Original article

Occurrence of gestational diabetes mellitus, maternal and fetal outcomes beyond the 28th week of gestation in women at high risk of gestational diabetes. A prospective study

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Abstract

Aim. – Among the numerous guidelines defining the diagnostic strategy of gestational diabetes mellitus (GDM), none of them suggest a follow-up in women with risk factors beyond the 28th week of gestation (WG). The primary objective of this study was to assess the incidence of GDM beyond 28 WG in a group of women at high risk. The secondary objectives were to evaluate maternal and fetal outcomes in early and late GDM (between 24–28 WG, and beyond 28 WG), as well as to compare them to a normal glucose tolerance (NGT) group.

Methods. – A prospective study conducted in 191 consecutive women. Between 24–28 WG, the diagnosis of GDM was performed in a two-step approach (50 then 75 g). Beyond the 28 WG, the diagnosis of GDM was based on self-monitoring blood glucose (SMBG). All women were educated about an individualized diabetic diet and to perform SMBG daily glucose profiles.

Results. – Seventy-two percent of the women at risk had developed GDM. Among these, 54% had developed early GDM, between 24–28 WG, and 18% had developed late GDM, beyond the 28th WG. Gestational age of late GDM was estimated 30 WG. In late GDM, onset of diabetes seems to be predicted by an increase in capillary glucose value determined at 22:00 hours, but this needs to be confirmed. Women who develop GDM2 have a significantly higher rate of macrosomia and more important pre-pregnancy overweight, underlining this impact in the occurrence of macrosomia. Finally maternal outcomes were not different in the 3 groups with intensive intervention.

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Résumé

Étude prospective de survenue d’un diabète gestationnel et des événements maternels et fœtaux au-delà de la 28e semaine de gestation chez des femmes à haut risque de diabète gestationnel

Objectif. – Il n’existe actuellement pas de consensus de dépistage et de diagnostic du diabète gestationnel (DG) au-delà de 28 semaines d’aménorrhée (SA) chez des femmes à haut risque de diabète gestationnel. L’objectif primaire de cette étude était d’évaluer l’incidence du DG après 28 SA chez des femmes à haut risque. Les objectifs secondaires étaient d’évaluer les événements maternels et fœtaux en cas de DG précocé (diagnostiqué entre 24 et 28 SA), et tardif (après 28 SA), en les comparant à ceux observés chez les femmes restées normoglycémiques durant toute la grossesse.

Méthodes. – Étude prospective menée chez 191 femmes consécutives à haut risque de DG. Entre 24 et 28 SA, le diagnostic de DG a été fait en deux temps (HGPO 50 puis 75 g). Après 28 SA, le diagnostic de DG a été fait par l’autosurveillance glycémique. Toutes les femmes ont bénéficié d’une éducation individualisée diabétique et diététique et à la réalisation d’un profil glycémique quotidien par l’autosurveillance glycémique.

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Résultats. – Soixante-douze pour cent des femmes à risque de DG ont développé un DG. Parmi elles, 54 % ont développé un DG précoce entre 24 et 28 SA, et 18 % un DG tardif après 28 SA. Le terme du DG tardif est estimé à 30 SA. La survenue du DG tardif est en corrélation avec l’élévation de la glycémie capillaire à 22 heures. Les femmes qui ont développé un DG tardif avaient un taux de macrosomes significativement plus élevé et un surpoids antérieur plus prononcé et plus fréquent, ce qui souligne l’impact de celui-ci sur la survenue de la macrosomie. Enfin, la survenue des événements maternels n’était pas différente dans les trois groupes en cas de prise en charge intensive.

Keywords: Gestational diabetes mellitus; Late onset gestational diabetes mellitus; Maternal outcomes; Fetal outcomes; Risk factors

Mots clés : Diabète gestationnel ; Diabète gestationnel tardif ; Événements maternels ; Événements fœtaux ; Facteurs de risque

1. Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. GDM is associated with an increase in maternal and fetal outcomes [1]. Thus, diagnosis of GDM aims at reducing maternal and fetal complications and at identifying women at high risk to develop type 2 diabetes mellitus. While no international consensus defining strategy of screening and diagnosis of GDM is available, the majority of guidelines recommend systematic screening between 24–28 weeks of gestation (WG) in all women. In women with risk factors, screening should be performed starting at the beginning of pregnancy [1]. Most studies are comparative and retrospective and have focused on specific clinical populations [2–10]. No data is available concerning the specific issue of GDM (incidence, maternal and fetal prognosis) occurring beyond 28 WG.

Therefore, we have studied prospectively 191 women at high risk of GDM. The primary goal of our study was to assess the incidence of GDM beyond 28 WG. The secondary goal was to evaluate maternal and fetal outcomes in these women: Comparison of early GDM (between 24–28 WG), and late GDM (beyond 28 WG), versus women with normal glucose tolerance (NGT) during all pregnancy.

2. Research design and methods

2.1. Study population

We conducted a prospective study in 191 consecutive pregnant women. Eligible women had one or more risk factors for GDM including age (> 35 years), pre-pregnancy overweight (body mass index, BMI ≥ 25 kg/m²), personal history of GDM or macrosomia, multiparity, first-degree family history of diabetes, personal history of abnormal glucose tolerance, history of poor obstetrics outcomes (prior neonatal death or preterm delivery, caesarean delivery) and a risk ethnic/racial group (Hispanic American, African-American, South or East Asian and Pacific Islander) [1]. All women at risk were referred to the Department of Obstetrics between 24–28 WG. Diagnosis of GDM was performed in a two-step approach: initial screening was performed by oral glucose load (plasma glucose concentration 1 hour after a 50 g ≥ 130 mg/dl (7.2 mmol/l)). Diagnosis of GDM was based on a 75 g glucose load OGTT (criteria included fasting plasma glucose values ≥ 95 mg/dl (5.3 mmol/l) and/or ≥ 155 mg/dl (8.6 mmol/l) 2 hours after glucose load) [1]. Diagnosis of early GDM (GDM1) was retained in women with positive test between 24–28 WG. Beyond 28 WG, diagnosis of late GDM (GDM2) was made on the analysis of the results of capillary glucose self-monitoring. Diagnosis of late GDM was retained in the presence of pre-prandial capillary plasma glucose > 95 mg/dl (5.3 mmol/l) and/or 2 hours postprandial capillary glucose > 120 mg/dl (6.6 mmol/l) during 7 consecutive days. Study protocol was approved by the local institutional review board.

2.2. Intervention

All women (with GDM or risk factors) were educated about an individualized diabetic diet according to their activity level, dietary intake, weight gain and pre-pregnancy weight (30 kcal/kg/24 hours) with calorie restriction in obese women (25 kcal/kg/24 hours). All women were instructed to self-monitor blood glucose (SMBG) by performing a daily glucose profile (three pre- and 2 hours-postprandial). The accuracy of capillary glucose values was compared bi-weekly with laboratory plasma glucose values (glucose oxidase method). The glycemic targets were to maintain fasting capillary glucose level of < 95 mg/dl (5.3 mmol/l), and 2 hours-postprandial level of < 120 mg/dl (6.6 mmol/l). Women who did not meet these targets with diet alone were treated with insulin. The frequency of follow-up visits with the diabetologist during pregnancy was weekly or bi-weekly.

2.3. Clinical and biological evaluations

Microvascular complications were assessed by performing fundus photography, urinary albumin excretion and physical examination for peripheral neuropathy. The maternal surveillance included blood pressure, weight, daily glucose profile and diet revision twice weekly. The laboratory evaluation included monthly plasma fructosamine level (Randox on Olympus AU640 method, normal range 122–236 μmol/l) and glycated hemoglobin (HbA1c) levels every 3 months (high-performance liquid chromatography method, normal range 4.1–6.4%). Fetal biometry was determined by ultrasound at the second and third trimester evaluates of abdominal circumference (AC), head circumference (HC) and amniotic fluid. Fetal outcomes were analyzed, including Apgar score, congenital malformation, stillbirth, birth weight, hy-
poglycemia (≤ 0.40 mg/l, capillary blood glucose was measured at 1, 3, 6 and 12 hours postpartum), jaundice, anemia, hypocalcemia, respiratory distress syndrome, shoulder dystocia, bone fracture, nerve palsy, neonatal care admission, infections, inhalation of amniotic fluid, pneumothorax, and infant death. Macrosomia was defined as birth weight greater than 4000 g.

Maternal outcomes were analyzed, including hypertension, weight gain, threatened premature delivery, caesarean delivery (elective or emergency).

2.4. Statistical analysis

Data were reported as mean ± S.D. Student’s test was used to compare the three groups, with $P < 0.05$ considered as significant.

3. Results

A total of 191 consecutive women at risk of GDM have been included in the study and were followed from 24–28 WG until delivery. Microvascular complications were absent in all women.

3.1. Incidence of GDM

Between 24–28 WG, 104 women (54%) had GDM1 and 87 (46%) had a NGT. Beyond the 28th WG, 34/87 (39%) developed GDM2. A total of 72% of women had developed GDM, 54% between 24–28 WG, and 18% beyond the 28th WG. At the end of the study, three groups could be identified: GDM1 ($N = 104$), GDM2 ($N = 34$), and NGT group ($N = 53$). The investigation of food evaluation was not different in the three groups.

3.2. Distribution of the risk factors of GDM (Table 1)

No statistically significant difference was found between the three groups regarding age (> 35 years), multiparity, and family history of diabetes. The ethnic group largely prevalent was North African (skew inherent to our Hospital). Pre-pregnancy BMI and BMI $≥ 25$ kg/m$^2$ were significantly higher in the GDM2 group compared to the GDM1 group.

3.3. Fetal outcomes (Table 2)

3.3.1. Macrosomia

The fetal biometry evaluated by ultrasound showed that AC and HC were significantly larger in GDM2 compared with the other groups at the second and third trimester. Excess in amniotic fluid was rare in the three groups. In agreement with ultrasound data, mean birth weight and macrosomia were significantly higher in GDM2 compared with the other groups.

3.3.2. Other events

There was no difference between the three groups concerning the incidence of stillbirth, hypoglycemia, and jaundice requiring phototherapy. One case of respiratory distress syndrome was observed in the NGT group, one case of anemia in the GDM1 and GDM2 groups, one case of infection and two cases of pneumothorax in the GDM1 group. One case of death in utero (twin pregnancy) occurred in the GDM2 group, its cause remains unknown. Occurrence of the fetal outcomes was the same in GDM1 and NGT groups, and was significantly

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<td>Comparisons of risk factors of gestational diabetes in the three groups</td>
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<td>Age (years)</td>
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<td>BMI pre-pregnancy (kg/m$^2$)</td>
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No personal history of hyperglycemia in the three groups, and mother birth weight was unknown in 80% of cases. GDM1: early GDM, diagnosed between the 24–28th WG, GDM2: late GDM, diagnosed beyond the 28th WG, NGT: normal glucose tolerance; BMI: body mass index. Comparisons (Student’s test) $P_1$: GDM1 versus GDM2; $P_2$: GDM1 versus NGT; $P_3$: GDM2 versus NGT.
higher in GDM2 group. This difference was due to an excess in macrosomia.

3.4. Maternal outcomes

We observed no significant statistically significant difference between the three groups concerning gestational age of birth (38.8 ± 1.4, 39.1 ± 1.4 and 39.1 ± 1.9 WG), total weight gain (12.4 ± 9.6, 10.6 ± 6.1 and 11.5 ± 5.9 kg), rate of hypertension (0, 0 and 0%) of threatened premature delivery (1, 0 and 2%), cesarean delivery elective (6%, 6% and 0%) or emergency (6, 12 and 8%) in the GDM1, GDM2 and NGT groups, respectively. No cesarean complication was observed.

3.5. Screening and diagnostic tests (Table 3)

The analysis of the plasma glucose values of tests performed between 24–28 WG showed a heterogeneous metabolic pattern in the NGT group. Plasma glucose concentration values post-load (50 and 75 g) were significantly higher in the GDM2 group compared to the NGT group (Table 3).

3.6. HbA1c, fructosamine

HbA1c values were in the normal range, with no difference between the GDM1 and GDM2 groups (5.24 ± 0.85 vs 5.55 ± 0.88% between 14–27 WG, P = 0.54, and 5.14 ± 0.64 vs 5.35 ± 0.29% between 28–41 WG, P = 0.37, respectively). All fructosamine values remained in the normal range. However, in the GDM1 group, we had observed a decrease in fructosamine values starting from the 26th WG, corresponding to the medical intervention. In the GDM2 group, we had observed an increase in fructosamine values between 26–29 WG as well as 30–33 WG. This period precedes the onset of GDM2. Beyond the 29th WG, fructosamine values were not different in the two groups (Fig. 1).

3.7. Daily glucose profile preceding GDM2

Daily glucose profiles of the GDM2 women (N = 34) were evaluated. Analysis of the capillary glucose values was performed during the 4 weeks preceding diagnosis of GDM2 (5922 values). Daily glucose profiles were evaluated based on...
the average pre- and postprandial capillary glucose values measured at every meal and per week. Daily glucose profiles were noted as Week0 (diagnosis of GDM2), W-1, W-2, W-3 and W-4. The gestational age for GDM2 was the 30th WG. The capillary glucose value determined at 22:00 hours on W-1 was the only value significantly higher compared to other time values. Other time glucose values remained in the normal range from W-4 to W0 (Fig. 2).

4. Discussion

This is the first prospective study undertaken among women at risk of GDM with and without GDM between 24–28 WG, with a further follow-up until delivery. In agreement with the data of the literature, a total of 72% of women at risk develop GDM [11]. However, our study shows that GDM is diagnosed in 54% of cases between 24–28 WG, and in 18% beyond the 28th WG. Thus three groups of women can be distinguished: GDM between 24–28 WG (GDM1), GDM beyond the 28th WG (GDM2) and NGT during all the duration of pregnancy. These results make it possible to conclude that among women at risk, normal diagnostic tests between 24–28 WG may be falsely reassuring and do not exclude definitively GDM. The gestational age of GDM2 can be estimated around the 30th WG. A retrospective analysis of SMBG suggests that capillary glucose values determined at 22:00 hours may only be predictive of late GDM. This data may be of particular interest, but confirmation by a prospective study aimed at verifying this finding is needed.

We observed that the NGT group between 24–28 WG was heterogeneous regarding its metabolic evaluation. However, the normal range, plasma glucose values above 50 or 75 g glucose load, was significantly higher in women developing GDM later. Furthermore, it is also of interest to note the fructosamine kinetics. Fructosamine values increased during weeks preceding the onset of GDM2. By contrast, fructosamine values decreased after diagnosis and treatment of GDM1. In the GDM1 and GDM2 groups, all HbA1c values were within normal range. These data confirms a recent report, demonstrating that HbA1c levels are significantly lower in early and late pregnancy [12]. HbA1c determination is thus of little interest in the follow-up of pregnancy in women with or at risk of diabetes.

The analysis of risk factors in the three groups have shown that pre-pregnancy overweight was more frequent and pronounced among GDM2 women, compared to GDM1 women. All the other risk factors were not different between the three groups.

Maternal outcomes were not different between the three groups. It is surprising to find no hypertension in this population, this is not a common finding in this situation. In agreement with the Achois study [13] treatment of GDM reduces severe perinatal morbidity. In our study, no neonatal admission

Fig. 1. Fructosamine kinetics during pregnancies in the GDM1 and GDM2 groups. Fructosamine values were 216 ± 49, 195 ± 14*, 187 ± 18 and 186 ± 19 between 21–25, 26–29, 30–33 and 34–37 WG in GDM1 group. Fructosamine values were 150 ± 41*, 185 ± 29 and 184 ± 15 μmol/l between 26–29, 30–33 and 34–37 WG in GDM2 group.* P = 0.009.

Fig. 2. Mean capillary blood glucose (N = 5,922) fasting (white) and post-prandial (gray) in 34 women who developed a GDM beyond 28 WG during the 4 weeks (W4, W3, W2, W1) preceding the onset of the diabetes (W0). Capillary glucose value determined at 22:00 hours on W1 was the only value significantly higher compared to all other values (remained in the normal range from W4 to W0) [114 ± 2, 113 ± 18, 118 ± 25, 126 ± 21 and 127 ± 25 mg/dl, respectively, at 22:00 h W4, W3, W2, W1 and W0, P = 0.01 W2 versus W1; P < 0.001 22:00 versus 10:00 hours and 14:00 hours at W1].
has been recorded and fetal outcomes (prematurity, hypoglycemia, jaundice) were not different between the three groups. Macrosomia prevalence was not different between the NGT and GDM1 groups. One can suppose that early and intensive intervention in women with GDM1 has been beneficial, reducing the risk of fetal complications compared to the one observed in NGT women. On the other hand, prevalence of macrosomia was significantly higher in the GDM2 group. This data is in correlation with the AC of the second and third trimester determined by ultrasound. A recent report from the French High Authority of Health (HAS) concluded that “macrosomia is regarded as a relevant judgment criterion for the evaluation of the therapeutic, diagnostic strategies and of screening of the GDM”. Our data shows that macrosomia is higher in women with GDM2, and therefore monitoring of women at risk beyond the 28th WG is justified.

Lastly, factors responsible for macrosomia can be discussed. Macrosomia seems to be related to the pre-pregnancy overweight. This data is complementary with the literature. In fact, it has been shown that pre-pregnancy overweight and obesity and abnormal glucose tolerance categories were independent predictors of pregnancy outcomes including macrosomia [9,14–16]. Indeed late GD has not been eliminated in those studies. Our data have to assess that point. Macrosomia could be related to a late transient rise in plasma glucose levels, rather than a chronic moderate hyperglycemia. The rise of fructosamine before onset of GDM2 indicates an increase in mean plasma glucose levels.

5. Conclusions

Five principal conclusions can be drawn from this study. First, our study disclosed a glycemic heterogeneity in normoglycemic women between 24–28 WG, with significant higher plasma glucose values post-load in those who will become diabetics. Second, 72% of women at risk develop GDM, 54% between 24–28 WG, but 18% beyond the 28th WG. Third, gestational age of onset GDM2 can be located around the 30th WG. In normoglycemic women at high risk, glycemic monitoring is mandatory beyond the 28th WG. Women who develop GDM2 have significantly more frequent macrosomia and more important pre-pregnancy overweight underlining this impact in the occurrence of macrosomia. Other risk factors did not allow to discriminate a group with higher risk. Fourth, onset of diabetes seems to be predicted by the capillary glucose values determined at 22:00 hours, but this finding needs to be confirmed by a prospective study aiming at verifying this point. Fifth, maternal outcomes are not different in the three groups with intensive intervention.

References