Use of insulin glargine throughout pregnancy in 102 women with type 1 diabetes

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Abstract

Aim. – The aim of this study was to examine the safety of insulin glargine during pregnancy in women with type 1 diabetes mellitus (T1DM).
Methods. – This retrospective multicentre study involved women with T1DM treated with insulin glargine before conception and throughout pregnancy. The main investigated parameters were HbA1c during the first and third trimesters, major congenital malformations, and perinatal mortality and complications.
Results. – For the 102 women with T1DM in the study, HbA1c during the first and third trimesters was 6.7 ± 1.2% (95% CI 6.4–6.9%) and 6.2 ± 0.9% (95% CI 6.0–6.4%), respectively. Two congenital malformations (2%) were reported, and one stillbirth (1%) occurred at week 35 of gestation. The rate of preterm delivery was 23%. The mean birth weight was 3381 ± 595 g (95% CI 3255–3506 g), and the proportion of large-for-gestational-age infants was 30%.
Conclusion. – Insulin glargine use throughout pregnancy does not appear to be associated with an increased rate of severe congenital malformations.

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Keywords: Glargine; Insulin; Pregnancy; Type 1 diabetes mellitus

1. Introduction

In women with type 1 diabetes mellitus (T1DM), excellent glycaemic control is mandatory before conception and
throughout pregnancy to prevent adverse outcomes such as congenital malformations and macrosomia. This can be achieved by the use of daily multiple injections of rapid- and long-acting insulin, or an external insulin pump, together with intensive blood glucose self-monitoring. Rapid-acting insulin analogues such as lispro and aspart are now widely used during pregnancy in women with T1DM, and have demonstrated efficacy and safety [1,2].

In contrast, the use of long-acting insulin analogues (glargine and levidem) is currently not recommended during pregnancy. However, as treatment with glargine can facilitate good glycaemic control with a reduced risk of hypoglycaemia, it might be a valuable alternative in the management of pregnant women with T1DM. Moreover, as many patients with T1DM are usually already being treated with short- and long-acting insulin analogues, they may be reluctant to change their insulin regimen when planning a pregnancy if their diabetes is well controlled.

Also, on the basis of animal studies showing the safety of insulin glargine during pregnancy [3] as well as other previous reports [4–6], increasing numbers of French diabetologists are using this analogue during pregnancy to improve glycaemic control.

For this reason, we report here on the perinatal outcomes in 102 women with T1DM treated with insulin glargine before conception and throughout their pregnancy.

2. Study design and methods

This observational study involved three perinatal centres in France during 2005–2008. All data were prospectively collected using the Obstetrical Quality Indicators and Data Collection (OBSQID) aggregated database [7]. The main investigated parameters were HbA1c during the first and third trimesters of pregnancy, major congenital malformations, and perinatal mortality and complications. Fetal deaths were defined as stillbirths at ≥ 22 weeks of gestation, or if the infant weighed ≥ 500 g. Neonatal death was defined as the death of a live-born infant before day 28 of life. Perinatal mortality included both fetal and neonatal deaths. Major congenital malformations were classified according to EUROCAT [8]. Preterm delivery was defined as delivery before week 37 of gestation; infants with birth weights higher than the 90th percentile for gestational age (LGA). Admissions to the neonatal intensive care unit (NICU) were recorded.

3. Results

The main clinical characteristics and neonatal outcomes of the 102 pregnant women with T1DM, treated with insulin glargine from preconception to delivery, are shown in Tables 1 and 2. HbA1c during the first trimester was 6.7 ± 0.9% (95% CI 6.0–6.4%), but was lower in the 49 (48%) women who had planned their pregnancy compared with the 53 (52%) who did not (6.1 ± 0.7% vs 7.2 ± 1.3%, respectively; P < 0.0001). In addition, first-trimester HbA1c values were < 6.5% in 34 (69%) of the 49 women who had planned their pregnancy compared with 6.1 ± 0.7% vs 7.2 ± 1.3%, respectively; P < 0.0001).

Table 1 Main characteristics of the insulin glargine-treated women with T1DM at enrollment and during pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Women (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy [n (%)]</td>
<td>35 (34)</td>
</tr>
<tr>
<td>Nephropathy [n (%)]</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Preconception care [n (%)]</td>
<td>49 (48)</td>
</tr>
<tr>
<td>First-trimester HbA1c (%)</td>
<td>6.7 ± 1.2</td>
</tr>
<tr>
<td>HbA1c at delivery (%)</td>
<td>6.2 ± 0.9</td>
</tr>
<tr>
<td>Gestational hypertension, preeclampsia [n (%)]</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Caesarean delivery [n (%)]</td>
<td>66 (65)</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD unless otherwise stated.

with 17 (32%) of the 53 women who did not. During the third trimester, the overall HbA1c was 6.2 ± 0.9% (95% CI 6.0–6.4%), but remained lower in those who had planned their pregnancy vs those who did not (5.9 ± 0.7 vs 6.5 ± 1.0%, respectively; P = 0.0012).

Five spontaneous abortions were reported in five unplanned pregnancies (first-trimester HbA1c ranged from 6.7 to 7.8%), and three voluntary terminations were performed at the mothers’ request. Also, two congenital malformations were reported: one was a case of Down syndrome in a 40-year-old woman that was not related to either diabetes or glargine; the other was a case of hydrocephalus in an unplanned pregnancy, where the first-trimester HbA1c was 7.8%. Fetal cerebral magnetic resonance imaging (MRI) revealed intracerebral haemorrhage with no malformation; alloimmune thrombocytopenia was also excluded.

One stillbirth occurred at week 35 of gestation. In this case, the prenatal follow-up was uneventful; there was no preeclampsia and the biweekly non-stress tests were normal. Indeed, a non-stress test performed 72 h before fetal death was normal, and no adverse event was recorded during those 72 h. The third-trimester HbA1c was 7.7%. The infant was a non-malformed boy weighing 2510 g (50th percentile), and fetal autopsy and placental pathology revealed no anomalies.

Altogether, there were 97 live births ~89 from singleton pregnancies and eight from twin pregnancies. Among the singletons, gestational age at delivery was 37.4 ± 1.6 weeks (95% CI 37.1–37.8 weeks), and the rate of preterm delivery was 23%. The mean birth weight was 3381 ± 595 g (95% CI 3255–3506 g), and the rate of LGA was 30%. Two infants had an Apgar score < 7 at 5 min. Also, 19 infants, 11 of whom were preterm, Table 2 Neonatal outcomes in women with T1DM treated with insulin glargine during pregnancy.

<table>
<thead>
<tr>
<th></th>
<th>Live births (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>37.2 ± 1.9</td>
</tr>
<tr>
<td>Preterm delivery [n (%)]</td>
<td>22 (23)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3284 ± 691</td>
</tr>
<tr>
<td>Large for gestational age [n (%)]</td>
<td>29 (30)</td>
</tr>
<tr>
<td>Respiratory distress syndrome [n (%)]</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Neonatal intensive care unit [n (%)]</td>
<td>21 (22)</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD unless otherwise stated.
required admission to the NICU. The four twin pregnancies delivered live-birth infants at a gestational age ranging from 30 to 36 weeks.

4. Conclusion

In the present study, two congenital malformations and one fetal death were reported out of 97 infants born to women with T1DM and treated with insulin glargine throughout their pregnancy. The rate of planned pregnancies remained low at 48%, and these women had lower HbA1c values during the first trimester than those who had not planned their pregnancy. Interestingly, in 86% of the women who had planned their pregnancy, the HbA1c was < 6.5%, the currently recommended target for reducing the risk of congenital malformations in women with T1DM.

The observed rate of LGA infants (30%) compares favourably with the rate of macrosomia seen in infants of women treated with human insulin, and is in accordance with a recent pilot study showing that the use of insulin glargine is not associated with an increased risk of fetal macrosomia [9]. Some concerns, however, have been raised over the use of glargine during pregnancy, as the analogue exhibits an increased affinity for the insulin-like growth factor-1 (IGF-1) receptor, a tendency that is not seen with human insulin [10]. However, a recent study using the human perfused placental lobule technique showed that insulin glargine at therapeutic concentrations is not likely to cross the placenta [11].

However, the present study has certain important limitations that need to be taken into account when interpreting the results. It has the inherent weaknesses of all observational studies, including recall bias and the absence of matching. There is also a potential for selection bias, as it involved self-selected centres rather than being population-based. Furthermore, data on maternal age, body mass index (BMI), duration of diabetes, socioeconomic status and occurrence of severe hypoglycaemia were not included in the data-collection process.

However, when pooling our results with those of other studies [4–6], the rate of major congenital malformations was 2.7% in 366 women treated with insulin glargine throughout pregnancy (Table 3), a rate that is lower than the 4.1% observed in a previous national survey [12]. Of the 10 reported congenital malformations, one was chromosomal, two were neurological, three were cardiovascular, two were genitourinary and two were osteoarticular [4–6]. Evaluation of the teratogenicity of a medicinal product in humans requires a sample size large enough to show an increase in the occurrence of rare events. If the risk of malformation in a given population is only 3%, then at least 220–240 pregnancies need to be analyzed to detect a two- to threefold increase with a power of 80% [13]. Indeed, the pooled results had sufficient power to detect such an increase in major congenital malformations, but was not enough to detect an increase in the frequency of any specific malformation. Nevertheless, the probability of glargine-induced teratogenic effects in humans appears to be low, and no such effects have been seen in animals [3].

The pooled perinatal mortality rate was 0.5%, with one stillbirth occurring at week 35 of gestation in the present study, and one neonatal death in a preterm infant delivered at week 29 of gestation in an Italian study [6].

The present study was not designed to examine whether or not glargine is more effective than other insulin preparations at improving pregnancy outcomes in women with T1DM. However, there is a need for other observational studies, and for large randomized studies comparing glargine with conventional insulin therapy throughout pregnancy. Nevertheless, bearing in mind the admitted limitations, glargine use throughout pregnancy does not appear to be associated with an increased rate of severe congenital malformations.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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