Influence of gestational diabetes on the long-term control of glucose tolerance

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Abstract

Aims/hypothesis Gestational diabetes (GDM) carries a high risk of subsequent diabetes. We asked what impact prior GDM has on beta cell function and insulin action in women who maintain normal glucose tolerance (NGT) for a long time.

Methods Ninety-one women with NGT (aged 41 ± 8 years, mean $\pm$ SD) were studied (by mathematical modelling of the C-peptide response to an OGTT) 7 [6] years (median [interquartile range]) after the index pregnancy, during which 52 had GDM (pGDM) and 39 had NGT (pNGT). In all women an OGTT had also been performed at 29 ± 3 weeks of the index pregnancy.

Results Women with pGDM were matched with women with pNGT for age, familial diabetes, time and weight gain since index pregnancy, parity, BMI (25.4 ± 3.9 vs 26.8 ± 6.4 kg/m²), and fasting (4.64 ± 0.56 vs 4.97 ± 0.46 mmol/l) and 2 h plasma glucose levels (5.91 ± 1.14 vs 5.91 ± 1.21 mmol/l). Nonetheless, fasting (49 [29] vs 70 [45] pmol min⁻¹ m⁻², $p < 0.001$) and total insulin secretion (32 [17] vs 48 [21] nmol m⁻², $p < 0.0001$) and beta cell glucose

sensitivity (slope of the insulin secretion/plasma glucose concentration–response function) (95 [71] vs 115 [79] pmol min⁻¹ m⁻² (mmol/l)⁻¹, $p = 0.025$) were reduced in the pGDM group compared with the pNGT group, while insulin sensitivity was preserved (424 [98] vs 398 [77] ml min⁻¹ m⁻²). At index pregnancy, women with pGDM and those with pNGT had similar age and BMI. However, both insulin sensitivity (359 [93] vs 417 [92] ml min⁻¹ m⁻², $p = 0.0012$) and the insulin/glucose incremental area ratio (an empirical index of beta cell function; 98 [74] vs 138 [122] pmol/mmol, $p = 0.028$) were reduced in women with pGDM.

Conclusions Even in women who maintain normal insulin sensitivity, impaired beta cell function is carried over into the NGT status several years after a GDM pregnancy.

Keywords Beta cell function · Gestational diabetes · Insulin resistance · Pregnancy

Abbreviations

GDM	gestational diabetes mellitus
NGT	normal glucose tolerance
pGDM	gestational diabetes mellitus during the index pregnancy
pNGT	normal glucose tolerance during the index pregnancy
sd.r	standardised regression coefficient

Introduction

Women with gestational diabetes (GDM) have a higher risk of developing type 2 diabetes or altered glucose metabolism during the postpregnancy period [1–5]. The cumulative incidence of type 2 diabetes increases markedly in the first

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5 years after delivery, reaching a plateau after 10 years [1]. It has been suggested that the higher risk of postpregnancy diabetes represents a partial remission of GDM [6–9]. In fact, insulin resistance and beta cell dysfunction are the main pathophysiological factors of GDM just as they are for diabetes outside of pregnancy [10].

It has been repeatedly reported (reviewed in [11]) that women with normal glucose tolerance (NGT) and prior GDM carry some trace of altered glucose homeostasis, essentially, insulin resistance [8] and/or beta cell dysfunction [12–19]. Several of these studies, however, have been carried out in obese women or shortly after GDM; moreover, not all have related the abnormalities detected after GDM to those found during GDM. In the present study, we assessed beta cell function and insulin action in women with NGT with or without prior GDM both during the index pregnancy and several years later.

Methods

Participants The study participants were drawn from a larger cohort enriched with women with familial diabetes or obesity (or other reasons to suspect altered glucose tolerance), who were screened during the third trimester. While those with diabetes or IGT were systematically tested after pregnancy (and at each subsequent pregnancy) (prospective group), those with NGT were invited to return for a repeat OGTT (matching group). The present cohort included all women ($n=91$) currently with NGT (pNGT; based on a standard 75 g OGTT) who had also been studied during the third trimester of a pregnancy (index pregnancy) at least 2 years previously. The study protocol was approved by the local ethics committee, participants gave their informed consent to participate, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical studies A frequently sampled OGTT was carried out in all participants, with measurements of plasma glucose, insulin, NEFA and C-peptide concentrations. At 29 ± 3 weeks (mean $\pm$ SD) of the index pregnancy, all women had received another 75 g OGTT, with measurement of plasma glucose and insulin (but not C-peptide) concentrations at baseline and 1, 2 and 3 h after glucose ingestion.

Measurements Plasma glucose was measured by the glucose oxidase method (Glucose Analyzer; Beckman Instruments, Fullerton, CA, USA). Plasma NEFA were assayed spectrophotometrically (Wako, Neuss, Germany); plasma insulin and C-peptide were assayed with specific RIA kits (Linco Research, St. Louis, MO, USA).

Data analysis Insulin sensitivity was estimated from the plasma glucose and insulin levels measured during the OGTT by the oral glucose insulin sensitivity (OGIS) method [20]. From the frequently sampled OGTT at follow-up, beta cell function was resolved by mathematical modelling [21, 22]. In brief, insulin secretion rates were reconstructed by deconvolution of C-peptide concentrations and related to plasma glucose levels (in a concentration–response relationship, the average slope of which was taken as beta cell glucose sensitivity) and to the rate of change of plasma glucose levels (representing rate sensitivity). Insulin clearance was calculated as the ratio of total post-OGTT insulin secretion to the average post-OGTT plasma insulin concentration.

In order to compare beta cell function between the two OGTTs, an empirical index was obtained as the insulin/glucose incremental area ratio ($\Delta\text{AUC}_I/\Delta\text{AUC}_G$, pmol/mmol) [23]. This index expresses the overall ability of the beta cell to increase its release rate in response to the total glycaemic stimulus presented. In the present data set, this index and the

Fig. 1 Plasma glucose (a) and insulin (b) concentrations, insulin secretion rates (c) and insulin/glucose concentration–response functions (d) in women with (squares and dotted line) or without (circles and continuous line) previous GDM during the OGTT at follow-up

model-derived specific index of beta cell function (i.e. beta cell glucose sensitivity) were directly related to one another ($\rho=0.47$, $p<0.0001$).

Statistical analysis Results are given as mean $\pm$ SD and median [interquartile range] for variables with a normal and non-normal distribution respectively. The AUCs were calculated by the trapezoidal rule. Group comparisons were carried out with the χ^2 , Student's t and Mann–Whitney U tests as appropriate. Simple associations were tested by Spearman rank correlation (ρ); multiple regression analysis was carried out after log-transformation of non-normally distributed variables; results are given as standardised regression coefficients (sd.r). An alpha level of 0.5 was considered statistically significant.

Results

Women with pGDM were matched to women with pNGT for age, prevalence of familial diabetes, time from index

pregnancy, parity, BMI, fasting and 2 h plasma glucose levels. The two groups had gained weight similarly both during and since the index pregnancy. Fasting plasma insulin and NEFA concentrations and insulin sensitivity were not significantly different between the two groups. In contrast, the plasma insulin response to glucose was markedly reduced in the pGDM group, particularly early after ingestion (Fig. 1). Insulin secretion (fasting as well as post-glucose) and both rate sensitivity and glucose sensitivity were significantly reduced in the pGDM group (Table 1). In the pGDM group, the concentration–response curve of insulin secretion was shifted downwards compared with that in the pNGT group, such that insulin release was lower at any given plasma glucose concentration (Fig. 1). The insulin/glucose incremental area ratio was also significantly reduced in the pGDM group (Table 1).

At the time of the index pregnancy, the two groups were matched for age, pregestational weight and weight gain during pregnancy. By definition, fasting and 2 h glucose levels were higher in the pGDM than in the pNGT group. Both insulin sensitivity and the insulin/glucose incremental

Table 1 Clinical and metabolic parameters

	pGDM (<i>n</i> =52)	pNGT (<i>n</i> =39)	<i>p</i> value ^a
Post index pregnancy			
Age (years)	41 $\pm$ 5	41 $\pm$ 5	NS
Familial diabetes (%)	41	43	NS
Time from index pregnancy (years)	7 [6]	8 [5]	NS
Parity (<i>n</i>)	2.0 [1.0]	2.0 [1.5]	NS
BMI (kg/m ²)	25.4 $\pm$ 3.9	26.8 $\pm$ 6.4	NS
Weight change since index pregnancy (kg)	4.3 $\pm$ 6.9	5.7 $\pm$ 8.9	NS
Fasting plasma glucose (mmol/l)	4.64 $\pm$ 0.56	4.97 $\pm$ 0.46	NS
2 h plasma glucose (mmol/l)	5.91 $\pm$ 1.14	5.91 $\pm$ 1.21	NS
Fasting plasma NEFA (mmol/l)	0.57 $\pm$ 0.16	0.57 $\pm$ 0.18	NS
Fasting plasma insulin (pmol/l)	71 [45]	72 [29]	NS
Δ AUC _I / Δ AUC _G (pmol/mmol)	143 [146]	296 [287]	0.002
Insulin sensitivity (ml min ⁻¹ m ⁻²)	424 [98]	398 [77]	NS
Insulin clearance (l/m ²)	0.75 [0.53]	0.81 [0.35]	NS
Fasting insulin secretion (pmol min ⁻¹ m ⁻²)	49 [29]	70 [45]	<0.001
Total insulin output (nmol/m ²)	32 [17]	48 [21]	<0.0001
Beta cell glucose sensitivity (pmol min ⁻¹ m ⁻² [mmol/l] ⁻¹)	95 [71]	116 [79]	0.025
Beta cell rate sensitivity (nmol m ⁻² [mmol/l] ⁻¹)	0.71 [0.75]	1.15 [1.42]	<0.01
At index pregnancy			
Age (years)	33 $\pm$ 4	33 $\pm$ 4	NS
Pre-pregnancy BMI (kg/m ²)	23.8 $\pm$ 3.2	24.6 $\pm$ 4.3	NS
Pregnancy weight gain (kg)	9.1 $\pm$ 3.9	9.9 $\pm$ 3.1	NS
Fasting plasma glucose (mmol/l)	4.98 $\pm$ 0.65	4.71 $\pm$ 0.53	0.043
2 h plasma glucose (mmol/l)	9.52 $\pm$ 1.07	7.07 $\pm$ 1.46	<0.0001
Fasting plasma insulin (pmol/l)	60 [52]	54 [44]	NS
Insulin sensitivity (ml min ⁻¹ m ⁻²)	349 [93]	403 [95]	0.0012
Δ AUC _I / Δ AUC _G (pmol/mmol)	98 [74]	138 [122]	0.028

Data are mean $\pm$ SD or median [interquartile range]

^a χ^2 , Student's t or Mann–Whitney U

area ratio were significantly lower in the pGDM than in the pNGT group (Table 1).

In multivariate analysis, insulin release (as the insulin/glucose incremental area ratio) and insulin sensitivity were independent determinants of 2 h plasma glucose levels both at the index pregnancy (sd.r=−0.54 and −0.76, respectively; $p<0.0001$ for both, $r^2=0.46$) and follow-up (sd.r=−0.52 and −0.46 respectively; $p<0.0001$ for both, $r^2=0.43$), independently of age and BMI. In the pGDM group but not the pNGT group, beta cell glucose sensitivity at follow-up was directly associated with time since index pregnancy (sd.r=0.67, $p<0.0001$) independently of age (sd.r=−0.38, $p<0.02$; total $r^2=0.28$; $p=0.0003$) (Fig. 2).

Discussion

Several years after the index pregnancy, our previously GDM but NGT women had plasma glucose profiles that were minimally different from those of a well-matched group of women with documented NGT during the index pregnancy (Fig. 1). Nevertheless, they showed multiple defects in beta cell function. Thus, their rates of glucose-mediated insulin release (fasting as well as post-glucose) were reduced in absolute terms. When these insulin secretory rates were related to the concomitant plasma

glucose levels by modelling analysis, the ability of beta cells to sense glucose and to respond to its rate of change was clearly impaired. This impairment was reflected also by the insulin/glucose incremental area ratio, an empirical proxy for beta cell glucose sensitivity [23]. In the pGDM group, NGT was maintained by virtue of the fully preserved (in fact slightly superior) insulin sensitivity (Table 1). During the index pregnancy, on the other hand, the diabetes of women with pGDM was precipitated by the combination of impaired beta cell function (as the insulin/glucose incremental area ratio) with insulin resistance. Thus, the only abnormality that was carried over to the NGT state of later years was a defective beta cell response to glucose.

The reason why insulin sensitivity was worse in women with GDM than in ‘normotolerant’ women during pregnancy remains undefined, as age, BMI and weight gain during gestation, the main determinants of insulin sensitivity, were similar in the two groups. It is possible that raised glucose levels throughout the 29 weeks of pregnancy in the GDM group depressed insulin sensitivity by glucose toxicity. Whatever the cause, this insulin resistance resolved over the following several years.

The notion that some metabolic memory persists in women with prior GDM even when they present NGT has emerged from a number of previous studies [12–19]. The majority of these studies have clearly indicated that previous GDM is associated with a significant reduction in insulin sensitivity, insulin secretion or both in women who maintain NGT at follow-up [12–19]. However, uncertainty remains as a result of some bias in the design of most of these studies. Thus, the time since the index pregnancy has been very variable and, mostly, short (1–3 years) [12, 14, 15, 19]. In other cases, mean OGTT glucose values, even if normal by diagnostic criteria, were significantly higher in normotolerant women with previous GDM than in women who had NGT during the index pregnancy [15, 19]. Not infrequently, groups were not well matched for actual or pregestational BMI or age [16, 18, 19], thereby conferring a presumably different burden of background insulin resistance [24].

Our study was free of these biases since the median time from index pregnancy to follow-up examination (7–8 years) was beyond the high-risk window for developing diabetes [1]. Furthermore, the groups were well matched both at index pregnancy and at follow-up for such confounders as age and obesity (Table 1). Finally, average glucose values during the OGTT were similar at follow-up in women with pGDM and those with pNGT (6.82 ± 1.02 and 6.66 ± 1.24 mmol/l respectively; Fig. 1). Under these conditions, the only detectable abnormality in the pGDM group was impaired beta cell function.

Of further interest is that beta cell glucose sensitivity at follow-up was better in pGDM women with a longer time

Fig. 2 Age-adjusted relationship between beta cell glucose sensitivity and time since index pregnancy in women without (a) (sd.r=0.16, NS) or with (b) (sd.r=0.67, $p<0.0001$) previous GDM. Lines of best fit are shown with their 95% CIs

interval since index pregnancy irrespective of age (Fig. 2). This finding may suggest that beta cell competence might improve with time after a GDM pregnancy. This putative phenomenon, however, would only be proven by sequential post-GDM testing over years. A more likely explanation for a cross-sectional series is selection bias, whereby NGT is increasingly more frequent in women with pGDM who are past the highest risk window of post-GDM diabetes. In general, our results do not imply that only beta cell dysfunction, and not insulin resistance, prevails in the pGDM population; they simply prove that, even in the absence of significant insulin resistance, beta cell dysfunction can still be detected in normotolerant women with pGDM. Thus, secretory impairment stands out as the dominant pathophysiological feature of gestational diabetes. Clearly, women who also maintain insulin resistance into the postgestational period are at heightened risk of incident diabetes.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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