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Rapid communication

Postpartum reversibility of impaired incretin effect in gestational diabetes mellitus ☆

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ABSTRACT

The potential reversibility of a reduced incretin effect is unclear. We investigated the incretin effect during third trimester and 3 to 4 months postpartum in women with and without gestational diabetes mellitus (GDM). Ten women with GDM (plasma glucose (PG) concentration at 120 min after 75 g-oral glucose tolerance test (OGTT) (PG_{120min}): 10.1 ± 0.6 mmol/l (mean ± SEM)) and eight women with normal glucose tolerance (NGT; PG_{120min}: 7.0 ± 0.1 mmol/l) were investigated on four occasions: 4 h 50 g-OGTT and isoglycaemic intravenous glucose infusion during third trimester and 3 to 4 months postpartum. In women with GDM, the incretin effect increased significantly postpartum (31 ± 6 vs. 56 ± 6%, p = 0.02), whereas the increment in women with NGT was insignificant (35 ± 12 vs. 56 ± 9%, p = 0.08). Similarly, the gastrointestinal-mediated glucose disposal ($GIGD = 100\% \times (glucose_{OGTT} - glucose_{IIGI})/glucose_{OGTT}$) was reduced to diabetic levels in women with GDM (37 ± 3%), but increased (p = 0.030) to normal levels post partum (58 ± 6%). GIGD did not change significantly in NGT women (48 ± 3 vs. 57 ± 6%, p = 0.94). Women with GDM exhibit a reduced incretin effect which is fully reversible alongside the restoration of normal glucose homeostasis, whereas the reduction in incretin effect during pregnancy in women with NGT was insignificant. Our results suggest that decreased incretin effect in women with GDM is a fully reversible phenomenon.

1. Introduction

The incretin effect is believed to be of crucial importance for controlling postprandial glucose excursions [1]. It is well known that the incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are responsible for the incretin effect which accounts for up to 70% of the insulin secreted in response to ingestion of nutrients. Patients with type 2 diabetes (T2D) exhibit a markedly reduced incretin effect [1], however, the available studies investigating the causality of the reduced incretin effect in patients with diabetes have not addressed whether the incretin defect is due to decreased sensitivity to insulin and/or glucose intolerance. In order to answer this question, we utilised the physiological phenomenon of pregnancy-induced decreased insulin sensitivity, which under normal circumstances is compensated for by increased pancreatic insulin secretion, so that normal glucose tolerance (NGT) is maintained [2], but in some women causes gestational diabetes mellitus (GDM) (due to inadequate insulin secretion). Thus, in the present study we investigated the incretin effect during third trimester (TT) pregnancy in women with NGT and GDM and again 3 to 4 months after delivery (postpartum (PP)).

2. Methods

2.1. Subjects and experimental design

Caucasian pregnant women in TT of pregnancy were included; twelve women diagnosed with GDM and eight women with NGT—characteristics are shown in Table 1. Two of the women with GDM were excluded from the analyses because they did not return to NGT. All women agreed to participate after receiving oral and written information. None of the women had first or second-degree relatives with diabetes and they had not been diagnosed with diabetes before pregnancy. GDM was diagnosed according to WHO guidelines (plasma glucose (PG) concentration at 120 min after 75 g-oral glucose tolerance (OGTT) ($PG_{120\ min}$) ≥7.8 mmol/l) in gestational week 22–26. None of the women with GDM had received anti-diabetic treatment on the first experimental day. At time of delivery, four women with GDM were treated with insulin and the rest with diet only. Three to four months following delivery, all included patients with GDM returned to NGT, i.e. a PG_{120min} <7.8 mmol/l. Women with $PG_{120\ min}$ <7.8 mmol/l during TT of pregnancy were enrolled as NGT controls. Following an initial screening visit, each participant was studied on two paired

☆ Trial registration: The study was registered with the Scientific-Ethical Committee of the County of Lodz, Poland (registration no. 43/2007) and ClinicalTrials.gov (ID: NCTNCT01307995) and conformed to the latest revision of the Declaration of Helsinki.

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Table 1
Titel should be changed to:Characteristics of participants included in the trial.

	GDM ($n = 10$)	NGT ($n = 8$)	*p (GDM vs. NGT)*
Age (years)*	30 ± 1	29 ± 1	*0.45*
Body weight (kg), TT/PP	76 ± 4/69 ± 4	75 ± 3/70 ± 3	*0.91/0.86*
p (TT vs. PP)	*<0.001*	*<0.001*	
2 h PG (mmol/l), TT/PP	10.1 ± 0.6/ 6.4 ± 0.4	7.0 ± 0.1/5.7 ± 0.3	*<0.001/0.18*
p (TT vs. PP)	*0.01*	*0.001*	
HbA_{1c} (%), TT/PP	5.4 ± 0.2/5.2 ± 0.1	4.8 ± 0.1/4.7 ± 0.1	*0.01/<0.001*
p (TT vs. PP)	*0.08*	*0.01*	
Insulin			
Baseline (pmol/l), TT/PP	82 ± 16/63 ± 14	67 ± 11/67 ± 17	*0.50/0.84*
p (TT vs. PP)	*0.36*	*0.99*	
$iAUC_{OGTT}$ (nmol/lxmin), TT	4.9 ± 1.1	3.5 ± 0.4	*0.09*
$iAUC_{IIGI}$ (nmol/lxmin), TT	3.3 ± 0.9	1.4 ± 0.4	*0.04*
p (OGTT vs. IIGI)	*0.003*	*0.023*	
$iAUC_{OGTT}$ (nmol/lxmin), PP	2.5 ± 0.4	2.2 ± 0.4	*0.11*
$iAUC_{IIGI}$ (nmol/lxmin), PP	1.1 ± 0.4	0.7 ± 0.2	*0.18*
p (OGTT vs. IIGI)	*<0.001*	*0.005*	
C-peptide			
Baseline (nmol/l), TT/PP	0.72 ± 0.1/ 0.57 ± 0.1	0.52 ± 0.1/ 0.64 ± 0.2	*0.13/0.72*
p (TT vs. PP)	*0.05*	*0.43*	
$iAUC_{OGTT}$ (nmol/lxmin), TT	280 ± 40	169 ± 40	*0.05*
$iAUC_{IIGI}$ (nmol/lxmin), TT	186 ± 42	99 ± 19	*0.16*
p (OGTT vs. IIGI)	*<0.001*	*0.08*	
$iAUC_{OGTT}$ (nmol/lxmin), PP	201 ± 32	141 ± 37	*0.24*
$iAUC_{IIGI}$ (nmol/lxmin), PP	121 ± 26	63 ± 34	*0.18*
p (OGTT vs. IIGI)	*0.001*	*0.69*	
Relative incretin effect (%) **Insulin**			
TT/PP	31 ± 6/56 ± 6	35 ± 12/56 ± 9	*0.654/0.982*
p (TT vs. PP)	*0.020*	*0.080*	
C-peptide			
TT/PP	20 ± 5/48 ± 6	29 ± 6/59 ± 11	*0.375/0.626*
p (TT vs. PP)	*0.004*	*0.070*	
ISR			
TT/PP	19 ± 6/44 ± 8	38 ± 15/48 ± 8	*0.270/0.797*
p (TT vs. PP)	*0.050*	*0.550*	
GIGD			
TT/PP	37 ± 3/58 ± 6	48 ± 3/57 ± 6	*0.039/0.944*
p (TT vs. PP)	*0.030*	*0.940*	

Data are means ± standard error of the mean (SEM). GIGD: gastrointestinal-mediated glucose disposal; GDM: gestational diabetes mellitus; NGT: normal glucose tolerance; TT: third trimester; PP: postpartum; PG, plasma glucose; iAUC: incremental area under the curve. Incretin effect values are calculated on the basis of insulin responses, C-peptide responses or insulin secretion rate (ISR) values during isoglycaemic oral (50 g-oral glucose tolerance (OGTT)) and intravenous glucose stimuli performed during TT and 3–4 months PP.

occasions (50 g-OGTT and isoglycaemic intravenous glucose infusion (IIGI)); one to two weeks after the diagnostic 75 g-OGTT and again 3–4 months PP.

2.2. Biochemical analyses, calculations and statistical analyses

PG concentrations were measured during the experiments using Accu-Chek Active Glucometer (Roche). Plasma insulin and C-peptide concentrations were measured as previously described [3]. Insulin secretion rates (ISRs) were calculated as previously described [3]. Area under curve (AUC) values, were calculated using the trapezoidal rule and incremental values were obtained by subtracting the area below baseline values from total AUCs. Incretin effects were calculated by relating the difference in integrated beta cell secretory responses (AUC for insulin, C-peptide and ISR) between stimulation with OGTT and IIGI using the following formula: incretin effect (%) = 100% × (AUC_{OGTT} − AUC_{IIGI})/AUC_{OGTT}. The gastrointestinal-mediated glucose disposal (GIGD) was calculated using the formula: GIGD (%) = 100% × ($glucose_{OGTT}$ −$glucose_{IIGI}$)/$glucose_{OGTT}$ [4]. Continuous variables are presented as means ± standard error of the mean (SEM). Normally distributed data were compared using paired two-tailed *t* tests within groups and comparisons between groups were made using unpaired analyses. *P* values <0.05 were considered statistically significant.

3. Results

Time courses for plasma concentrations of glucose, insulin and C-peptide during all experiments are depicted in Fig. 1. Similar fasting PG (FPG) concentrations were seen in women with GDM and NGT, without differences between TT and PP. In contrast, but as expected, women with GDM exhibited significantly larger PG excursions during pregnancy compared to NGT women (incremental AUC: 571 ± 81 vs. 373 ± 28 mmol/l × min, p = 0.04 (Fig. 1)). After delivery, the exaggerated glycaemic responses of GDM patients were significantly reduced and normalised according to incremental AUCs (426 ± 45 vs. 250 ± 38 mmol/l × min, p = 0.03 (Fig. 1)). In order to obtain isoglycaemic conditions during the two glucose administration forms in women with GDM, 32 ± 1 g of glucose was infused intravenously during pregnancy as compared to 22 ± 4 g following delivery ($p \leq 0.05$). In women with NGT, 26 ± 2 and 21 ± 3 g glucose (p = 0.76), respectively, were used. The GIGD was reduced to 'diabetic' levels in women with GDM (37 ± 3%) [5], but significantly (p = 0.03) increased to normal levels following delivery (58 ± 6%) [5]. No significant change in GIGD was observed in NGT women (48 ± 3 vs. 57 ± 6%, p = 0.94). As illustrated in Fig. 1, the reduced incretin effect during pregnancy (based on insulin, C-peptide and in ISR values) in women with GDM (31 ± 6/56 ± 6 (TT/PP), 20 ± 5/48 ± 6 and 19 ± 6/44 ± 8, p = 0.020, p = 0.004 and p = 0.050, respectively) normalised after delivery, whereas the women with NGT (35 ± 12/56 ± 9, 29 ± 6/59 ± 11 and 38 ± 15/48 ± 8, p = 0.080, p = 0.070 and p = 0.550 respectively) during pregnancy exhibited an insignificant increase in incretin effect after delivery (Table 1).

4. Discussion

In the present study, pregnancy was associated with reduced incretin effect and GIGD, both of which normalise 3–4 months following delivery when normal glucose homeostasis is re-established; a phenomenon which seems most pronounced in pregnant women with GDM since no statistical significant improvement was seen in women with NGT.

Our study is the first to describe the incretin effect and GIGD in women with GDM in third trimester of pregnancy *and* after delivery. In the current paper plasma concentrations of GIP and GLP-1 were not included. Our group has previously found normal levels of both GIP and GLP-1 during an OGTT in patients with GDM [6] when compared to pregnant NGT women, but reduced postprandial GLP-1 responses and gastric emptying in GDM and NGT women during pregnancy after meal ingestion [7]. Very recently our group published a systematic review of clinical studies investigating GLP-1 secretion in patients with type 2 diabetes and non-diabetic controls and found no reduced secretion of GLP-1 [8] in response to an oral glucose or meal test indicating that the reduced incretin effect is *mainly* caused by deterioration in the effects of the incretin hormones.

These findings support the notion that a decrease in incretin effect is secondary to the development of diabetes, as also demonstrated in patients with diabetes secondary to destruction of insular tissue (chronic pancreatitis), who exhibit an almost complete loss of incretin effect compared to patients with a similar degree of chronic pancreatitis, but normal glucose tolerance, who have a normal incretin effect [9]. On top of this, recent studies have found that impairment of the incretin effect is a very early characteristic of insulin resistance and obesity, which may be observed before other signs of beta cell dysfunction are