG criteria, and accordingly, demonstrate a higher prevalence of abnormal glucose tolerance using OGTT; 45.9% in Picon et al and 27.8% in Megia et al. This is despite a shorter interval to postpartum retesting- 3 months (Megia) and one year (Picon) versus 2.6 years in our cohort. Other important differences include the ethnic composition of the cohorts- our cohort is 100% white European, compared to 8.5% of Megia et al's cohort being comprised of ethnic minorities (predominantly Arabic and Hispanic). Differences in HbA1c between ethnic groups have

been well described previously [27], and our findings may therefore be only applicable to Caucasian women. Given the relatively low GDM prevalence of 12.4% in previous studies from our group (compared to the 17.8% across all HAPO centres [28]) the overall burden of follow-up testing, although significant, may be less than other centres. Also, the HbA1c assay used in the Megia and Picon studies is DCCT aligned, while our assay is fully metrologically traceable to the newer IFCC standard.

Another study by Kim et al [29] in 54 women with a history of GDM further demonstrates the limitations of using HbA1c in isolation to predict abnormal glucose tolerance, showing an AuROC of 0.76 for abnormal glucose tolerance on OGTT, and a sensitivity of 65% and specificity of 68% for predicting abnormal glucose tolerance when an HbA1c cut-off of greater than or equal to 5.7% (39 mmol/mol) is used.

One of the limitations in our study is that 11% of women (n=29) did not undergo a repeat OGTT for this study, but had fasting glucose levels only. Removing these women from the analysis, and taking the proposed cut-offs of HbA1c of 39 mmol/mol (5.7%) and fasting glucose of 5.6 mmol/L, the sensitivity drops slightly to 85% (95% CI 70, 94), with a slightly increased specificity of 86% (95% CI 80, 90). PPV and NPV are similar at 50% (95% CI 38, 62) and 97% (95% CI 94, 99) respectively. However, given that those women who had fasting glucose levels only represent a higher-risk group (69% of these 29 women were known to have abnormal glucose tolerance at their first post-partum visit), we feel the best approach is to include these women in the analysis. This approach would also be similar to

that taken in the clinical management of these women. Also, the majority of the women invited for retesting for this study (89%) underwent an OGTT. Offering the option of just a single blood draw for FPG and HbA1c (or even a single non-fasting sample for HbA1c alone) may well have a significant effect on the relatively low (58%) uptake of our offer of retesting. Although this study demonstrates that our approach is clinically feasible, a randomised controlled trial to compare uptake and effectiveness of the various testing modalities would be useful.

In summary, the combination of HbA1c and FPG measurements to predict abnormal glucose tolerance shows results superior to either one used alone. 90% of women with abnormal glucose tolerance are identified using cut offs of greater than or equal to 39 mmol/mol for HbA1c or 5.6 mmol/l for fasting plasma glucose, while reducing the number of OGTTs performed by over two-thirds. This proposed approach is likely to have a significant economic and social benefit from both a patient and healthcare provider perspective, although detailed economic evaluation will be necessary to provide an accurate cost-benefit analysis.

Declaration of Interest/Funding

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Contribution statement

EN was involved in the study design, collected and analysed data, and wrote the manuscript.

CC was involved in the study design, collected and analysed data and reviewed the manuscript. LC was involved in study design, collected data and reviewed the manuscript. GA was involved in study design, analysed data, and reviewed the manuscript. BK collected data and reviewed the manuscript. JI was involved in study design, researched data and reviewed the manuscript. AO'D was involved in study design, researched data and reviewed the manuscript. JN, BMG, and CO'N were involved in study design. PO'S was involved in the study design, analysed data and reviewed the manuscript. FD is ATLANTIC DIP PI and was involved in study design, analysed data, edited the manuscript and made the decision to publish.

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ATLANTIC DIP Collaborators

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