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Gestational diabetes mellitus and the risk of metabolic syndrome: a population-based study in Lausanne, Switzerland

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RESUME EN FRANÇAIS

BUTS. Etudier les relations entre le diabète gestationnel (GDM) et le syndrome métabolique (MS), comme la résistance à l'insuline est une des caractéristiques des deux conditions. Analyser le dépistage du diabète dans le post-partum pour identifier les facteurs de risque associés au développement d'un diabète de type 2 ultérieur.

METHODES. Etude rétrospective de toutes les grossesses uniques diagnostiquées avec un diabète gestationnel à l'hôpital universitaire de Lausanne, pendant une durée de trois ans. La présence d'une obésité, d'une hypertension ou d'une dyslipidémie avant la grossesse définissent les composants du syndrome métabolique.

RESULTATS. Sur 5788 grossesses, 159 patientes (2.7%) présentaient un diabète gestationnel. Des composants du syndrome métabolique étaient présents avant la grossesse chez 26% des patientes (n=37/144) : 84% (n=31/37) étaient obèses, 38% (n=14/37) présentaient une hypertension et 22% (n=8/37) une dyslipidémie. Le développement d'une hypertension gravidique était associé à l'obésité (OR=3.2, p=0.02) et à la dyslipidémie (OR=5.4, p=0.002). Septante-quatre patientes (47%) sont revenues pour l'HGPO dans le post-partum. Celle-ci était anormale chez 20 femmes (27%): 11% (n=8) présentaient un diabète de type 2 et 16% (n=12) avaient une intolérance au glucose. Les facteurs de risque indépendants associés à une anomalie de la tolérance au glucose dans le post-partum étaient d'avoir plus de 2 valeurs anormales au test diagnostique durant la grossesse et présenter des composants du syndrome métabolique (OR=5.2, CI 1.8-23.2 et OR=5.3, CI 1.3-22.2).

CONCLUSIONS. Dans un quart des grossesses avec un diabète gestationnel, des anomalies métaboliques précèdent l'apparition de l'intolérance au glucose. Ces patientes présentent un haut risque de développer un syndrome métabolique et un diabète de type 2 ultérieurement. Là où le dépistage du diabète gestationnel n'est pas systématique, les praticiens devraient être avertis de ces risques métaboliques chez les patiente se présentant avec une obésité, une hypertension ou une dyslipidémie, afin de mieux les diagnostiquer et surtout de mieux les suivre et traiter après leur grossesse.

Gestational diabetes mellitus and the risk of metabolic syndrome: a population-based study in Lausanne, Switzerland

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SUMMARY

Aims: To investigate the relationships between gestational diabetes mellitus (GDM) and the metabolic syndrome (MS), as it was suggested that insulin resistance was the hallmark of both conditions. To analyse post-partum screening in order to identify risk factors for the subsequent development of type 2 diabetes mellitus (DM).

Methods: A retrospective analysis of all singleton pregnancies diagnosed with GDM at the Lausanne University Hospital for 3 consecutive years. Pre-pregnancy obesity, hypertension and dyslipidaemia were recorded as constituents of the MS.

Results: For 5788 deliveries, 159 women (2.7%) with GDM were identified. Constituents of the MS were present before GDM pregnancy in 26% (n = 37/144): 84% (n = 31/37) were obese, 38% (n = 14/37) had hypertension and 22% (n = 8/37) had dyslipidaemia. Gestational hypertension was associated with obesity (OR = 3.2, P = 0.02) and dyslipidaemia (OR = 5.4, P = 0.002). Seventy-four women (47%) returned for post-partum OGTT, which was abnormal in 20 women (27%): 11% (n = 8) had type 2 diabetes and 16% (n = 12) had impaired glucose tolerance. Independent predictors of abnormal glucose tolerance in the post-partum were: having > 2 abnormal values on the diagnostic OGTT during pregnancy and presenting MS constituents (OR = 5.2, CI 1.8-23.2 and OR = 5.3, CI 1.3-22.2).

Conclusions: In one fourth of GDM pregnancies, metabolic abnormalities precede the appearance of glucose intolerance. These women have a high risk of developing the MS and type 2 diabetes in later years. Where GDM screening is not universal, practitioners should be aware of those metabolic risks in every pregnant woman presenting with obesity, hypertension or dyslipidaemia, in order to achieve better diagnosis and especially better post-partum follow-up and treatment.

Key-words: Gestational diabetes mellitus · Metabolic syndrome · Post-partum impaired glucose tolerance · Post-partum type 2 diabetes mellitus.

RÉSUMÉ

Le diabète gestationnel et le risque de syndrome métabolique ; une étude de population à Lausanne, Suisse

Buts : Étudier les relations entre le diabète gestationnel (GDM) et le syndrome métabolique (MS), car la résistance à l'insuline est une des caractéristiques des deux conditions. Analyser le dépistage du diabète dans le post-partum pour identifier les facteurs de risque associés au développement d'un diabète de type 2 ultérieur.

Méthodes : Éude rétrospective de toutes les grossesses uniques diagnostiquées avec un diabète gestationnel à l'hôpital universitaire de Lausanne, pendant une durée de trois ans. La présence d'une obésité, d'une hypertension ou d'une dyslipidémie avant la grossesse définissent les composants du syndrome métabolique.

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Mots-clés : Diabète gestationnel · Syndrome métabolique · Intolérance au glucose dans le post-partum · Diabète de type 2 dans le post-partum.

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Introduction

Gestational diabetes mellitus (GDM) is defined as varying degrees of carbohydrate intolerance with onset or first recognition during pregnancy [1, 2]. Its prevalence varies between 1 and 14%, depending on the populations studied and the criteria used for diagnosis [2]. GDM is frequently associated with adverse pregnancy outcomes [1, 3, 4]. Prevention of macrosomia and perinatal complications are primary goals in the treatment of women with pregnancies complicated by GDM.

It has long been known that women with a history of GDM are at increased risk of developing type 2 diabetes mellitus (type 2 DM) later in life, and this was originally the purpose of identifying GDM [5]. Long-term follow-up studies indicate a conversion rate to type 2 diabetes between 10 and 50% [6]. Likewise, recent studies have shown that GDM also increases the risk of long-term development of hypertension and dyslipidaemia, and therefore also atherosclerosis and coronary heart disease [7, 8]. The frequently recognized association between glucose intolerance, obesity, hypertension and dyslipidaemia has led to the recognition of what is now known as the metabolic syndrome (MS). The major adverse consequence of the MS is cardiovascular disease (CVD), as several of its constituent metabolic abnormalities are in fact CVD risk factors. Insulin resistance is considered a central pathophysiological process both behind the metabolic syndrome and the development of gestational diabetes mellitus [8, 9]. Indeed several groups have hypothesized that GDM may be one of the first metabolic abnormalities to be recognized in the development of the metabolic syndrome [8, 10, 11]. Recently, two groups have also shown that the metabolic syndrome increases the risk for diabetes independently of other risk factors, including glycaemia or insulin measurements [12, 13].

Results from diabetes prevention studies have shown that lifestyle modifications and/or treatment with oral anti-diabetics can reduce the incidence of diabetes in individuals with impaired glucose tolerance (IGT) and in other high-risk populations [14-16]. Because of these positive results, it has become more relevant to identify subjects at risk for diabetes. Women diagnosed with GDM make up one of those high-risk populations. It is therefore of critical importance both that they are diagnosed during pregnancy and that they have a regular and long-term post-partum follow-up, to allow for the identification and the treatment of any persistent metabolic abnormality.

The first purpose of our study was to analyse the population characteristics of pregnant women with GDM in relation to the metabolic syndrome constituents. Our second aim was to evaluate the post-partum results and the identification of the risk factors associated with post-partum impaired glucose tolerance and type 2 diabetes.

Methods

Patients

We conducted a retrospective analysis of all singleton pregnancies diagnosed with GDM between January 2000 and December 2002 at the Lausanne University Hospital. The patients were identified by the GDM diagnosis listed on the medical record of the delivery. Medical history, physical examination and laboratory values were then obtained by reviewing the hospital medical records of the obstetric and diabetic outpatient clinics. We excluded from the study all patients with pre-existent type 1 or type 2 diabetes.

Diagnosis of GDM

During pregnancy follow-up, gynaecologists at the obstetric outpatient clinic use the following risk factors to screen women for GDM: a first degree relative with diabetes, a history of GDM or macrosomia, a suspicion of macrosomia in the current pregnancy, persistent glucosuria, a rapid or excessive weight gain during early pregnancy, obesity, or a random plasma glucose ≥ 7.0 mmol/l. Women with one or more of these factors underwent the standard 100 g 3-h oral glucose tolerance test (OGTT) after an overnight fast. The diagnosis of GDM was made according to the National Diabetes Data Group (NDDG) criteria (≥ 2 abnormal values; glucose concentrations of ≥ 5.8 mmol/l for fasting, ≥ 10.6 mmol/l at 1 hour, ≥ 9.2 mmol/l at 2 hours, and ≥ 8.1 mmol/l at 3 hours) [17]. The glucose values for the OGTT were all measured by the central laboratory of the University Hospital.

Metabolic syndrome (MS)

Both the WHO and the National Cholesterol Education Program (NCEP) have proposed extensive definitions of the metabolic syndrome [18, 19]. These definitions are however not usually applied in the clinical setting of an obstetric outpatient clinic. Furthermore, as microalbuminuria and insulin values are not routinely measured, we used our own definition, based on the data actually recorded by the gynaecologists at the first antenatal visit, to remain as close as possible to the proposed definitions. We considered that a GDM diagnosis was a marker of an insulin-resistant state and therefore comparable to the impaired glucose tolerance (IGT) diagnosis. We thus identified the MS in women with IGT defined by their GDM diagnosis and at least one of the following factors: hypertension, dyslipidaemia and/or obesity. The term metabolic syndrome (MS) used in the results refers to this particular definition, keeping in mind that it does not completely correspond to the definitions given by the WHO or the NCEP. Hypertension was diagnosed if the patient was receiving antihypertensive drugs before her pregnancy and/or if blood pressure was higher than 140/90 mmHg at the first antenatal visit, in accordance with the obstetric criteria. Dyslipidaemia was recognized if the woman was taking a hypolipaemic treatment before her pregnancy. Obesity was present if the pre-pregnancy body mass index (BMI) was ≥ 30 kg/m².

Pregnancy and post-partum follow-up

Women with GDM were regularly seen during their pregnancy by a team composed of a diabetologist, a trained dietician and a diabetes nurse. They were managed initially with self-monitoring of blood glucose 4-6 times daily and dietary measures. The therapeutic aims were blood glucose levels before meals < 5.0 mmol/l and 2 hour postprandial < 6.5 mmol/l. If two blood glucose levels in one to two weeks were above these aims despite adequate dietary measures, insulin of the rapid type was started or doses were increased. If these measures were insufficient to reach the therapeutic aims, a basal insulin was added [2]. During pregnancy maternal complications were diagnosed as: oedema, proteinuria on dipstick test, gestational hypertension and pre-eclampsia. These complications were defined and recorded at the Obstetric Outpatient Unit. Gestational hypertension was defined as the development of a blood pressure ≥ 140/90 mmHg during pregnancy. Pre-eclampsia was defined as blood pressure ≥ 140/90 mmHg combined with proteinuria on dipstick test.

Diet and insulin therapy were discontinued after delivery. On the second post-partum day, a fasting plasma glucose (FPG) value was measured in all women. Recommendation was given to all the patients that they should undergo a postnatal test with the WHO 2-h 75 g glucose challenge test 8 weeks after delivery [2, 18]. The diagnosis of post-partum diabetes was made according to the World Health Organization criteria [18].

Statistical analyses

Continuous variables normally distributed were expressed in means ± standard deviation (SD) and were compared using the unpaired Student's t test. Non-normally distributed continuous variables were expressed in median, P10 — P90 interval and Mann-Whitney U test was used for correlation. Categorical variables were expressed in frequency and differences were based on the chi-square test. For several analyses we used a fasting plasma glucose threshold of 5.6 mmol/l based on the new criteria for fasting plasma glucose recommended by the Expert Committee on the diagnosis and classification of Diabetes Mellitus in November 2003 [20]. Forward stepwise logistic regression analyses were performed with Stata 8.0 (Stata Corporation, College Station, TX, USA); all other statistical analyses were performed using JMP 5.0 (SAS Institute, Cary, USA). A P value ≤ 0.05 was considered statistically significant.

Results

Diagnosis and investigation of GDM

For the 3-year study period, there were 5788 deliveries at the Obstetric ward. A total of 159 women were diagnosed with GDM during that time, their characteristics are presented in Table I. The calculated prevalence of GDM was 2.7%. The 100 g 3-h OGTT test results were available for 89% of the patients (n = 141). Eighteen women could not complete the OGTT because of nausea and/or vomiting. We therefore recorded only the fasting plasma glucose. To make the diagnosis, these women were followed with self-monitoring of blood glucose 4-6 times daily over one week, and if the blood glucose levels before meals were repeatedly > 5.0 mmol/l and/or 2 hour postprandial > 6.5 mmol/l, we considered them to have GDM and treated them as the others. We cannot give the respective frequencies of the factors used for screening, because they were not recorded specifically for each woman. The median gestational age at GDM

Table I
Population characteristics (n = 159).

	GDM population (n = 159)
Age at diagnosis (y)	33 ± 5
Caucasian origin	62%
Pre-pregnancy weight (kg)	68 ± 14
Pre-pregnancy BMI (kg/m²)	25.9 ± 5.1
Obesity (BMI ≥ 30 kg/m²)	22%
Parity ≥ 1	61%
History of macrosomia	40%
History of GDM	26%
Familial history of diabetes mellitus	47%
Familial history of obesity	13%
Familial history of CVD	29%
Hypertension	9%
Dyslipidaemia [1]	5%
Metabolic syndrome	26%

BMI: body mass index; CVD: cardiovascular disease.
[1] We only have information for 108 (68%) patients.

Abbreviations

AGT :	Abnormal glucose tolerance
FPG :	Fasting plasma glucose
GDM :	Gestational diabetes mellitus
HbA$_{1C}$:	Glycated haemoglobin
IFG :	Impaired fasting glucose
IGT :	Impaired glucose tolerance
MS :	Metabolic syndrome
OGTT	Oral glucose tolerance test
TYPE 2 DM :	Type 2 diabetes mellitus

diagnosis was 28 (21-34) gestational weeks (GW). Forty-two percent of the women (n = 60) had the OGTT after the recommended 24-28 GW interval [2]. Median HbA_{1c} recorded at diagnosis was 5.4 (4.7-6.6)%. The cut-off $HbA_{1c} \geq 5.4\%$ was used for further analyses.

Metabolic syndrome and its consequences during pregnancy

In our GDM population, the total prevalence of the metabolic syndrome before pregnancy was 26% (n = 37/144), which means that one woman in 4 had metabolic abnormalities. Among the constituents of the MS, obesity was present in 84% (n = 31/37), hypertension in 38% (n = 14/37) and dyslipidaemia in 22% (n = 8/37). Moreover obesity was significantly associated with pre-existent hypertension (OR = 5.1, P < 0.001), dyslipidaemia (OR = 2.9, P = 0.02) and with insulin therapy need during pregnancy (OR = 2.7, P = 0.003). Lipid profiles were measured only in 68% of the patients (n = 108/159), which might indicate that we are under-estimating the true prevalence of dyslipidaemia.

The patients were divided according to their ethnic background in 4 groups and the metabolic abnormalities within each group are presented in *Table II*. Sixty-two percent were Caucasians from European countries (n = 98), 12% were Asian Indians mostly from Sri Lanka (n = 19), 13% came from North Africa and the Middle East (n = 20) and 14% represented several other African and Asian countries (n = 22). The groups were not large enough to gain significant statistical power.

The MS was strongly correlated with several maternal complications. These were recorded as follows: oedema (48%), proteinuria on dipstick test (32%), gestational hypertension (11%) and pre-eclampsia (5%). The presence of the MS before the onset of pregnancy was an important risk factor for the development of gestational hypertension (OR = 5.1, P = 0.001). Results are presented in *Table III*. Pre-eclampsia on the other hand was only correlated with a FPG ≥ 5.6 mmol/l on the OGTT (OR = 4.5, P = 0.04), but not with other metabolic disturbances such as obesity, hypertension or dyslipidaemia.

Table II
Pre-pregnancy metabolic syndrome constituents in different ethnic groups (n = 159).

	Caucasians (n = 98)	Asian Indians (n = 19)	North Africans (n = 20)	Others (n = 22)
Obesity	19%	5%	25%	27%
Hypertension	7%	0	15%	18%
Dyslipidaemia	6%	5%	5%	0

The differences were all non-significant.

Table III
Maternal complications (n = 135).

	No MS (n = 100)	With MS (n = 35)	OR	P
Age	32.3 ± 0.45	33.6 ± 0.78	—	0.1
Oedema	46%	66%	1.8	0.05
Proteinuria	26%	49%	2.0	0.01
Pre-eclampsia	4%	9%	1.7	0.3
	(n = 100)	(n = 21)		
Gestational hypertension	6%	30%	3.7	0.001

Gestational hypertension is defined as the new development of hypertension during pregnancy, and thus we did not include the 14 patients with pre-existent hypertension in the analysis.

Insulin treatment during pregnancy

At the time of delivery, 60% of the women (n = 96) were treated with insulin. Twenty-eight percent (n = 27) were treated only with rapid insulin, 10% (n = 10) only with basal insulin and 61% (n = 59) with both. The median doses recorded at delivery were: rapid insulin 16 (6-44) units and basal insulin 14 (8-50) units. *Table IV* shows the factors predicting basal insulin need: obesity, hypertension, high glycaemic values, early GDM diagnosis and multiparity. Forward stepwise logistic regression analysis confirmed FPG ≥ 5.6 mmol/l (OR = 11.6, CI 3.5-37.9), a GDM diagnosis made before 28 GW (OR = 3.0, CI 1.1-8.2) and multiparity (OR = 3.3, CI 1.2-9.4) to be significant independent risk factors for basal insulin treatment during pregnancy.

Post-partum population

After an average of 9.5 (6.4-45.0) weeks, 47% of the mothers (n = 74) returned for the post-partum 75 g OGTT.

Table IV
Factors predicting basal insulin need (n = 159).

	No insulin need (n = 90)	Basal insulin need (n = 69)	OR	P
FPG ≥ 5.6 mmol/l	17%	57%	2.5	< 0.001
Pre-pregnancy hypertension	3%	15%	1.9	0.01
Pre-pregnancy obesity	12%	33%	1.8	0.003
GA at diagnosis < 28 weeks	34%	57%	1.7	0.004
$HbA_{1c} \geq 5.4\%$	45%	69%	1.7	0.01
Parity ≥ 1	53%	72%	1.6	0.02

GA: gestational age.

Table V shows that the population characteristics of the patients that came for post-partum testing were similar to those that did not come. A few points were nonetheless interesting. The women who underwent an OGTT during pregnancy were 9 times more likely to come back after delivery to take a second test (OR = 8.8, P < 0.001). Likewise, women who were treated with insulin during their pregnancy also returned more frequently for follow-up (OR = 1.9, P = 0.001).

Post-partum OGTT results

Results are shown in *figure 1*. A total of 8 women (11%) had a diagnosis of type 2 diabetes mellitus, and 12 patients (16%) had impaired glucose tolerance. Of these, three (25%) also had impaired fasting glucose (FPG ≥ 6.1 mmol/l). These 20 patients were collectively identified as having abnormal glucose tolerance (AGT) and were analysed as one group. There were interesting but non-significant ethnic differences: among Asian Indians 70% returned for post-partum testing and 38% had AGT, compared to 46% of Caucasians who returned of which 20% had AGT and only 35% of North Africans took the OGTT and 14% had AGT.

Factors predicting post-partum AGT in univariate analysis are presented in *Table VI*. These variables can be divided into two main groups: those concerning glycaemic values (high FPG at diagnosis of GDM, > 2 abnormal values on the OGTT, HbA_{1c} and 2nd post-partum day FPG) and those associated with the MS (pre-pregnancy BMI, dyslipidaemia and gestational hypertension). In forward step-wise logistic regression analysis two independent predictors were identified: the metabolic syndrome (OR = 5.3, CI 1.3-22.2) and > 2 abnormal values on the OGTT (OR = 5.2, CI 1.8-23.2).

Figure 1
The results of the post-partum Oral Glucose Tolerance Test (OGTT).

Table V
Population characteristics at diagnosis (n = 159).

	No post-partum follow-up (n = 85)	Post-partum follow-up (n = 74)	OR	P
Age at diagnosis (y)	33	33	—	0.9
Caucasian origin	54%	51%	0.9	0.7
Pre-pregnancy weight (kg)	68	67	—	0.8
Pre-pregnancy BMI (kg/m²)	25.9	25.1	—	0.9
Obesity (BMI ≥ 30 kg/m²)	21%	23%	1.1	0.7
Parity ≥ 1	57%	66%	1.2	0.3
History of macrosomia	48%	33%	0.7	0.15
History of GDM	28%	24%	0.9	0.7
Familial history of diabetes mellitus	48%	47%	1.0	0.9
Familial history of obesity	14%	13%	1.0	0.9
Familial history of CVD	26%	32%	1.2	0.4
Hypertension	13%	4%	0.4	0.05
Dyslipidaemia	7%	3%	0.5	0.2
Metabolic syndrome	27%	24%	0.9	0.7
Took the 100g OGTT	81%	99%	8.8	< 0.001
Were treated with insulin	49%	75%	1.9	0.001

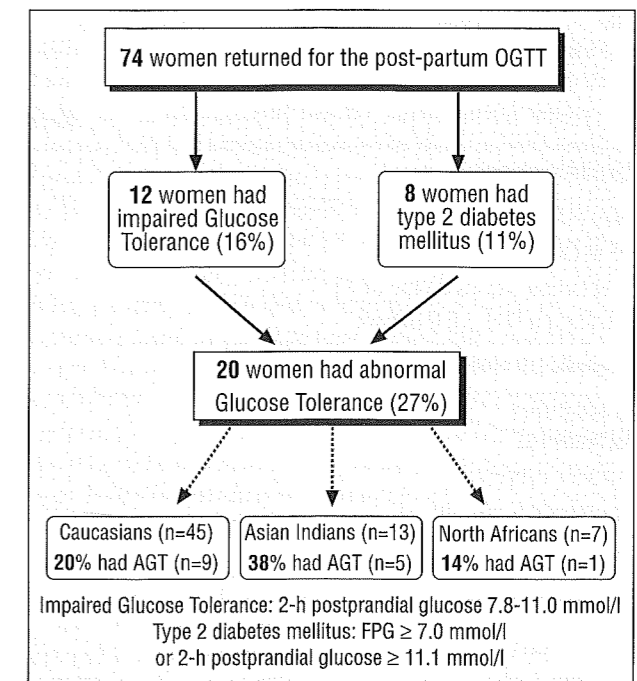BMI: body mass index; CVD: cardiovascular disease; NS: non-significant.

Table VI
Factors predicting post-partum abnormal glucose tolerance (n = 74).

	Normal GT (n = 54)	Abnormal GT (n = 20)	OR	P
Glycaemic values:				
HbA$_{1c}$ ≥ 5.4%	45%	94%	10.7	0.001
FPG at OGTT ≥ 5.3 mmol/l	38%	85%	5.5	< 0.001
> 2 abnormal values on the OGTT	33%	81%	5.3	0.001
Post-partum FPG ≥ 5.6 mmol/l	7%	55%	4.8	< 0.001
Metabolic parameters:				
Pre-pregnancy dyslipidaemia	3%	13%	4.0	0.02
Metabolic syndrome	16%	50%	3.1	0.006
Pre-pregnancy obesity	16%	44%	2.6	0.02
Gestational hypertension	6%	21%	2.3	0.07

GT: glucose tolerance.

Figure 2 shows the Receiver Operator Characteristic (ROC) curve for AGT by fasting plasma glucose at OGTT during pregnancy. The area under the curve (AUC) is 0.812 and P < 0.0001, demonstrating the highly discriminative power of FPG in predicting post-partum AGT. The FPG value closest to the ideal of 100% sensitivity and 100% specificity was 5.3 mmol/l. This cut-off was 88% sensitive and 70% specific. As illustrated in *figure 3*, the concomitant presence of metabolic syndrome constituents before preg-

nancy and a FPG ≥ 5.6 mmol/l at GDM diagnosis increased the prevalence of post-partum AGT to 78% compared to the 10% in women with no metabolic disturbances (OR = 7.6, P < 0.001).

After the post-partum OGTT, all women with AGT continued to be followed at the diabetic outpatient clinic. Thirteen (65%) were managed only with nutritional advice, whereas 4 (20%) were started on oral antidiabetic drugs and 3 (15%) needed to restart insulin therapy.
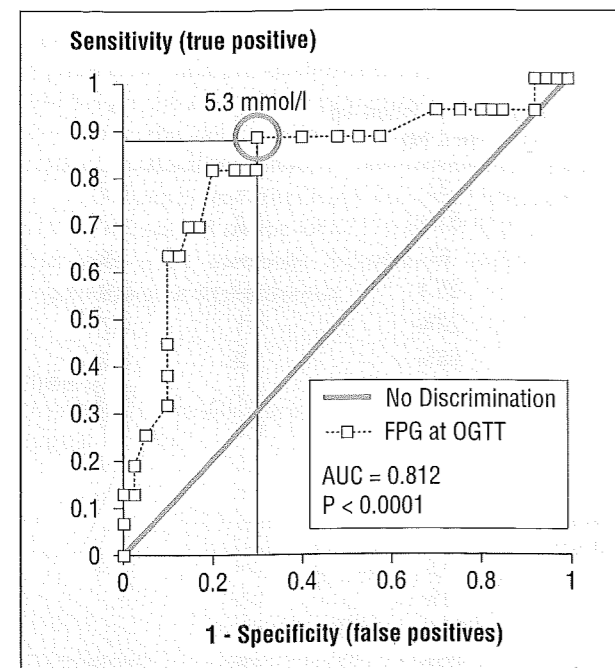

Figure 2
ROC curve for the occurrence of post-partum Abnormal Glucose Tolerance by OGTT fasting plasma glucose (FPG) during pregnancy.
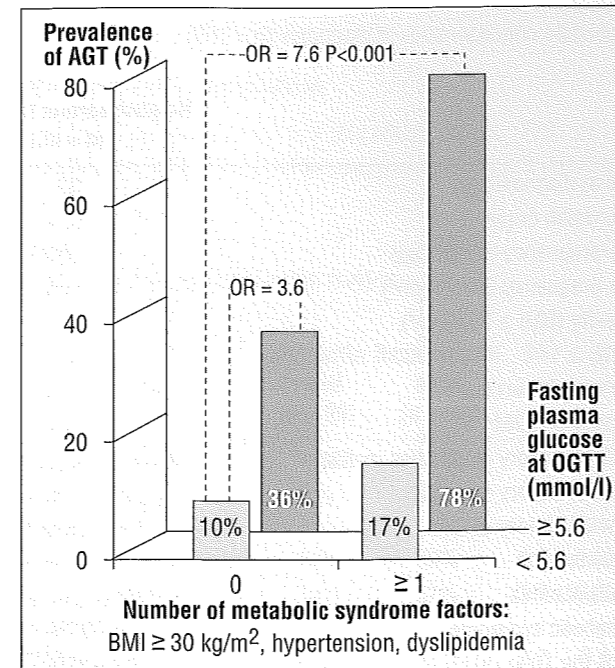

Figure 3
Prevalence of abnormal glucose tolerance (AGT) in function of the presence of the metabolic syndrome and/or fasting plasma glucose at OGTT.

Discussion

Several studies have examined the development of the metabolic syndrome in parous women and suggested that a history of GDM in a previous pregnancy was an important risk factor [8, 10]. They have also postulated that GDM might be considered an early expression of the metabolic syndrome. In our study we analysed the pre-pregnancy presence of obesity, hypertension and dyslipidaemia in women with GDM and their influence on the subsequent development of impaired glucose tolerance and type 2 DM. The importance of these issues is emphasized by the continuous increase in the prevalence of obesity, diabetes, hypertension and other obesity related health risk factors in the Western world [21, 22].

The main findings of our study were the important prevalence of metabolic syndrome constituents present in women before their GDM pregnancy and the associated increased risk of future type 2 DM, as measured in the post-partum. Indeed, 26% of the patients presented metabolic abnormalities before their GDM pregnancy, mostly obesity in 84% of them. These metabolic abnormalities were independently associated with a 5-fold increase in the risk of developing an abnormal glucose tolerance in the close post-partum.

An interesting point to note concerned the timing of the diagnostic OGTT during pregnancy. Forty-two percent of the patients with risk factors for GDM were tested after the recommended 24-28 GW. As stated before, there is no consensus on the screening strategy of GDM and our patients were taken up in the study by the means of their obstetric diagnosis. Gynaecologists might be less sensitive to the importance of the metabolic syndrome and its consequences and this is a fact that we tried to improve with this study.

Among our GDM population, 22% of the women presented pre-pregnancy obesity and 9% had hypertension. Blood pressure, lipid profiles and height were not systematically measured in pregnant women without GDM and we were thus unable to compare the prevalence of these factors. An interesting point to note, although not significant, was the distribution of obesity among different ethnic groups. The lowest prevalence of obesity was found in Asian Indians (5%), followed by Caucasians (18%) and was highest in North Africans (25%). In our study, Asian Indians showed a high degree of abnormal glucose tolerance in the post-partum. This could in part be explained by their high compliance (70% returned for the post-partum test), but may also support the known fact that even without being overweight they have a high degree of insulin resistance, because of adverse upper body adiposity [23, 24].

Obesity is a simple criterion recommended by the WHO for non-systematic screening of GDM and gynaecologists use it to guide their screening because obesity is also associated with other obstetric complications. Of course, this

could also act as a screening bias and explain the high prevalence of obesity among our GDM patients. Obesity was moreover significantly associated with hypertension, dyslipidaemia and increased insulin need during pregnancy, emphasizing the interdependence of these parameters [25]. Insulin therapy was further associated with a GDM diagnosis before 28 gestational weeks, high fasting plasma glucose on the OGTT and multiparity, all three markers of serious disturbances in carbohydrate metabolism [4, 26, 27]. We can thus postulate that in this subgroup of women the insulin resistance was already present before the current pregnancy. The metabolic burden of pregnancy led to a progression of the insulin resistance and its clinical complications. Indeed, the additional role of the placental hormones in the development and accentuation of insulin resistance, even in non-diabetic women, is well established [28]. These women also had most of the risk factors for post-partum abnormal glucose tolerance, namely components of the metabolic syndrome, and high glycaemic values at diagnosis and in the immediate post-partum days. The risk of AGT was increased 7-fold compared to patients without these criteria. This suggests that these factors act synergistically to produce adverse metabolic outcomes.

In most women luckily, the insulin resistance decreases after delivery and the glucose intolerance disappears. These women can be considered to have more subtle metabolic disturbances than the patients presenting with constituents of the metabolic syndrome before their pregnancy. However, as known from many studies, all women with a history of GDM are at increased risk for the future development of IGT and type 2 DM [6, 27, 29]. Thus, these women have a lower resilience to the metabolic challenges of pregnancy because they eventually have a decreased pancreatic beta-cell function reserve [29]. One central pathogenic mechanism has been shown to be the progression of insulin resistance, together with endothelial dysfunction and low-grade inflammation [30, 31]. Even in the absence of pre-pregnancy obesity, women with a history of GDM have an almost 5-fold additional independent risk of developing the metabolic syndrome compared to controls without GDM [10]. Winzer *et al.* showed that women with prior GDM had reduced adiponectin concentrations independently of obesity and metabolic abnormalities and this was associated with sub-clinical inflammation and atherogenic parameters [31]. The important consequence of this relationship is the greatly increased risk of cardiovascular disease in patients with the metabolic syndrome [32-34].

Different studies have shown that with appropriate lifestyle modifications (diet, regular exercise) or glitazone treatment the β-cell function can be preserved and this in turn reduces the progression to type 2 DM in high-risk populations, for example in women with a previous GDM pregnancy [14-16]. In view of the serious metabolic and clinical complications of the metabolic syndrome and the new possibility to delay their appearance, it is of particular

importance to regularly follow these women after their pregnancy. The risk of developing impaired glucose tolerance and type 2 DM should be assessed by an oral glucose challenge test or a fasting plasma glucose measurement, as recommended by many guidelines [2, 18, 35].

Several limitations to our study need to be mentioned. As this was a retrospective study and that at the time of the study the patients were not systematically summoned after their delivery to take the post-partum OGTT, many women were lost to follow-up, and we cannot increase this percentage for the present study. Secondly, there are several points in which the patients that participated in the post-partum follow-up differ from the others, and thus our post-partum population might not be entirely representative of the total population. Interestingly, women that underwent an OGTT during pregnancy were 9 times more likely to come back after delivery, likely because they already knew what was to be expected from the procedure. Insulin treatment also prompted women to come back, as mentioned in other studies [27]. Complying with an intensive treatment during their pregnancy might have increased those patients' awareness of the importance and risks attached to these metabolic abnormalities. But it could also bias our results towards glucose intolerance. The participation rate also differed among ethnic groups and this bias could be related to insulin treatment: 40% of Caucasians needed insulin treatment, only 32% of North Africans but 58% of Asian Indians. Thus, if Asian Indians needed insulin treatment more frequently, it could also explain their overrepresentation at follow-up. Yet, for all other variables, the two groups were quite similar in pre-pregnancy variables. In a systematic review, Kim *et al.* showed very variable retention rates (38%-100%) for post-partum follow-up, suggesting that this is a widespread problem, reflecting clinical practice [6]. Last, the women were seen just once 8 weeks after their pregnancy, and we thus have no knowledge of the long-term evolution of our population.

In spite of these limitations, we feel that our results support the fact, presented in other studies, that GDM can be looked upon as an important metabolic abnormality, appearing before, at the same time or after obesity, hypertension and dyslipidaemia, in the development of the metabolic syndrome [8, 11]. As the prevalence of obesity and MS are increasing throughout the world, particularly in younger subjects [22, 36], more and more young pregnant women will present these metabolic disturbances. Recognizing GDM as part of the metabolic syndrome, with all its potential cardiovascular complications, is therefore increasingly important. Because GDM screening is non-systematic in many centres, we wish to improve the awareness of these high-risk women and we suggest adding obesity, hypertension and dyslipidaemia to the traditional risk factors used for screening. Moreover, every post-partum visit should include measures of all the components of the metabolic syndrome and not only glucose intolerance. These meas-

ures aim at improving post-partum monitoring to allow earlier identification and treatment of all CVD risk factors.

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