Poor prognosis of pregnancy in women with autoimmune type 1 diabetes mellitus masquerading as gestational diabetes


Abstract

Aim. – To describe the clinical presentation and the prognosis of autoimmune type 1 diabetes (T1D) that was first revealed during pregnancy masquerading as gestational diabetes mellitus (GDM).

Methods. – We reviewed the files of 21 women in whom diabetes was revealed during a pregnancy (“index pregnancy”) and progressed to T1D after delivery, and in whom GAD and/or IA-2 autoantibodies were found.

Results. – The median age and BMI of the women were 31 years and 19.8 kg/m². Eleven women had at least one risk factor for GDM. Eight of the 12 multiparous women had had an abnormal outcome of previous pregnancy, including GDM in 5. GDM was diagnosed at week 26 (range: 4–38) of gestation by screening in 18, because of macrosomia in 2 and during hyperglycaemic crises in 3. All were treated with insulin, from the time of diabetes diagnosis in 10 and after 4 weeks (range: 2–15) in 11. Term of delivery was 38 (range: 26–41) weeks. Abnormal outcomes occurred in 14 pregnancies, including 2 fetal deaths, 4 preterm deliveries and 8 macrosomic infants. No congenital malformations were reported. After delivery, insulin therapy was stopped in 18 women for 6 months (range: 2–48). The diagnosis of the autoimmune origin of diabetes was established during the index pregnancy in only 8 cases.

Conclusion. – T1D may reveal as GDM in women with or without risk factors for GDM and is associated with a poor prognosis, partly because the correct diagnosis and treatment are delayed. Whether screening for autoimmune markers of T1D should be performed more systematically in women with GDM deserves to be studied.

© 2010 Published by Elsevier Masson SAS.

Keywords: Gestational diabetes; Pregnancy; Autoimmunity; Fetal death

Résumé

Le pronostic de la grossesse est péjoratif chez les femmes ayant un diabète de type 1 auto-immun initialement considéré comme un diabète gestationnel.

Objectif. – Décrire la présentation et le pronostic du diabète de type 1 auto-immun (DT1) révélé pendant la grossesse et considéré comme un diabète gestationnel (DG).

Méthodes. – Nous avons revu les dossiers de 21 femmes chez qui le diabète a été révélé pendant une grossesse, a évolué vers un DT1 après l’accouchement et qui avaient des autoanticorps anti-GAD et/ou anti-IA-2.

* Corresponding author. Tel.: +33 1 48 51 24 36; fax: +33 1 48 51 24 45.

E-mail address: jose.timsit@ch.aphp.fr (J. Timsit).

1262-3636/$ – see front matter © 2010 Published by Elsevier Masson SAS.
doi:10.1016/j.diabet.2010.07.005

Conclusion. – Le DT1 peut se révéler comme un DG chez des femmes ayant ou non des facteurs de risque. Il est associé à des complications, en particulier du fait d’un retard diagnostique et thérapeutique. L’intérêt d’une recherche systématique des marqueurs d’auto-immunité du DT1 au cours du DG mérite d’être évalué.

Mots clés : Diabète gestationnel ; Grossesse ; Auto-immunité ; Mort fœtale

1. Introduction

Gestational diabetes mellitus (GDM) is defined as “an impairment of glucose tolerance with onset or first recognition during pregnancy” [1]. Although this definition has some practical advantages, it covers various situations. In fact, due to the physiological decrease of insulin sensitivity associated with pregnancy, all pathological processes leading to decreased insulin secretion may present during pregnancy as GDM [2]. For example, unrecognized pregestational type 2 diabetes may account for 15–30% of GDM and is associated with severe adverse outcomes of pregnancy [3].

The first occurrence of autoimmune type 1 mellitus diabetes (T1D) during pregnancy is a rare event [2]. Several studies have assessed the prevalence of T1D-related autoantibodies in women with GDM (see review in [4]). They have confirmed the prognostic value of such antibodies for the eventual onset of T1D in these cases. However, there are scant data in the literature concerning the clinical presentation of diabetes and the prognosis of the pregnancy in this particular situation.

In the present report, we describe the clinical characteristics of pregnancy in 21 women thought to have GDM, but who eventually developed autoimmune T1D. We show that the prognosis of pregnancy was poor in the majority of these patients.

2. Methods

We sought for women in whom autoimmune T1D was revealed during pregnancy – that is, women (1) whose diabetes was initially regarded as GDM. This pregnancy was thereafter referred to as “index pregnancy”; (2) who further developed permanent insulin-dependent diabetes, according to World Health Organization criteria; (3) and in whom the presence of autoimmune markers, at least one autoantibody among anti-GAD (GADab) and anti-IA-2 (IA-2ab) antibodies whatever the time of sampling, eventually led to the correct diagnosis.

For this purpose, the files of the women with established autoimmune T1D seen consecutively over a 6-month period by one of us (J.T.) were systematically reviewed. Out of 130 women, five fulfilled the above-mentioned inclusion criteria. We also asked colleagues whether they could recall of such cases. This led to the inclusion of 16 further patients fulfilling the same criteria. Thus, a total of 21 women were included in this retrospective, descriptive study.

Data were collected on the presence of risk factors for GDM, the term and the way in which diabetes was discovered, the course and outcome of the index pregnancy, and the course of diabetes during and after the index pregnancy. Risk factors for GDM were: age >25 years; family history of diabetes in first-degree relatives; belonging to an ethnic group with a high prevalence of GDM; abnormal body weight before pregnancy; history of abnormal glucose metabolism; history of abnormal obstetric outcome [5].

As for the infants, the main analyzed outcomes were perinatal mortality, presence of congenital malformations, preterm delivery (defined as delivery before 37 weeks of gestation), macrosomia (defined as a birth weight ≥4000 g), and the occurrence of neonatal complications. Infants were characterized as large for gestational age (LGA) according to French growth standard curves [6]. Gestational age at delivery was determined from the date of the last menstrual period confirmed by first-trimester ultrasonography.

3. Results

3.1. Main characteristics of the patients and outcomes of previous pregnancies

The main characteristics of the 21 women are summarized in Table 1. Eighteen were of Caucasian–European origin, one was from Asia, one from North Africa and one from Reunion Island. Nine of these women were nulliparous, and 12 had previously had one (n = 10), two (n = 1), or three (n = 1) pregnancies. GDM had been diagnosed in five women at 1–5 years prior to the index pregnancy. Of these five, three had been treated by diet alone and delivered a macrosomic infant (birth weights were 4120, 4200 and 5250 g, respectively), a fourth one had been treated with insulin and given birth to a normal-weight infant and the fifth woman had started insulin therapy, but fetal death had occurred at 40 weeks of gestation. In the seven other women, no GDM was diagnosed. Of the 10 infants, three were macrosomic (birth weights were 4200, 4500 and 4710 g, respectively). Altogether, of the 12 multiparous women, one abnormal pregnancy outcome was recorded in eight. In no case the possibility...


Table 1
Main characteristics of 21 women with type 1 diabetes revealed as gestational diabetes.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at index pregnancy (years)</td>
<td>31 [20–38]</td>
</tr>
<tr>
<td>Eurocaucasian/other</td>
<td>18/5</td>
</tr>
<tr>
<td>Nulliparous/multiparous</td>
<td>9/12</td>
</tr>
<tr>
<td>Risk factors for GDM+/−</td>
<td>11/10</td>
</tr>
<tr>
<td>Family history of diabetes Y/N</td>
<td>8/13</td>
</tr>
<tr>
<td>History of gestational diabetes Y/N</td>
<td>5/7</td>
</tr>
<tr>
<td>Abnormal outcome of previous pregnancy Y/N</td>
<td>8/4</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td>19.8 [17.5–31.3]</td>
</tr>
<tr>
<td>Gestational age at diabetes diagnosis (weeks)</td>
<td>26 [4–38]</td>
</tr>
<tr>
<td>Gestational age at insulin therapy (weeks)</td>
<td>28 [4–38]</td>
</tr>
<tr>
<td>Remission of insulin therapy+/−</td>
<td>18/5</td>
</tr>
<tr>
<td>Duration of remission of insulin therapy (months)</td>
<td>6 [2–48]</td>
</tr>
</tbody>
</table>

Data are expressed as absolute numbers or medians and ranges in brackets. **a** Excluding age > 25 years.

of T1D was raised, and only two women required insulin during pregnancy.

3.2. Risk factors for GDM at the time of the index pregnancy

The median age of the women was 31 years, and their median prepregnancy body mass index (BMI) was 19.8 kg/m². All patients except two had a normal prepregnancy body weight, and weight gain during pregnancy was normal in all (median: 11.8 kg, range: 6–18 kg). Two women had none of the classical risk factors for GDM whereas in eight an age over 25 years was the only risk factor. The 11 other women had one or several risk factors among ethnicity, first-degree family history of type 2 diabetes, abnormal outcome during a previous pregnancy or a pre-pregnancy BMI over 25 kg/m² (Table 1). Of note, a family history of T1D was recorded in four women.

3.3. Course and outcome of index pregnancy

There were only single pregnancies. The median gestational age at delivery was 38 weeks (range: 26–41 weeks). The median birth weight of the live-birth infants was 3600 g (2550–5200). No congenital malformations were reported in the 21 infants (Table 2). The outcome of pregnancy was normal in only seven out of 21 (33%). Three of the seven women had had no previous pregnancy; of the remaining four, one had previously delivered a macrosomic infant, and the three others had had uneventful previous pregnancies.

In 14 index pregnancies, one or several abnormal outcomes occurred (Table 2). Birth weight was greater or equal to 4000 g in five infants, and eight live-birth infants were LGA. Four were delivered preterm (at 34.5–36.7 weeks of gestation), two of which were LGA. Two fetal deaths occurred – both in the context of hyperglycaemic crises – at 26 and 38 weeks of gestation, respectively. Of these 14 women, six were nulliparous, three had a diagnosis of GDM during a previous pregnancy and a further three delivered a macromosmic infant with no diagnosis of GDM. In total, of these 14 women with abnormal outcomes for the index pregnancy, seven had at least one risk factor for GDM. However, it should be pointed that the two fetal deaths involved women with no previous pregnancy and no risk factors for GDM.

3.4. Course of diabetes during and after the index pregnancy

Various circumstances led to the diagnosis of diabetes during the index pregnancy. In one woman, diabetes was revealed by ketoacidosis and major hyperglycaemia (61 mmol/L) that occurred 26 weeks of gestation, and was complicated by fetal death. In a second woman, diabetes was diagnosed at 38 weeks of gestation because of fetal death; at that time, blood glucose concentration was 16.6 mmol/L. As already mentioned, these two women were nulliparous with no risk factors for GDM. In a third woman, who had had a previous pregnancy with fetal death, diabetes was diagnosed at 4 weeks of gestation because of a random blood glucose value of 24 mmol/L.

In the 18 remaining women, diabetes was diagnosed by screening at a median term of 26 weeks of gestation (10–32 weeks). In two, screening was performed because macrosomia was detected on ultrasonography at 22 and 32 weeks of gestation, respectively. In six cases, screening was performed because glycosuria was detected at planned visits at a median term of 26.5 weeks of gestation (10–30) while in the 10 others, screening was routine at 25 weeks of gestation (18–28). Various tests were used, including measurements of fasting and postprandial blood glucose concentrations, O’Sullivan test, and oral glucose tolerance test. The median value of fasting blood glucose, measured in 14 women, was 7.2 mmol/L (5.1–13.5), while the median postprandial or posttest blood glucose, measured in 12 women, was 13 mmol/L (5–21.6). HbA1c was available in nine women at the time of diabetes diagnosis and was 6.9% (5.3–10.0).

All women required insulin therapy during pregnancy. In 10, it was started at the time of diabetes diagnosis. The 11 others were first treated by diet only, with insulin therapy delayed by a median of 4 weeks (2–15). After delivery, insulin therapy was stopped in all women but three. Remission of insulin dependency lasted for a median duration of six months (2–48) and was for more than one year in six cases. Insulin therapy was resumed in four women because a new pregnancy was planned, in a further four women because of high capillary blood glucose values and
in 10 women because diabetes became clinically overt. Finally, the diagnosis of autoimmune type 1 diabetes was established in all cases on the presence of GADab \((n = 12)\), IA-2ab \((n = 1)\), or both antibodies \((n = 8)\). It was made during the index pregnancy in eight women and at the time of diabetes relapse in the others.

4. Discussion

We have reported the clinical histories of 21 women in whom GDM eventually proved to be autoimmune T1D, and we have shown that the prognosis of pregnancy was poor in these women. The incidence of autoimmune T1D arising during pregnancy has not been systematically assessed. However, many studies have been performed to assess the presence of T1D-related autoantibodies in women with GDM, and have been extensively reviewed [4,7]. As the prevalence of islet-cell antibodies (ICA) is highly dependent on the assay used, and that of anti-insulin autoantibodies is lower in adults than in young subjects, GADab, IA2ab, and their combination remains the most sensitive and specific markers of autoimmune T1D. GADab and/or IA2ab have been found in about 10% of women with GDM, with the highest prevalences reported in countries where the prevalence of T1D itself is high [4,7–9]. Several factors have been associated with the presence of diabetes-related autoantibodies in women with GDM, including being younger in age, having a low prepregnancy BMI, a low prevalence of a family history of diabetes, i.e. low risk for GDM, and a frequent need for insulin therapy during pregnancy [10]. This is in keeping with our observations, since 50% of our patients had no risk factor for GDM at the time of index pregnancy except for an age over 25 years.

Several studies have shown that, in women with GDM, the presence of such autoantibodies predicts the eventual occurrence of overt T1D [4,7]. For example, in one study the risk of developing T1D two years after delivery was 29% in the women with GDM and at least one diabetes-related autoantibody (ICA, GADab and IA-2ab), while it increased to 84% in those with the three antibodies [11]. In other women, progression to overt T1D was slower, lasting up to several years [11,12]. This confirms that the presence of autoantibodies in GDM identifies patients who are in the preclinical phase of T1D – just as in relatives of patients with T1D [13]. In the same vein, one study showed that women with ICA and normal tolerance to oral glucose after delivery had impaired insulin response to intravenous glucose [14]. In our study, eight (38%) women had had a previous pregnancy with a diagnosis of GDM or a macrosomic infant 1–5 years prior to the index pregnancy. It is likely that these women already had defective insulin secretion related to the autoimmune process. This suggests that the course of autoimmune T1D may be very slow also in young adult women as reported in the so-called “latent autoimmune diabetes in the adult” (LADA) [15]. Whether pregnancy itself may alter the course of the autoimmune process leading to T1D is unknown. However, recent data demonstrated a partial recovery of C-peptide secretion at the end of pregnancy in women with pregestational T1D [16].

In our study, various circumstances led to the diagnosis of diabetes during the index pregnancy. In three women, acute decompensation of diabetes occurred, associated with fetal death in two cases. In two other women, macrosomia revealed GDM. In 16 women, GDM was diagnosed by planned screening. Fasting blood glucose concentrations were moderately increased (median: 7.2 mmol/L). To our knowledge, only one study has reported clinical and biological data in a large series of 63 women with T1D diagnosed during pregnancy [17]. However, those women were selected on the basis of overt clinical symptoms of diabetes during pregnancy and a fasting blood glucose above 8 mmol/L; actually, their mean fasting blood glucose was 15.6 mmol/L, and 81% had ketonuria. In our series, nine women had fasting blood glucose below 8 mmol/L, and all the women but three were clinically asymptomatic. Thus, although blood glucose concentrations largely exceeded the current thresholds for diagnosis of GDM [18], the severity of hyperglycaemia can vary widely in such women and does not allow correct identification of all patients with T1D arising during pregnancy.

The course of diabetes in our patients suggests that the physiological insulin resistance associated with pregnancy played a major role in the onset of diabetes. The diagnosis of diabetes was made after 24 weeks of gestation in the majority of the women (71%). Moreover, insulin therapy, that was required in all women during their pregnancy, could be stopped after delivery in 85% of the cases. After a remission period that lasted 6 months (median), and more than one year in one-third of the women, insulin therapy had to be resumed in all patients. These observations are very similar to those of Buschard et al. who found that 80% of the women with T1D diagnosed during pregnancy had a remission of insulin dependency that lasted for 8.5 months [17]. Data on metabolic control were not available for all our patients during the remission phase. Abnormal capillary blood glucose values led to the resumption of insulin therapy in some cases, and diabetes became clinically overt in the others. In the study by Buschard et al., all the patients who were off insulin had normal tolerance to oral glucose [17].

Overall, the prognosis of pregnancy was poor in our patients (Table 2). No congenital malformation was observed, as already reported elsewhere by others [17]. However, in two-thirds of the women, one or several adverse outcomes were occurred. Two fetal deaths (9%) in the context of a during sudden decompensation that revealed diabetes in women with no risk factor for GDM. In the other cases, macrosomia was the most frequent complication. Although we have no precise information about the modalities of insulin therapy and the level of glycaemic control in our patients, it is likely that it was no optimal. It should be noted that, in these women, insulin therapy was delayed for 2–15 weeks after the diagnosis of diabetes.

Finally, in 62% of the women the correct diagnosis of T1D was delayed until a relapse of overt diabetes was observed. In almost all cases anti-GAD antibodies were present, in keeping with the known sensitivity of these antibodies in adult-onset T1D and in women with GDM who progress to T1D. In a single patient, anti-IA-2 antibodies were the only positive marker of autoimmunity.

Our study has several limitations. It was retrospective and based on clinicians’ memories of women with this condition. As such it did not allow to draw any epidemiological conclusions about this situation. Moreover, a recall bias may have led to the
inclusion of cases with poor prognosis. No comparative group was available to assess this particular point but, in a previous study, the prognosis of T1D revealed by pregnancy seemed to be comparable to that of pregestational T1D except for congenital malformations [17]. Lastly, we could not assess the quality of glycaemic control after diagnosis of diabetes during pregnancy.

In conclusion, T1D revealed by pregnancy is part of GDM, according to its current definition. However, clinicians need to be aware of this condition, as it requires urgent diagnosis and treatment. Our study shows that there are no specific criteria to identify these patients. A young age at onset, a low BMI, the absence of a family history of type 2 diabetes and the need for insulin therapy during pregnancy should suggest this diagnosis. A family history of T1D, that was present in 20% of our cases, should also alert the physician. However, our study also shows that half of the patients may have one or several risk factors for classical GDM. Since GADab are a highly sensitive assay for the diagnosis of T1D, whether should be performed more routinely in women with GDM deserves further studies.

Conflict of interest statement

The authors have not declared any conflicts of interest.

References