Abnormal glucose tolerance post-gestational diabetes mellitus as defined by the International Association of Diabetes and Pregnancy Study Groups criteria

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Abstract

Objective: An increase in gestational diabetes mellitus (GDM) prevalence has been demonstrated across many countries with adoption of the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria. Here, we determine the cumulative incidence of abnormal glucose tolerance among women with previous GDM, and identify clinical risk factors predicting this.

Design: Two hundred and seventy women with previous IADPSG-defined GDM were prospectively followed up for 5 years (mean 2.6) post-index pregnancy, and compared with 388 women with normal glucose tolerance (NGT) in pregnancy.

Methods: Cumulative incidence of abnormal glucose tolerance (using American Diabetes Association criteria for impaired fasting glucose, impaired glucose tolerance and diabetes) was determined using the Kaplan–Meier method of survival analysis. Cox regression models were constructed to test for factors predicting abnormal glucose tolerance.

Results: Twenty-six percent of women with previous GDM had abnormal glucose tolerance vs 4% with NGT, with the log-rank test demonstrating significantly different survival curves ($P < 0.001$). Women meeting IADPSG, but not the World Health Organization (WHO) 1999 criteria, had a lower cumulative incidence than women meeting both sets of criteria, both in the early post-partum period (4.2% vs 21.7%, $P < 0.001$) and at longer-term follow-up (13.7% vs 32.6%, $P < 0.001$). Predictive factors were glucose levels on the pregnancy oral glucose tolerance test, family history of diabetes, gestational week at testing, and BMI at follow-up.

Conclusions: The proportion of women developing abnormal glucose tolerance remains high among those with IADPSG-defined GDM. This demonstrates the need for continued close follow-up, although the optimal frequency and method needs further study.

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Introduction

The first diagnostic criteria for gestational diabetes mellitus (GDM) were published by O'Sullivan and Mahan in 1964 (1). These criteria (and their modified forms:

the National Diabetes Data Group (2) and Carpenter–Coustan criteria) (3) identified women at greatly increased risk of future diabetes (cumulative incidence

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60% at 16 years) (4). The World Health Organization (WHO) criteria (1980, revised 1985 and 1999) (5) used the same criteria as for diagnosis of diabetes mellitus and impaired glucose tolerance (IGT) in non-pregnant adults. Therefore, none was based on the prediction of pregnancy outcomes. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed new diagnostic criteria (6) based on perinatal outcomes, using data from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study (7). However, given the paucity of data on the effect of application of the new criteria on clinical outcomes, as balanced against the resource and clinical implications of the increase in GDM prevalence seen with the newer criteria (17.8%, range 9.8–25.5%, across HAPO study sites) (8), debate regarding their adoption continues. While WHO have adopted these criteria (9), the National Institutes of Health (10) and American College of Obstetricians and Gynecologists (11) have both recommended to retain the Carpenter–Coustan criteria, while the American Diabetes Association (ADA) adopted the IADPSG criteria in 2011 (12), and now present them as an alternative to the Carpenter–Coustan/National Diabetes Data Group criteria (13). Given the on-going debate, any data on foetal or maternal outcomes, both perinatally and longer-term, when the new criteria are applied, will be useful. However, as cohorts defined using the new criteria include women with milder degrees of glycaemic abnormality than those identified using older criteria, the longer-term risk of abnormal glucose tolerance may be less than when the older criteria are used.

Using IADPSG criteria, our group has shown a 12.4% prevalence of GDM, employing universal screening, as compared with 9.4% using the WHO 1999 criteria (14), while 19% of women with IADPSG-defined GDM demonstrated abnormal glucose tolerance (defined as impaired fasting glucose (IFG), IGT, or type 2 diabetes, using ADA criteria) at testing up to 6 months after delivery (15). Our primary objective in this study was to determine the cumulative incidence of abnormal glucose tolerance up to 5 years post-partum (the time period during which the cumulative incidence of diabetes shows the most marked increase) (16) in a cohort of women meeting IADPSG criteria for GDM. Our secondary aim was to identify which routinely available clinical variables are useful in predicting which women are more likely to progress to abnormal glucose tolerance.

Subjects and methods

From January 2007 to December 2010, women attending five antenatal care centres were screened for GDM using a one-step method (75 g oral glucose tolerance test (OGTT) with fasting, 1 and 2-h values). Women who met IADPSG criteria for the diagnosis of GDM from four of the five centres were eligible for inclusion in this study (ATLANTIC-DIP 2: GDM screening and intervention in the community). The remaining centre was not included due to practical and resource constraints. Women were invited to participate using an invitation letter, with a follow-up telephone call if there was no response. If a participant failed to attend a scheduled appointment, they were contacted again by telephone, and invited to re-attend.

The original study period (during the index pregnancy) for this cohort included an 18-month period of universal screening (all pregnant women presenting for antenatal care with an estimated last menstrual period between September 2007 and March 2009 were offered a 2-h 75 g OGTT). Selective screening (women with GDM risk factors only) was otherwise used. Women underwent an OGTT before the 24- to 28-week window if there was a previous history of GDM or if glycosuria was present, with a second OGTT performed at 24–28 weeks if the first was negative. Modified WHO 1999 diagnostic criteria for IFG/GDM (fasting plasma glucose (FPG) ≥ 6.1 mmol/L, 2-h glucose ≥ 7.8 mmol/L) were in clinical use during the study. If GDM was diagnosed, women received dietary and lifestyle advice and were instructed in self-monitoring of blood glucose (SMBG). If fasting (<5.3 mmol/L) and 1-h postprandial (<7.8 mmol/L) glucose targets were not met, insulin was commenced. Although modified WHO criteria were in clinical use at the time of the index pregnancy, women were classified retrospectively as either GDM or normal glucose tolerance (NGT) according to the IADPSG criteria (fasting ≥ 5.1 mmol/L, 1-h ≥ 10.0 mmol/L, 2-h ≥ 8.5 mmol/L).

Exclusion criteria were current pregnancy and non-white European ethnicity. The rationale for the latter exclusion criterion was to control for the potential bias of ethnicity; although women of non-white ethnicity accounted for only 7.1% of our population screened for GDM, they accounted for 16.7% of GDM diagnoses. Inclusion of this group would be likely therefore to overestimate risk for the majority of our population. Also, as our focus was on the progression to IFG, IGT

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and type 2 diabetes among women with previous GDM, we excluded women with a clinical diagnosis of type 1 diabetes following the index pregnancy ($n=3$ in the GDM group), who are likely to have a different underlying pathophysiology. A randomly selected control group, tested during the same period, but not meeting IADPSG criteria, and using the same exclusion criteria, was also invited (NGT group). Of note, women with twin pregnancies were included in the analysis.

All women with GDM were invited back for a 75 g OGTT at 12 weeks post-partum, as part of routine care, and were discharged back to their general practitioner if diabetes was not diagnosed. Women known to have type 2 diabetes, impaired glucose tolerance, or IFG ($n=42$) at this post-partum test were scheduled for retesting for the purposes of the current study with FPG and haemoglobin A1c (HbA1c) only rather than a 75 g OGTT and HbA1c. These women were included in the analysis as meeting the primary outcome for this study. Following an 8- to 12-h fast, and informed consent, participants underwent a 75 g OGTT, with plasma glucose values taken at 0 and 120 min. Samples for lipid profile, haemoglobin A1c (HbA1c) and Homeostatic Model Assessment 2-Insulin Resistance (HOMA2-IR) determination were also obtained, detailed results of which have been reported in separate papers (17, 18).

The ADA criteria (12) for diabetes (fasting glucose ≥ 7.0 mmol/L or 2-h glucose ≥ 11.1 mmol/L), IFG (fasting glucose 5.6–6.9 mmol/L) and IGT (2-h glucose 7.8–11.0 mmol/L) were used to diagnose abnormal glucose tolerance, in line with Irish national clinical guidelines (19). A family history of diabetes was defined as having either a first- or second-degree relative with diabetes. Blood pressure was the mean of two readings (Philips M3 physiological monitor), obtained 5 min apart while sitting quietly. Weight and height were recorded (Seca 635 scales), and waist circumference was measured (WHO technique). Laboratory samples for plasma glucose were analysed using the hexokinase method (Roche Modular P Analytics Chemistry Systems). The between-run coefficient of variation for glucose at mean concentrations of 2.56, 7.11 and 16.7 mmol/L were 1.1, 0.9 and 1.0% respectively. HbA1c was measured using the Menarini HA8160 automated analyser, employing reverse-phase cation exchange chromatography, and calibrated in accordance with the International Federation for Clinical Chemistry standards. Total and HDL-cholesterol, and serum triglycerides, were determined using the Roche Modular Analytics <P> Chemistry Systems, while LDL-cholesterol was calculated using the Friedewald equation.

Ethics committee approval

Relevant regional research ethics committee approval (Clinical Research Ethics Committee, Galway University Hospitals) was obtained before recruitment.

Statistical analysis

Statistical analysis was carried out using SPSS version 20 and Minitab version 15 (State College, PA, USA). Cumulative incidence of abnormal glucose tolerance was determined using the Kaplan–Meier method of survival analysis to account for time elapsed between delivery and retesting for abnormal glucose tolerance. To investigate if women progressing to abnormal glucose tolerance post-partum could be identified on the basis of clinical risk factors assessed at the time of delivery of the index pregnancy, we constructed Cox proportional hazards regression models, using forward stepwise entry with a pre-selected set of predictive factors, with abnormal glucose tolerance up to 5 years post-partum as the outcome variable. We constructed two main explanatory models: one using variables available at the time of delivery only and one including variables available at follow-up testing for this study (Supplementary Material and Supplementary Table 1, see section on supplementary data given at the end of this article). We also constructed models including and excluding women who had abnormal glucose tolerance at the 12-week post-partum test, in order to control for the effect of time since delivery, as women with persistent abnormalities on the OGTT at 12 weeks post-partum are likely to have a greater degree of abnormal glucose tolerance than those who are normal initially, but develop abnormal glucose tolerance later. Only variables contributing significantly to the fit were included in the final models. Student's *t*-test and Mann–Whitney *U* test were used to assess between-group differences in means and medians respectively of baseline characteristics. Statistical significance was set at $P<0.05$.

Results

We identified 4405 potential participants (491 meeting IADPSG criteria for GDM, 3914 with NGT) from the 5500 universally screened participants in the original ATLANTIC-DIP study (Fig. 1). In addition, we identified 874 (184 with IADPSG-defined GDM, 690 with NGT) women who were tested using selective screening. A total of 675 women of white European origin were identified

Figure 1

Flow diagram for study participants. GDM, gestational diabetes mellitus; NGT, normal glucose tolerance.

who met IADPSG GDM criteria between 2007 and 2010. Of these women, 607 met the inclusion criteria for this study, while 262 declined or could not be contacted. Of those agreeing to participate, 72 (21%) did not attend, while 3 did not complete testing. Two hundred seventy women (45% of eligible population) attended and completed retesting. Of the control group of 2254 women invited, 500 agreed to participate – 112 (22%) did not attend, while 388 completed retesting.

Comparison of the groups at retesting for this study is shown in Table 1. The mean duration of follow-up was

shorter in women with previous IADPSG-defined GDM (2.6 vs 3.3 years in women with NGT, $P<0.001$). Women with IADPSG-defined GDM were younger than those with NGT (36.6 vs 37.6 years, $P=0.022$). Nine percent of women with IADPSG-defined GDM had undergone the index pregnancy OGTT before 24 weeks gestation, as compared with 5% with IADPSG-defined NGT ($P=0.046$). Women with previous GDM had a higher BMI, higher glucose and HbA1c values; a more adverse lipid profile; and higher blood pressure. They also had higher mean glucose values at each point on the pregnancy OGTT,

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Table 1 Characteristics of participants meeting criteria for IADPSG-defined GDM and NGT. Figures represent means (s.d.) unless otherwise stated.

Variable	GDM (n=270)	NGT (n=388)	95% CI for difference	P value for difference
Characteristics at the time of the index pregnancy				
Age in years at time of delivery in index pregnancy	34.0 (5.0)	34.2 (5.1)	−1.0, 0.6	0.626
BMI in kg/m ² at time of pregnancy OGTT*	31.3 (6.6)	27.1 (4.3)	3.2, 5.1	<0.001
SBP in mmHg at time of pregnancy OGTT**	122.8 (12.3)	119.1 (12.2)	1.7, 5.8	<0.001
DBP in mmHg at time of pregnancy OGTT**	73.9 (8.7)	71.0 (8.8)	1.5, 4.4	<0.001
Gestational week OGTT performed	27.3 (4.2)	26.4 (2.6)	0.4, 1.5	0.001
Pregnancy fasting glucose (mmol/L)	5.16 (0.89)	4.31 (0.32)	0.74, 0.96	<0.001
1-h glucose (mmol/L)	10.37 (1.73)	6.75 (1.61)	3.4, 3.9	<0.001
2-h glucose (mmol/L)	8.13 (2.06)	5.42 (1.29)	2.4, 3.0	<0.001
Proportion using insulin in index pregnancy [§]	35.6%	2.1%	27.7, 39.5	<0.001
Offspring birth weight in kg	3.47 (0.69)	3.56 (0.62)	−0.20, 0.01	0.076
Pre-eclampsia or pregnancy-induced hypertension in index pregnancy (%)	24.9%	11.0%	8.1, 20.1	<0.001
Polyhydramnios (%)	7.8%	2.8%	1.5, 9.0	0.005
Congenital malformation present (%)	1.5%	4.1%	−0.1, 5.3	0.040
Shoulder dystocia (%)	0.7%	3.1%	0.0, 4.7	0.053
Neonatal death (%)	0.4%	1.8%	−0.5, 3.0	0.095
Neonatal intensive care unit admission required (%)	22.2%	14.9%	1.3, 13.5	0.011
Caesarean section (%)	47.8%	26.8%	13.5, 28.2	<0.001
Emergency Caesarean section (%)	19.3%	11.3%	2.4, 13.8	0.005
Breastfeeding status relating to index pregnancy				
Any breastfeeding (%)	59%	55.2%	−3.8, 11.5	0.184
Continued post hospital discharge (%)	45.6%	53.4%	0.0, 15.4	0.029
Continued 1 month or more (%)	41.5%	44.6%	−4.5, 10.7	0.239
Continued 3 months or more (%)	31.9%	35.8%	−3.4, 11.2	0.165
Characteristics at retesting for this study				
Age (years)	36.6 (5.0)	37.6 (5.1)	0.13, 1.70	0.022
Years since delivery	2.6 (1.0)	3.3 (0.7)	0.6, 0.9	<0.001
BMI (kg/m ²)	29.7 (6.9)	26.1 (4.9)	2.6, 4.5	<0.001
Waist circumference (cm)	93.2 (16.3)	84.5 (12.5)	6.4, 11.1	<0.001
Fasting glucose (mmol/L)	5.07 (0.95)	4.65 (0.41)	0.30, 0.54	<0.001
2-h glucose (mmol/L)	5.62 (1.75)	4.85 (1.02)	0.53, 1.02	<0.001
HbA1c IFCC (mmol/mol)	36.2 (4.8)	33.6 (2.7)	1.9, 3.2	<0.001
HbA1c DCCT (%)	5.56 (0.45)	5.32 (0.26)	0.18, 0.30	<0.001
Total cholesterol (mmol/L)	5.0 (1.0)	4.7 (0.8)	0.2, 0.5	<0.001
Triglycerides (mmol/L)	1.3 (0.9)	0.9 (0.5)	0.3, 0.5	<0.001
HDL-cholesterol (mmol/L)	1.5 (0.4)	1.6 (0.4)	0.1, 0.2	<0.001
LDL-cholesterol (mmol/L)	2.9 (0.8)	2.7 (1.0)	0.1, 0.4	<0.001
SBP (mmHg)	124.7 (15.4)	116.1 (13.4)	6.4, 11.0	<0.001
DBP (mmHg)	73.6 (10.4)	68.8 (9.2)	3.2, 6.3	<0.001
Proportion with family history of diabetes (%)	65.2%	50.0%	7.5, 22.5	<0.001

*Incomplete data set – 10% of GDM and 16% of NGT participants did not have values recorded; **Incomplete data set – 15% of GDM and 16% of NGT participants did not have values recorded; [§]Note some women with WHO-defined GDM are defined as NGT using the IADPSG criteria, and were prescribed insulin during the index pregnancy.

DBP, diastolic blood pressure; GDM, gestational diabetes mellitus; HbA1c, haemoglobin A1c; IADPSG, International Association of Diabetes in Pregnancy Study Groups; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; SBP, systolic blood pressure.

and were more likely to have a family history of diabetes. There was no significant difference in the number of multiple pregnancies between the GDM and NGT groups (3% vs 2.1%, $P=0.526$).

As compared with women with IADPSG-defined GDM participating in this study, women with IADPSG-defined GDM who participated in the original ATLANTIC-DIP study, but did not attend for the current study ($n=318$),

were of similar age, had a similar BMI during pregnancy, and similar fasting glucose values ([Supplementary Table 2](#)). They did, however, have significantly lower 1 and 2-h glucose values on the pregnancy OGTT. Women with IADPSG-defined NGT attending this study ($n=388$), compared with those who did not, and had full data available from the index pregnancy ($n=3563$), were significantly older, had a significantly higher BMI during

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pregnancy, had significantly higher 2-h glucose levels on the pregnancy OGTT, and were significantly more likely to have a family history of diabetes (Supplementary Table 3).

Cumulative incidence of abnormal glucose tolerance

The survival curves in Fig. 2 demonstrate the cumulative probability of abnormal glucose tolerance at follow-up for this study, split by the IADPSG criteria into women meeting NGT and GDM criteria. When the GDM and NGT groups were tested for differences using the log-rank test, their survival curves were significantly different ($P < 0.001$). The differences remained significant when adjusted for age, BMI and family history of diabetes ($P < 0.001$). Of 270 women with previous GDM by IADPSG criteria, 10.4% met the criteria for a new diagnosis of abnormal glucose tolerance (Table 2). In addition to the 15.6% ($n = 42$) of women already known to have abnormal glucose tolerance at initial post-partum testing, this yielded a cumulative incidence of abnormal glucose tolerance of 25.9% ($n = 70$) in women with prior IADPSG-defined GDM, compared with 3.6% ($n = 14$) of those with NGT ($P = 0.001$). Of the 270 women with prior GDM, at the time abnormal glucose tolerance was diagnosed, 12.2% ($n = 33$) had IFG, 5.9% ($n = 16$) had IGT, 5.6% ($n = 15$) had combined IFG/IGT, while 2.2% ($n = 6$) had diabetes. Of 388 women with previous NGT, 1.8% ($n = 7$) had IFG, 1.5% ($n = 6$) had IGT, 0.3% had combined IFG/IGT ($n = 1$), and none had diabetes.

Prediction of progression to abnormal glucose tolerance

The Cox proportional hazards regression results are summarised in Table 3. Within the models including pregnancy variables only, fasting glucose and 1-h glucose values on the pregnancy OGTT, and family history of diabetes, proved the strongest predictors on both models. Of these, when all participants were included, family history had the highest hazard ratio at 2.04 ($P = 0.014$). Both fasting glucose and 1-h glucose values on the pregnancy OGTT were highly significant. With regard to timing of testing during the pregnancy, earlier gestation at diagnosis of GDM became significant only when women diagnosed at the 12-week post-partum visit were included. Family history of diabetes, fasting glucose and 1-h glucose all remained significantly associated with abnormal glucose tolerance when participants with abnormal glucose tolerance at 12 weeks were removed.

Figure 2

Kaplan–Meier curves showing the cumulative probability of abnormal glucose tolerance in women with previous IADPSG-defined GDM vs those with IADPSG-defined NGT. (A) includes all participants (GDM $n = 270$, NGT $n = 388$), while (B) excludes women known to have abnormal glucose tolerance at 12 week post-partum testing (GDM $n = 228$, NGT $n = 385$). Abnormal glucose tolerance is defined as any one of impaired fasting glucose, impaired glucose tolerance or diabetes, using the American Diabetes Association criteria. GDM, gestational diabetes mellitus; IADPSG, International Association of the Diabetes and Pregnancy Study Groups; NGT, normal glucose tolerance.

The model including all participants showed a log-likelihood ratio (-2LL) of 673.726 (4df, $P < 0.001$), while the model excluding participants with abnormal glucose tolerance at 12 weeks had a -2LL of 238.984, 3df, $P < 0.001$; the lower value indicating a better overall fit. When we constructed models including variables available at

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Table 2 Proportion of women with abnormal glucose tolerance at 12-week post-partum testing and at retesting for the current study.

	GDM (n=270)	NGT (n=388)	95% CI for difference	P value for difference
Number of participants with abnormal glucose tolerance at early post-partum testing				
IFG	18	0		
IGT	8	2		
IFG/IGT	12	1		
DM	4	0		
Total early post-partum	42 (15.6%)	3 (0.8%)	10.7, 19.6	0.001
Number of participants with newly diagnosed abnormal glucose tolerance at this study				
IFG	15	7		
IGT	8	4		
IFG/IGT	3	0		
DM	2	0		
Total for this study	28 (10.4%)	11 (2.8%)	3.8, 11.9	<0.001
Total number	70 (25.9%) [†]	14 (3.6%)	16.9, 28.0	0.001

[†]Added and calculated percentages differ slightly due to rounding error.

DM, diabetes mellitus; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

follow-up for this study, again, index pregnancy OGTT values (fasting, 1- and 2-h) and family history of diabetes were significant predictors, while BMI at follow-up was the only variable available since the index pregnancy associated with development of abnormal glucose tolerance. Two-hour glucose was significant only when women with abnormal glucose at 12 weeks post-partum were included in the model. With regard to models including variables available at follow-up, the model including all participants showed a -2LL of 806.84 (5df, $P<0.001$), while the model including women at follow-up only showed a better overall fit, with a -2LL of 338.07 (4df, $P<0.001$).

Comparison of modified WHO 1999 vs IADPSG criteria

When data on women attending for this study were analysed according to the modified WHO 1999 criteria in clinical use at the time of the study, 214 women met modified WHO 1999 criteria for GDM diagnosis, while 444 met NGT criteria (Supplementary Table 4 for figures for IADPSG and modified WHO criteria). The cumulative incidence of abnormal glucose tolerance was 29.4% among women with WHO-defined GDM and 4.7% among women with WHO-defined NGT. Neither of these proportions differed significantly from those seen when

Table 3 Predictive factors for the presence of abnormal glucose tolerance at any time up to 5 years post-index pregnancy ($n=658$) and abnormal glucose tolerance developing after the 12-week post-partum test ($n=613$). Two separate Cox proportional hazards regression models were constructed for each of these; the first using variables available at the time of delivery only, and the second using variables from the first model (BMI and age replaced with BMI and age at follow-up), with variables available post-delivery included.

Variable	AGT up to 5 years ($n=658$)		AGT at later follow-up only ($n=613$)	
	Index pregnancy variables only	Including variables at follow-up	Index pregnancy variables only	Including variables at follow-up
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Fasting glucose on pregnancy OGTT	1.69 (1.29, 2.21) $P<0.001$	1.52 (1.13, 2.06) $P=0.006$	2.01 (1.27, 3.20) $P=0.003$	1.99 (1.27, 3.12) $P=0.003$
1-h glucose on pregnancy OGTT	1.23 (1.07, 1.41) $P=0.004$	1.27 (1.11, 1.45) $P=0.001$	1.25 (1.02, 1.54) $P=0.032$	1.31 (1.09, 1.57) $P=0.004$
2-h glucose on pregnancy OGTT	1.1 (0.99, 1.23) $P=0.082$	1.15 (1.02, 1.29) $P=0.021$	1.07 (0.90, 1.28) $P=0.444$	1.08 (0.91, 1.77) $P=0.397$
Week of gestation at pregnancy OGTT	0.94 (0.90, 1.00) $P=0.032$	0.95 (0.90, 1.07) $P=0.068$	0.94 (0.88, 1.01) $P=0.092$	0.95 (0.88, 1.01) $P=0.103$
Family history	2.04 (1.16, 3.62) $P=0.014$	1.81 (1.04, 3.15) $P=0.035$	2.94 (1.17, 7.41) $P=0.022$	2.45 (1.07, 5.59) $P=0.033$
BMI at follow-up	N/A	1.04 (1.01, 1.29) $P=0.009$	N/A	1.05 (1.00, 1.09) $P=0.036$

HR represents increase per 1 mmol/L (18 mg/dL) of glucose concentration; per week of gestation, and per 1 kg/m² increase in BMI.

AGT, abnormal glucose tolerance; GDM, gestational diabetes mellitus; HR, hazard ratio; OGTT, oral glucose tolerance test.

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IADPSG criteria were used ($P=0.390$ for women with GDM, $P=0.421$ for women with NGT). One hundred and seventy-five women met both IADPSG and modified WHO 1999 criteria, 95 met IADPSG criteria only, 39 met modified WHO 1999 criteria only, and 349 met neither IADPSG nor modified WHO criteria. Women meeting both IADPSG and modified WHO 1999 criteria had a significantly greater cumulative incidence of abnormal glucose tolerance at follow-up than those meeting IADPSG criteria alone (32.6% vs 13.7%, $P<0.001$), or women meeting modified WHO 1999 criteria alone (32.6% vs 15.4%, $P=0.033$). There was no significant difference seen in cumulative incidence between women meeting IADPSG criteria only and those meeting modified WHO 1999 criteria only ($P=0.798$). Comparison of baseline characteristics for women meeting IADPSG criteria only and those meeting both IADPSG and modified WHO criteria are also shown in [Supplementary Table 5](#).

Risk factor-based vs universal screening

Of note, our cohort contains a group of women identified by risk factor-based screening. However, only 9% ($n=18$) of women with IADPSG-defined GDM in this cohort did not have at least one risk factor for GDM, of whom only three developed abnormal glucose tolerance by the time of this study. Overall, no difference was seen in the proportion of women with abnormal glucose tolerance post-delivery (24.6% identified during risk factor-based screening vs 26.3%, for those identified during universal screening, $P=0.782$), although it should be noted that due to the study design, time since delivery was shorter in the risk factor-screened group (1.3 vs 3.0 years, $P<0.01$). Women identified as having IADPSG-defined GDM during the universal screening period, when compared with those identified using risk factor-based screening, were slightly younger at delivery (33.6 (s.d. 5.0) vs 35.2 (s.d. 4.8) years, $P=0.024$), and had a lower (10.12 (s.d. 1.74) vs 11.2 (s.d. 1.42) mmol/L, $P<0.001$) 1-h, but similar fasting (5.15 (s.d. 0.85) vs 5.18 (s.d. 1.02) mmol/L, $P=0.790$) and 2-h (8.04 (s.d. 2.02) vs 8.39 (s.d. 2.19) mmol/L, $P=0.235$) glucose values ([Supplementary Table 6](#)).

Discussion

Our results show that, despite the IADPSG criteria being based on adverse pregnancy outcome, they still define a cohort at significantly increased future risk of abnormal glucose tolerance. Over a quarter demonstrate

abnormal glucose tolerance at this relatively short post-partum interval, as compared with women with normal glucose tolerance in pregnancy. Of note, the women with normal glucose tolerance are representative of the Irish background population in this age group, showing a similar prevalence of abnormal glucose tolerance (20). As expected, given less strict diagnostic thresholds, those women who meet the IADPSG criteria alone are at lower (although still relatively high; prevalence of 14%) risk of abnormal glucose tolerance at a mean of 2.6 years post-index pregnancy, as compared with women attending for this study who also meet the older modified WHO criteria. Of note also, 2-h glucose on the pregnancy OGTT demonstrates a less strong relationship than the fasting or 1-h value. This may be of clinical relevance; despite the increased threshold of 2-h glucose for diagnosis of GDM, as compared with the modified 1999 WHO criteria, the risk of abnormal glucose tolerance at follow-up remains similar. It should also be noted that women meeting modified WHO criteria (but not women meeting IADPSG criteria alone) would have received information about the future risk of diabetes at the time of the post-partum visit. Although no structured post-partum lifestyle programme was in place, we cannot exclude that the general advice given by either the hospital team, or the patient's primary care physician, regarding weight management after delivery could have influenced progression to abnormal glucose tolerance in this cohort. Further prospective data on women meeting IADPSG criteria only will be useful in clarifying this issue.

The factors associated with progression to abnormal glucose tolerance are similar to those noted in previous studies using older criteria – pregnancy OGTT values (fasting glucose in particular) (16, 21, 22, 23, 24) and elevated BMI after pregnancy (25, 26). Earlier diagnosis of GDM, noted in previous studies as a risk factor (22, 24, 27, 28, 29, 30), is associated with abnormal glucose tolerance at the first post-partum visit, but not with later progression. Family history of diabetes is associated with abnormal glucose tolerance, using both index pregnancy variables, and variables available at follow-up, and whether or not women with abnormal glucose tolerance at the 12-week test are included in the analysis. Family history has been identified as a risk factor (15, 31), although less consistently than the above factors. All of these factors are routinely available clinically, but cannot reliably discriminate between those women who require more frequent follow-up from those who do not. This is a clinically important point – identification of glucose abnormalities before progression to type 2

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diabetes is important in these women for two reasons. First, the Diabetes Prevention Program (32) showed a 71% increased crude incidence rate for women with a history of GDM versus those with no GDM history (38.4% vs 25.7% 3 years post-randomisation), despite similar characteristics at baseline, but also showed that treatment (lifestyle measures or metformin) reduced the rate of progression to type 2 diabetes (32). Second, detection of abnormal glucose tolerance in women considering further pregnancy allows timely intervention to attempt to reduce the risk of undiagnosed type 2 diabetes and the potential foetal complications associated with this presenting for the first time in a subsequent pregnancy (6).

A limitation of this study is the relatively low uptake on rescreening (45%). However, comparing those women with IADPSG-defined GDM who did not attend for follow-up for this study with those who did (Supplementary Table 2), mean age at delivery, BMI during pregnancy and parity are similar. In contrast, 1- and 2-h pregnancy OGTT levels are slightly higher, and insulin use during pregnancy was more prevalent in the group who attended for follow-up, potentially causing a selection bias toward the more severe GDM cases, which could in turn lead to overestimation of abnormal glucose tolerance at follow-up. There is, however, no difference in fasting glucose, which shows a stronger association with future abnormal glucose tolerance in both this and previous studies. Women with IADPSG-defined NGT attending for follow-up, as compared with those who did not, were older, more likely to have a family history of diabetes (Supplementary Table 3). These factors mean that the prevalence of abnormal glucose tolerance in the NGT group may also overestimate the true prevalence of abnormal glucose tolerance. Low uptake on follow-up testing is a common issue among women with previous GDM, both for early (33) and long-term follow-up (34), and is a potential source of bias. To address this issue of low uptake on post-partum screening, we have initiated close follow-up of women with previous GDM with the help of a central coordinator for the region who makes verbal and written contact with each woman diagnosed with GDM to arrange early post-partum testing with a 75 g OGTT, and has achieved follow-up rates in excess of 75% (35). Further research into strategies for increasing longer-term follow-up rates will be valuable in determining the optimal approach to this issue. Also, our cohort contains women identified using risk factor-based screening, raising the possibility of bias due to the possibility of a more adverse risk profile, and therefore possibly a higher

risk of glycaemic abnormalities at retesting. However, no difference in the cumulative incidence of abnormal glucose tolerance is seen here between the groups, and indeed, 91% of women screened during the universal screening period had at least one risk factor for GDM, which would have mandated screening if selective screening was used. It should be noted, however, that, due to study design, time since delivery was shorter in the risk factor-based screening group, raising the possibility that the cumulative incidence in this group may be longer if followed for as long as the universally screened group.

Finally, we did not include women of non-white European origin, leading to a potential bias. Women of non-white European ethnicity have previously been found to have a higher risk of progression to diabetes post-GDM, despite similar attendance for follow-up screening (36). Our group has previously shown that, of a group of 300 women with IADPSG-defined GDM screened at 3 months post-partum, 31% of women of non-white European ethnicity had abnormal glucose tolerance, versus only 18% of women of white European origin (15). Therefore, exclusion of these women is likely to underestimate the true risk of abnormal glucose tolerance in our population with IADPSG-defined GDM.

In summary, although it has been proposed that women meeting IADPSG criteria are likely to require less intensive follow-up for progression to type 2 diabetes than those meeting older criteria (37), our figures show that the risk remains high. Given that differentiation of those at lower risk cannot be reliably performed clinically, follow-up should be as frequent as for those women meeting the older criteria. Given the increase in numbers of GDM pregnancies associated with adoption of the IADPSG criteria, further study is essential to both determine the optimal method and frequency of follow-up.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-15-1260>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

E N was involved in study design, collected and analysed data, and wrote the manuscript. C C was involved in study design, collected data and revised the manuscript for important intellectual content. L A C, B K, A O D, P G, L G G, B E M, C O N and P M O S were involved in study design and revised the manuscript for important intellectual content. J A S conducted the statistical analysis, wrote the statistical methods section, and revised the manuscript for important intellectual content. F P D conceived the study, revised the manuscript for important intellectual content, had full access to the data and made the decision to publish.

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