

## Editorial

# Insulin analogs in pregnancy

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Several clinical studies<sup>1</sup> have shown that control of maternal glycemia before conception reduces the frequency of congenital malformations, which remain the leading cause of mortality and severe morbidity in the infants of diabetic mothers<sup>2,3</sup>. Good metabolic control throughout pregnancy can also reduce the maternal and other fetal complications typical of pregnancy complicated by diabetes<sup>4</sup>. The levels of glycemia and HbA<sub>1c</sub> that should be achieved before conception and maintained during pregnancy, as recommended by the American Diabetes Association<sup>5</sup>, demand intensive blood glucose self-monitoring and optimized insulin therapy so that these values can be obtained with the lowest possible number of hypoglycemic episodes.

Pregnancy is characterized by changes in insulin requirements. To be more precise, the placental passage of glucose and gluconeogenic substrates causes maternal hypoglycemia in the first trimester (especially at night) and consequently the insulin dosage adopted before conception should be reduced by approximately 10%. During the second and third trimesters, the progressive increase in the production of placental contra-insulin hormones leads to a gradual increase in insulin requirements. Throughout pregnancy, moreover, blood glucose control becomes unstable, with a trend toward low fasting plasma glucose, high postprandial peaks and episodes of nocturnal hypoglycemia. Because of these changes, the dosage of short-acting insulin must be increased to cover the meal and the dosage of intermediate-acting insulin must be finely tuned to guarantee a constant basal rate without hypoglycemic episodes<sup>6</sup>.

The rapid-acting insulin analogs, i.e. lispro and aspart, may be useful because they are better able to reduce postprandial hyperglycemia than regular insulin. As for insulin glargine, its potential advantage in the management of pregnancy complicated by type 1 dia-

betes lies in its ability to reduce nocturnal hypoglycemia, which is particularly common in pregnant women with type 1 diabetes.

However, along with the potential benefits, the potential related risks (teratogenicity, embryo toxicity, immunogenicity with transplacental passage, mitogenicity) of using these new insulins in pregnancy must be carefully considered.

Concerning teratogenicity, studies in experimental animals have shown no embryotoxic or teratogenic effects of insulin lispro, aspart or glargine. The first report of fetal malformations in diabetic patients treated with insulin lispro involved two type 1 diabetic women<sup>7</sup> with good metabolic control, whose therapy with insulin lispro was started before conception in one patient and in the third week of pregnancy in the other. One pregnancy was aborted at the 20th week of gestation, and the fetus had multiple cardiac malformations; the other ended in term delivery, but the infant died 3 weeks after birth from a congenital diaphragmatic hernia.

Since this first report, a series of retrospective clinical studies have been published<sup>8</sup>. As a whole, 867 pregnant diabetic women treated with insulin lispro (99% with type 1 and 1% with type 2 diabetes) and 221 pregnant diabetic women treated with regular insulin (99.5% with type 1 diabetes) can be compared. Unplanned pregnancies occurred in 41% of the diabetic pregnant women treated with insulin lispro and in 68% of those treated with regular insulin. As for the timing of the insulin therapy, 98.3% of patients were treated with lispro at the time of conception and 1.7% were transferred from regular insulin to insulin lispro between the 7th and 17th weeks of gestation due to poor metabolic control. These studies show that HbA<sub>1c</sub> levels at conception vary considerably (from 5.2% to 13.1%). Cumulative data analysis shows that the frequency of malformations was 4.8% in patients on insulin lispro and 6.8% in those on regular insulin; this difference was non-significant ( $p = 0.3$ ). More recently, a retrospective study promoted by Eli Lilly<sup>9</sup> evaluated the outcome of pregnancy in 496 patients with pregestational diabetes from 55 centers in different parts of the world. This study examined patients

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on insulin lispro for at least 1 month before conception and during the first trimester of pregnancy and reported a frequency of malformations of 5.4%. Regarding insulin aspart, a randomized, controlled, open-label trial comparing the safety and efficacy of insulin aspart and human insulin in pregnant women with type 1 diabetes is currently underway<sup>10</sup>. As for insulin glargine, studies evaluating its potential teratogenicity in humans are unfortunately very scarce: a recent publication by DiCianni et al<sup>11</sup> reported no malformations or neonatal complications in five type 1 diabetic women treated with glargine during the first weeks of pregnancy.

Studies evaluating the capacity of insulin lispro, aspart and glargine to bind insulin-like growth factor-1 (IGF1) receptor generally report no differences with respect to regular insulin. These results are important, because they can be correlated with retinopathy during pregnancy. In this context, Kitzmiller et al<sup>12</sup> reported the onset of proliferative retinopathy requiring laser treatment in 3 diabetic women during the third trimester of pregnancy. The authors explained this finding as being related to the mitogenic activity of insulin lispro. In a subsequent editorial, Jovanovic<sup>13</sup> returned to the cases reported by Kitzmiller et al to emphasize that the rapid development of proliferative retinopathy in these patients might have been due to their longstanding diabetes (> 6 years), to the presence of proteinuria (in one patient), and especially to poor metabolic control, demonstrated by high HbA<sub>1c</sub> levels that improved rapidly during the first few months of gestation.

Since then, a series of retrospective clinical studies have been published on the topic, showing no progression or new onset of retinopathy in patients treated with insulin lispro<sup>8</sup>. Importantly, pregnancy itself can exacerbate retinopathy in cases of poor glycemic control at the beginning of the pregnancy followed by a rapid tightening of glycemic control during the pregnancy. Therefore, retinopathy must be carefully monitored in pregnancy.

As for immunogenicity, a relationship has been reported between neonatal morbidity (and macrosomia in particular) and placental transfer of insulin complexed with antibodies<sup>8</sup>. The immunological response to insulin lispro *versus* regular insulin has recently been evaluated in women with gestational diabetes mellitus (GDM) randomized to receive one or other type of insulin during pregnancy. Anti-insulin antibody levels were similar in the 2 groups and were within the reference range except in one patient. This study showed that insulin lispro is safe and has much the same antibody formation as regular human insulin<sup>8</sup>. No studies are available in the literature on the potential immune response to insulin aspart and glargine during pregnancy.

All studies assessing the possible benefits of insulin lispro treatment in patients with pregestational

and gestational diabetes are retrospective<sup>8</sup>. Some have identified significantly lower levels of HbA<sub>1c</sub> and plasma glucose and fewer hypoglycemic episodes in pregnant type 1 diabetic women treated with insulin lispro than in those on regular insulin. Conversely, other studies report no significant differences in HbA<sub>1c</sub> values between treatment groups. No studies are currently available in the literature on maternal and fetal outcome in patients treated with insulin aspart. For insulin glargine, the few reports on its use in pregnancy record no maternal or neonatal complications<sup>8,11</sup>.

Studies assessing the effect of insulin lispro treatment in women with GDM have shown a significant reduction in hypoglycemia before meals, postprandial hyperglycemia and HbA<sub>1c</sub> levels in comparison with GDM women, treated with regular insulin<sup>8</sup>. Furthermore, Mecacci et al<sup>14</sup> recently compared maternal glucose levels and neonatal outcome in GDM women randomly assigned to treatment with regular insulin or insulin lispro and reported that insulin lispro was able to normalize 1-hour postprandial glucose levels in GDM patients, and that this reduction was associated with normal anthropometric characteristics in the neonates. The effectiveness of insulin aspart was recently evaluated in GDM patients who were given a standard breakfast for 3 consecutive days, with no exogenous insulin on the first day, followed by injections of either regular insulin or insulin aspart on the next 2 days. The results of the study confirm the efficacy of insulin aspart in reducing postprandial glucose concentrations in GDM patients<sup>15</sup>.

As for maternal and fetal outcomes, no differences in the frequency of cesarean sections, gestational age at delivery, or frequency of preeclampsia or macrosomia were observed in diabetic pregnant women on insulin lispro *versus* those on regular insulin<sup>8</sup>.

In short, data in the literature analyzing the possible adverse effects of insulin lispro suggest that this medication can be used in pregnant women with pregestational diabetes liable to postprandial hyperglycemia and/or preprandial hypoglycemia. In our opinion, informed consent should be obtained from these patients and glucose control and retinopathy should be closely monitored during follow-up. The efficacy of insulin lispro in reducing postprandial glucose peaks provides us with a new tool for treating GDM characterized by postprandial hyperglycemia.

Insulin aspart can also be used successfully in GDM patients with postprandial hyperglycemia. The results of studies on insulin aspart in pregnant type 1 diabetic women will cast further light on its use in pregnancy in the near future.

Retrospective clinical studies on insulin glargine are needed to establish whether it is safe to use, particularly in pregnant type 1 diabetic patients, who often have nocturnal hypoglycemia.

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