Atlantic DIP: high prevalence of abnormal glucose tolerance post partum is reduced by breast-feeding in women with prior gestational diabetes mellitus

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Abstract

Objective: Gestational diabetes (GDM) is associated with adverse fetal and maternal outcomes, and identifies women at risk of future type 2 diabetes mellitus (T2DM). Breast-feeding may improve post partum maternal glucose tolerance. Our objective was to identify the prevalence of post partum dysglycemia after GDM, to delineate associated factors and to examine the effect of lactation on post partum glucose tolerance.

Design: We compared post partum 75 g oral glucose tolerance test (OGTT) results from 300 women with GDM and 220 controls with normal gestational glucose tolerance (NGT) in five regional centers. Breast-feeding data was collected at time of OGTT.

Methods: Post partum OGTT results were classified as normal (fasting plasma glucose (FPG) <5.6 mmol/l, 2 h <7.8 mmol/l) and abnormal (impaired fasting glucose (IFG), FPG 5.6–6.9 mmol/l; impaired glucose tolerance (IGT), 2 h glucose 7.8–11 mmol/l; IFG+IGT; T2DM, FPG ≥7 mmol/l±2 h glucose ≥11.1 mmol/l). Binary logistic regression was used to identify factors predictive of persistent hyperglycemia.

Results: Five hundred and twenty women were tested; six (2.7%) with NGT in pregnancy had post partum dysglycemia compared with 57 (19%) with GDM in index pregnancy (P<0.001). Non-European ethnicity (odds ratio (OR) 3.40; 95% confidence interval (CI) 1.45–8.02, P=0.005), family history of T2DM (OR 2.14; 95% CI 1.06–4.32, P=0.034), and gestational insulin use (OR 2.62; 95% CI 1.17–5.87, P=0.019) were associated with persistent dysglycemia. The prevalence of persistent hyperglycemia was significantly lower in women who breast-fed vs bottle-fed post partum (8.2 vs 18.4%, P<0.001).

Conclusions: Non-European ethnicity, gestational insulin use, family history of T2DM, and elevated body mass index were associated with persistent dysglycemia after GDM. Breast-feeding may confer beneficial metabolic effects after GDM and should be encouraged.

Introduction

Gestational diabetes (GDM) is associated with adverse fetal and maternal outcomes (1). GDM is also associated with an increased risk of persistent dysglycemia and development of type 2 diabetes mellitus (T2DM) in later life (2). Pre-diabetes and T2DM are associated with a two- to four-fold increased risk of coronary heart disease (CHD) compared with the risk in the non-diabetic population (3). Early recognition of pre-diabetes and diabetes with appropriate and cost-effective screening is advocated to allow early interventions for this high risk group and consequently reduce the risk of future vascular disease. Reported prevalence of pre-diabetes and T2DM following GDM ranges from 7 to 35% (4). The current literature suggests that the rate of uptake of post partum diabetes screening is low, and that a fasting plasma glucose (FPG) alone may miss up to 72% of cases of post partum dysglycemia (5, 6). To date studies on persistent post partum hyperglycemia have shown inconsistent results. Some authors have suggested that breast-feeding may offer a protective effect against post partum hyperglycemia in women with GDM in an index pregnancy (7). Further work is needed because there are few studies on the effects of lactation on early post partum glucose tolerance in a predominantly European population. We hypothesize that breast-feeding improves early post partum glucose tolerance after GDM. The primary objectives of this study were to identify the prevalence of persistent pre-diabetes (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)), diabetes and metabolic syndrome in
the early post partum period (up to 12 weeks), the maternal factors associated with these states, and to examine the effect of breast-feeding on post partum glucose tolerance after GDM.

Materials and methods

The Atlantic Diabetes in Pregnancy (Atlantic DIP) partnership was set up in 2005 and serves a population of 500,000 in five regional centers along the Irish Atlantic seaboard, with 11,000 deliveries annually, covering a geographical area of 7338 square miles (8). This partnership advocates universal screening for GDM by a 2 h 75 g oral glucose tolerance test (OGTT) at 24–28 weeks gestation using International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria.

We recalled women with GDM in the index pregnancy at 12 weeks post partum and repeated a 75 g OGTT. All women diagnosed with GDM in an index pregnancy between January 1st 2006 and December 31st 2007 (n = 323) were invited to participate in this study, which is a substudy of GDM patients from the ongoing Atlantic DIP collaboration (8). We also recalled a control group of women who had normal glucose tolerance (NGT) during an index pregnancy during the same time period in the same location. Women were originally classified as GDM/IGT or NGT in pregnancy according to WHO criteria, but IADPSG criteria were retrospectively applied to the database (9) after the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial (10). Participants with incomplete results were excluded from final analysis. The control group also received a 75 g OGTT at 12 weeks post partum. This study was approved by the Research Ethics Committee in each participating hospital. Written consent was obtained from all participants.

Breast-feeding data was collected from all women participating in the study at the time of OGTT at 12 weeks post partum. Diabetes clinical nurse specialists coordinating post partum OGTTs collected data on lactation by means of maternal questionnaire. Women were classified as lactating or non-lactating according to the following criteria, all of which were required: i) ongoing feeding (at least four times per day) at time of OGTT, ii) meeting maternal expectations, iii) duration >8 weeks, iv) infant reaching developmental milestones, in particular gaining weight, and v) infant receiving scheduled immunizations.

Women were categorized in pregnancy as having NGT or GDM according to IADPSG criteria (fasting glucose ≥ 5.1 mmol/l or 1 h value ≥ 10.0 mmol/l or 2 h value ≥ 8.5 mmol/l). Post partum OGTT results were classified as normal (NGT; FPG < 5.6 mmol/l; 2 h value < 7.8 mmol/l) or abnormal (dysglycemia) according to the following cut off values: i) IFG (fasting glucose 5.6–6.9 mmol/l; 2 h glucose value < 7.8 mmol/l), ii) IGT (fasting glucose < 5.6 mmol/l; 2 h glucose value 7.8–11.0 mmol/l), iii) IFG and IGT (fasting glucose 5.6–6.9 mmol/l and 2 h glucose value 7.8–11.0 mmol/l), and iv) T2DM (fasting glucose ≥ 7.0 mmol/l or 2 h glucose value ≥ 11.1 mmol/l). Weight from booking visit at 20–24 weeks gestation, body mass index (BMI), waist circumference, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides were also measured. Contributing associated maternal factors included in the analysis were age, ethnicity (European or non-European), family history of T2DM, insulin use in pregnancy, BMI at 20–24 weeks gestation, and breastfeeding.

Finally, we measured the prevalence of post partum metabolic syndrome as a further positive predictor of future cardiovascular disease using the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines based on the presence of three of the following five risk factors: waist circumference > 35 inches (89 cm); plasma triglycerides ≥ 1.7 mmol/l; plasma HDL ≤ 1.27 mmol/l; blood pressure > 130/85; and FPG > 6.1 mmol/l (11).

Age and BMI were analyzed as continuous variables. BMI was also categorized into groups for demographic assessment as normal (BMI ≤ 24.9 kg/m²), overweight (25.0–29.9 kg/m²), and obese (≥ 30.0 kg/m²). Binary logistic regression analysis was used to identify maternal factors predictive of persistent post partum dysglycemia, with adjustment for age, BMI, ethnicity, insulin use, positive family history, presence of metabolic syndrome, and breast-feeding. Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS), version 15.0 (Chicago, IL, USA). Statistical significance was reached at P < 0.05.

Results

Five hundred and sixty-four women were tested post partum. Complete ante- (IADPSG criteria) and post partum data for analysis were available on 520 women. Three hundred women had GDM in the index pregnancy in 2006–2007 according to IADPSG criteria and 220 had NGT (Table 1). The mean age of the whole group was 33.2 years (range 18–45), greater in women with previous GDM at 33.5 ± 4.7 years compared with 32.7 ± 5.5 years in the NGT group (P = 0.10). The majority of women were of European ethnicity (44.9, 86.4%). Specifically, the ethnic breakdown of non-European women (71, 13.6%) was as follows: Asian (Indian/Pakistani/Bangladeshi), n = 25 (35.2%); Black African, n = 22 (30.9%); Asian (other, including Chinese), n = 11 (15.5%); Mixed race, n = 3 (4.2%); and any other ethnicity, n = 10 (14.2%). Seventy-two women (13.8%) had pregnancy-induced hypertension. Within the GDM group, 75 were treated with insulin in pregnancy and 225 were managed with dietary

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Baseline characteristics of women with GDM and NGT. Data are presented as mean±s.e. or as n (%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GDM (n=300)</th>
<th>NGT (n=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (range)</td>
<td>33.5±4.7 (20–44)</td>
<td>32.7±5.5 (18–45)</td>
</tr>
<tr>
<td>Persistent positivity*</td>
<td>57 (19%)</td>
<td>6 (2.7%)</td>
</tr>
<tr>
<td>BMI (kg/m²) at booking</td>
<td>30.7±6.7*</td>
<td>27.8±4.4</td>
</tr>
<tr>
<td>MS post partum</td>
<td>31 (10.3%)</td>
<td>18 (8.2%)</td>
</tr>
<tr>
<td>Ethnicity (non-European)</td>
<td>51 (17%)*</td>
<td>20 (9.1%)</td>
</tr>
<tr>
<td>Family history of T2DM</td>
<td>148 (49.3%)*</td>
<td>87 (39.5%)</td>
</tr>
</tbody>
</table>

BMI, body mass index; GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes in Pregnancy Study Group; NGT, normal glucose tolerance; T2DM, type 2 diabetes mellitus; MS, metabolic syndrome. *P<0.05.

*Persistent positivity (dysglycemia) based on oral glucose tolerance test results at 12 weeks post partum: i) IFG, FPG 5.6–6.9 mmol/l, 2 h <7.8 mmol/l, ii) IGT, FPG <5.6 mmol/l, 2 h 7.8–11.0 mmol/l, iii) IFG and IGT and iv) T2DM, FPG ≥7.0 mmol/l or 2 h ≥11.1 mmol/l. IADPSG criteria for GDM.

measures alone. All glucose-lowering interventions were stopped at delivery.

Mean BMI was higher in the GDM group compared with NGT controls (30.7 vs 27.8 kg/m², P<0.001). There was a significantly greater number of non-European women in the GDM group (17.0 vs 9.1%, P=0.009). Only six of the 220 (2.7%) of NGT women went on to develop post partum dysglycemia. By comparison 57 of the 300 (19.0%) women with GDM remained glucose intolerant post partum, with the remaining 243 (81%) reverting to normal glucose metabolism. None of the GDM cohort developed T2DM post partum; nine women with GDM were subsequently diagnosed with T2DM post partum (3.0%) (Table 2). Only 44 of the 63 (69.8%) women with persistent hyperglycemia on post partum OGTT would have been identified with FPG alone.

Breast-feeding data was available on all 520 women. Three hundred and nineteen (61.3%) women were breast-feeding successfully at time of 12 weeks post partum OGTT. Age and BMI did not differ significantly between lactating and non-lactating women (Table 3). Non-European women were more likely to breast-feed than European women (90.1% compared with 56.7%, P<0.001). The rate of post partum hyperglycemia was significantly lower in women who breast-fed their babies (n=26, 8.2%) compared with those who bottle-fed alone (n=37, 18.4%), P<0.001.

Binary logistic regression analysis was used to identify maternal factors predictive of persistent dysglycemia post partum (Table 4). Ethnicity, family history of diabetes, elevated BMI in pregnancy, and requirement for insulin treatment during pregnancy were all significant predictors of persistent glucose intolerance. Non-European ethnicity was the strongest risk factor for post partum pre-diabetes/diabetes; non-European women were 3.4 times more likely to remain hyperglycemic compared with Europeans (adjusted odds ratio (OR) 3.40; 95% confidence interval (CI) 1.45–8.02, P=0.005). Family history of diabetes and insulin

<table>
<thead>
<tr>
<th>Post partum glucose status</th>
<th>Pregnancy glucose statusa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>GDM (n=300)</td>
</tr>
<tr>
<td>214 (97.3)</td>
<td>243 (81.0)</td>
</tr>
<tr>
<td>IFG</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>IGT</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>IFG + IGT</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>T2DM</td>
<td>0</td>
</tr>
</tbody>
</table>

GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes in Pregnancy Study Group; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

aAccording to IADPSG criteria.
women with GDM who reverted to NGT post partum (P < 0.001). Women with metabolic syndrome post partum were more likely to have had pre-eclampsia toxemia in the index pregnancy compared with those without (adjusted OR 2.77; 95% CI 1.18–6.48, P = 0.01). This subgroup with post partum metabolic syndrome was also more likely to have had an operative or instrumental delivery (C-section, ventouse or forceps, adjusted OR 2.15; 95% CI 1.14–4.20, P = 0.02). There was no significant association between post partum metabolic syndrome and polyhydramnios or ante- or post partum hemorrhage, but a trend toward significance on a composite of poor maternal outcomes (P = 0.08). The incidence of post partum metabolic syndrome increased as the degree of post partum glucose intolerance increased: NGT, n = 34 (7.4%); IFG, n = 26 (23.1%); IGT, n = 16 (18.8%); T2DM, n = 5 (55.6%), P < 0.001.

Discussion

GDM is associated with adverse fetal and maternal outcomes in the index pregnancy and an increased risk of diabetes in future years (12, 13). Our study highlights the importance of early post partum testing and quantifies the considerable disease burden of persistent hyperglycemia after GDM. Risk estimates of T2DM after GDM vary from 17 to 63% within 5–16 years after the index pregnancy depending on the ethnic background of the study population and the detection method for GDM and glucose intolerance (2, 14). We have demonstrated a possible protective effect on glucose metabolism conferred by breast-feeding in the immediate post partum period. While our study was not a randomized controlled trial, it suggests potentially beneficial metabolic effects in women who breast-feed after adjustment for confounding variables. Lactation reduced the odds of persistent dysglycemia by 60% compared with the non-lactating group. Previous studies have also suggested that breast-feeding may confer a protective role on maternal glucose regulation in the early post partum period (15, 16). Kjos et al. (16) studied glucose tolerance in 809 primarily Latino women with previous GDM at 4–12 weeks post partum. Breast-feeding women had improved glucose tolerance, lower fasting glucose levels and higher HDL cholesterol levels than women who were bottle-feeding. However, these findings are not supported in a recent South Korean study (17).

In addition to reducing immediate post partum dysglycemia after GDM, lactation may have sustained benefits on maternal glucose metabolism years after weaning. Compared with nulliparous women, child-bearing women who do not breast-feed have about a 50% increased risk of T2DM in later life (18). Schwarz et al. (19) studied the long-term metabolic health benefits of breast-feeding in a cohort of 1828 women aged 40–78 years, and noted an increased risk of future diabetes when term pregnancy was followed by < 1 month of lactation, independent of physical activity and BMI in later life. Other studies have also noted an association between increased duration of lactation and a reduction in future dysglycemia. An analysis of two large prospective cohorts found that duration of lactation was inversely associated with risk of T2DM in young and middle-aged women, independent of other diabetes risk factors such as BMI (20). In our study, follow-up of patients with prior GDM was discontinued in the event of a normal post partum OGTT. Follow-up studies are necessary to confirm if the beneficial effects of lactation on glycemia persisted at 6 months, 12 months, and beyond after weaning in our cohort.

The mechanism underlying a possible preventative role of breast-feeding for maternal diabetes is unclear. Tigas et al. (21) found that lactating women handle oral carbohydrate loads normally, but have increased insulin sensitivity. During ingestion of identical amounts of glucose, plasma glucose concentrations in lactating women were identical to those of non-lactating women.

Table 4 Maternal predictors of persistent post partum dysglycemia. Binary logistic regression analysis with odds ratio (OR) adjusted for age, BMI, ethnicity, insulin use, positive family history, presence of metabolic syndrome, and breast-feeding. Data are presented as OR (95% CI lower–upper limit).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 (0.95–1.10)</td>
<td>0.333</td>
</tr>
<tr>
<td>Non-European</td>
<td>3.40 (1.45–8.02)</td>
<td>0.005</td>
</tr>
<tr>
<td>Family history</td>
<td>2.14 (1.06–4.32)</td>
<td>0.034</td>
</tr>
<tr>
<td>G insulin</td>
<td>2.62 (1.17–5.87)</td>
<td>0.019</td>
</tr>
<tr>
<td>BMI</td>
<td>1.08 (1.03–1.14)</td>
<td>0.03</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>0.418 (0.19–0.888)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; G insulin, gestational insulin.

*Persistent positivity (dysglycemia) based on oral glucose tolerance test results at 12 weeks post partum: i) IFG, FPG 5.6–6.9 mmol/l, 2 h < 7.8 mmol/l; ii) IGT, FPG < 5.6 mmol/l, 2 h 7.8–11.0 mmol/l; iii) IFG and IGT and iv) T2DM, FPG ≥ 7.0 mmol/l or 2 h ≥ 11.1 mmol/l. Bold values denote statistical significance, P < 0.05.
but insulin levels were lower in the lactating group. Diniz & Da Costa have also suggested that breast-feeding women have improved insulin sensitivity that persists after childbirth (22), but further research is needed to understand the associations observed here.

Previous studies have shown that the risk of diabetes following GDM increases with the degree of carbohydrate intolerance in pregnancy, the need for insulin therapy and early diagnosis of GDM during the index pregnancy (23). High rates of persistent glucose intolerance in Indo-Asian women may reflect undiagnosed diabetes pre-dating pregnancy (5, 24, 25). We have also shown that GDM patients who required insulin therapy during the index pregnancy had significantly increased odds of post partum glucose intolerance compared with those managed with dietary measures alone. This is not surprising as these women have a more profound degree of insulin resistance and β-cell dysfunction necessitating exogenous insulin treatment. The β-cell defect in women with GDM is still present in the post partum period. Recent data suggest that subsequent further deterioration of β-cell function is a very early event in women with GDM and IGT of pregnancy, taking place within the first year post partum (26).

Raised BMI at booking visit (20–24 weeks) was associated with subsequent post partum hyperglycemia, particularly in non-European women; this corroborates some but not all previous studies (27, 28). Glucose-tolerant overweight and obese women also need to be targeted aggressively, however; as recent data show that these women have greater adverse fetal and maternal outcomes compared with controls, independent of pregnancy glucose status (29). Elevated HbA1c at term was also predictive of persistent hyperglycemia. Seventy percent of those with HbA1c ≥ 6.5% at term remained glucose intolerant at 12 weeks post partum, emphasizing the importance of tight glycemic control throughout pregnancy.

Metabolic syndrome was present in over 25% of those who remained glucose intolerant post partum. GDM predicts later manifestation of the metabolic syndrome including T2DM, both associated with vascular dysfunction and atherogenesis, and so these two metabolic abnormalities may be intimately connected (30). Women with a history of GDM have a markedly elevated risk of CHD compared with women without a history of same (31). It is likely that this risk is mediated in part by the presence of the metabolic syndrome and its component cardiovascular risk factors. Breast-feeding did not lower the incidence of post partum metabolic syndrome in our study; however the sample size may be too small to draw meaningful conclusions from this result.

Measurement of an abnormal FPG (≥ 5.6 mmol/l) in our study identified <70% of women with persistent glucose abnormalities on post partum OGTT. These results are similar to recent data from McClean et al. (6), who found that an FPG cut off value of ≥ 6.1 mmol/l identified abnormal glucose tolerance in 199 of the 272 cases (sensitivity 0.73). Interestingly, of these 272 women, 109 had frank diabetes, of whom 11 (10%) had an FPG ≤ 6.0 mmol/l. Kwong et al. (5) found that up to 72% of women with post partum hyperglycemia would have been missed if only an FPG (≥ 6.1 mmol/l) was performed. Clearly measurement of FPG alone lacks sensitivity, rendering it unacceptable as a screening test for post partum glucose abnormalities in comparison with an OGTT. The ADA recommends a 75 g OGTT at 12 weeks post partum after GDM, and this is currently implemented in our five regional centers. Women with GDM who have NGT on testing at 12 weeks post partum may still have a significant risk of becoming hyperglycemic within 12 months (32), and ideally require a follow-up OGTT at 6 and 12 months.

Our data are novel because other authors have not studied the impact of lactation on early post partum glycaemia in women with GDM and in glucose-tolerant controls in a predominantly European cohort. The majority of controlled studies to date have looked at long-term risk of diabetes after GDM, rather than in the early post partum period (2). In addition, most work on the effects of lactation on early post partum glycaemia has focused primarily on Asian and Latino populations (15, 16). Some recent studies on breast-feeding and post partum diabetes have had conflicting results (17), and further work was necessary.

There is clear evidence that addressing the long-term consequences of diabetes early in the course of the disease is of benefit (33). Aggressive intervention should be offered to those women who test positive on post partum testing, and early pharmacotherapy with insulin-sensitizing agents may be appropriate. Women with NGT post partum who are identified as high risk based on ethnicity, gestational insulin use, obesity or positive family history should also be encouraged to breast-feed, as large population-based studies have shown that the beneficial metabolic effects of lactation may persist for years after weaning (19). Our study supports a growing body of evidence that lactation may improve post partum glucose tolerance after GDM.

### Table 5 Predictive factors of persistent dysglycemia in European women.

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.006</td>
<td>0.893</td>
</tr>
<tr>
<td>BMI</td>
<td>1.062</td>
<td>0.09</td>
</tr>
<tr>
<td>G insulin</td>
<td>3.118</td>
<td>0.009</td>
</tr>
<tr>
<td>Family history</td>
<td>3.187</td>
<td>0.008</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>0.409</td>
<td>0.011</td>
</tr>
</tbody>
</table>

BMI, body mass index; OR, odds ratio; G insulin, gestational insulin. Bold values denote statistical significance, *P* < 0.05.
Breast-feeding must be strongly encouraged by health-care providers after GDM. The rate of lactation is low in European women, and this needs to be addressed. Similarly, uptake rates of post partum OGTT after GDM remain low internationally (5, 34). Electronic alerts via text message or email, automated letters, and nurse phone contact may increase uptake. Where such a facility is not in place, those at highest risk should be particularly targeted. Patients at high risk of post partum hyperglycemia need further glucose measurement at 6 and 12 months, and ideally annually thereafter. It is crucial that funding for this screening process is provided by health strategists and politicians, and supported at a regional and national level.

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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