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CASE REPORT

Insulin degludec in the first trimester of pregnancy: Report of two cases

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ABSTRACT

Insulin degludec is an extra-long-acting insulin analog that allows for enhanced efficacy and flexibility in the injection time. However, it is not approved for use during pregnancy. We report the pregnancy outcome and newborn conditions in two women with type 1 diabetes who continued preconception degludec treatment during embryogenesis. No pregnancy complication or congenital neonatal malformation was observed. Both babies presented with hypoglycemia and required neonatal intensive care unit admission. Degludec treatment did not cause adverse effects in the mothers or malformations in the newborns. The observed neonatal complications were probably independent of early pregnancy degludec treatment.

INTRODUCTION

In women with diabetes, pregnancy is associated with a higher risk of developing adverse outcomes[1]. Therefore, pregnancy planning is mandatory to obtain strict glycemic control both before and during pregnancy.

The use of insulin analogs has improved the possibility of reaching good metabolic control[2], but during pregnancy only the short-acting lispro and aspart analogs, and long-acting insulin glargine and detemir can be used in Italy[3]. Insulin degludec, an extra-long-acting analog that causes a flat, 24-h basal glucose-lowering, is not approved for pregnant women due to a lack of efficacy and safety studies, although its characteristics might be useful in people with difficult/unstable glycemic control[4].

We report two cases of unplanned pregnancy in women with Type 1 diabetes who continued pre-conception degludec treatment during early pregnancy.

CASE 1

A 34-year-old Caucasian woman with type 1 diabetes since the age of 26 years (diagnosis at the 7th month of her first pregnancy, which ended at term and was uneventful) was referred to the Endocrinology Unit, Garibaldi-Nesima Hospital, Catania, Italy, at 12 weeks of her second unplanned pregnancy.

Pre-pregnancy bodyweight was 61.4 kg (BMI 22.7 kg/m^2), and glycated hemoglobin (HbA1c) was 6.3% (45 mmol/mol) under treatment with insulin lispro before meals and degludec 15 IU (0.24 IU/kg/day) at bedtime. Blood pressure was 110/70 mmHg. Micro- and macrovascular complications were absent (Table 1).

In the second month of pregnancy, before presentation to our clinic, HbA1c was 6.0% (42 mmol/mol). However, her glycemic values were unstable, with frequent diurnal and nocturnal hypoglycemia unawareness. Degludec was immediately replaced during our first visit with the same amount of glargine at bedtime. The total insulin dose was continuously adjusted during the pregnancy, increasing from 0.64 to 1.6 IU/kg/day (the glargine dose increased from 0.24 to 0.52 IU/kg/day). HbA1c decreased to 5.8% and 5.2% (40 and 33 mmol/mol) during the second and third trimester, respectively. Also, glycemic variability significantly decreased (Table 1). Ultrasound monitoring of fetal growth, amniotic fluid and artery velocimetry were always regular.

The woman delivered by cesarean section (due to rupture of membranes without onset of labor) at 37 weeks-of-gestation when her bodyweight was 70.4 kg. The male baby was 3,330 g in weight (50–75th percentile) and 54.5 cm in length (>97th percentile). His Apgar score was 8 and 9 at 1 and 5 min, respectively. He was transferred to the neonatal intensive care unit due to respiratory distress syndrome, which was treated with nasal continuous positive airway pressure. Furthermore, he had mild hypoglycemia (37 mg/dL) that required glucose infusion for 6 h. No congenital malformation was present. The infant was fed mixed breast/bottle and, at 13 months-of-age, is in excellent health with normal growth (Table 1).

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Table 1 | Maternal and fetal outcomes in the two reported cases

	Case 1	Case 2
Mother		
Age (years)	34	22
Diabetes duration (years)	8	16
Pre-pregnancy BMI (kg/m^2)	22.7	36.1
Micro/macrovascular complications		
Before pregnancy	No	No
Progression during pregnancy	No	No
Degludec treatment during pregnancy		
Weeks	0–12	0–8
Dose (IU/kg/day)	0.24	0.32
Basal insulin treatment after degludec	Glargine (bedtime)	Detemir (b.i.d.)
Discontinuation		
Basal insulin dose increased during pregnancy (IU/kg/day)	0.24 to 0.52	0.32 to 0.53
HbA1c, % (mmol/mol)		
Pre-conception	6.3 (45)	7.7 (61)
First trimester	6.0 (42)	6.6 (49)
Second trimester	5.8 (40)	5.7 (39)
Third trimester	5.2 (33)	5.0 (31)
Median daily† glycemia, mg/dL (range)		
At first visit	101 (37–212)	117 (31–280)
At delivery	122 (60–195)	93 (56–130)
Weight gain at end of pregnancy (kg)	9	8
Time of delivery (gestational weeks)	37	37
Delivery	Cesarean	Induced
Newborn		
Birthweight (g)	3,330	3,300
Congenital malformations	No	No
APGAR score (at 1 and 5 min)	8 and 9	9 and 10
Neonatal hypoglycemia	Mild	Moderate
NICU admission (cause)	Respiratory distress	Hyperbilirubinemia

†Median values were calculated using six values protocol on five non-consecutive days. BMI, body mass index; HbA1c, glycated hemoglobin; NICU, neonatal intensive care unit.

The patient gave written informed consent to anonymously describe her case.

CASE 2

A 22-year-old Caucasian pregnant woman who had type 1 diabetes since she was aged 6 years was referred to our clinic 8 weeks into her second unplanned pregnancy. Her first pregnancy, which occurred 1 year earlier, ended at 10 gestational weeks with a miscarriage. Pre-pregnancy BMI was 36.1 kg/m^2.

She was undergoing treatment with insulin lispro before meals and degludec 28 IU at bedtime (0.32 IU/kg/day). Her glycemic control was poor. HbA1c was 7.7% (61 mmol/mol) 3 months before conception, and 6.6% (49 mmol/mol) when she was assessed at our clinic. She had severe glycemic instability (123.6 ± 62.2 mg/dL from six samples/day on 5 non-consecutive days), with frequent hypoglycemic events, primarily due to irregular insulin administration on demand to correct hyperglycemia.

The patient's bodyweight was 88 kg, and blood pressure was 120/70 mmHg. Vascular complications were absent (Table 1). Degludec was immediately replaced with an equal dose of insulin detemir split into two equal daily doses. The first week after degludec discontinuation, her glycemic profile worsened. The total insulin dose was increased slightly from 0.75 to 0.78 IU/kg/day as the pregnancy progressed, with an important shift to long-acting insulin prevalence (detemir was increased from 0.32 to 0.53 IU/kg/day). Glycemic control slowly improved, and a more stable glycemic profile was achieved (Table 1) with a significant decrease in the hypoglycemic events. The mean HbA1c decreased to 5.7% and 5.0% (39 and 31 mmol/mol) in the second and third trimester of gestation, respectively. Ultrasound monitoring of fetal growth, amniotic fluid and artery velocimetry were always normal.

Labor was induced at 37 weeks-of-gestation due to a sudden increase of blood pressure. The male newborn's weight was appropriate for his gestational age (3,300 g, 50 cm, 75–90th percentile). His Apgar score was 9 and 10 at 1 and 5 min,

respectively. He was transferred to the neonatal intensive care unit due to increased bilirubin plasma levels (17 mg/dL), and treated with phototherapy. He had moderate hypoglycemia (30 mg/dL), which remitted after 10 h of glucose infusion. No major or minor congenital malformation was present. He had mixed breast/bottle feeding. At 4 months-of-age, he is in excellent health, with normal growth (Table 1).

The patient gave written informed consent to anonymously describe her case.

DISCUSSION

This is the first report on degludec treatment in pregnant women with diabetes. In these people, degludec is not approved because of the lack of randomized controlled clinical trials on its safety and efficacy for both the mother and the newborn. No complications or adverse events were observed for degludec treatment in the first trimester and also during the following period of pregnancy.

Animal reproduction studies have found no difference between degludec and human insulin for embryotoxicity[5]. In the two cases described here, degludec was administered in early pregnancy, when embryogenesis occurs, and no major or minor malformation was observed in the two newborns, who have had regular growth and are in excellent health at 4 and 13 months-of-age.

Both newborns, however, had relevant adverse neonatal outcomes that required their transfer to the neonatal intensive care unit. These adverse events, particularly hypoglycemia, are correlated with poor maternal blood glucose control during parturition[6,7]. Degludec treatment had been discontinued 5 months before birth. It is likely, therefore, that inadequate metabolic control, rather than degludec treatment, might be responsible for the neonatal adverse events.

It has been reported that degludec improves glycemic control in diabetes patients[4,8], but no data are available for diabetes in pregnancy. Although its use could be suitable for the treatment of pregnant women affected by diabetes with difficulty maintaining glycemic targets, the use of this treatment in pregnancy needs to be confirmed by clinical trials.

The present observations appear to be promising as far as embryotoxicity and/or malformations are concerned. However, they need to be confirmed in larger controlled studies.

DISCLOSURE

RV was a member of the Novo Nordisk Advisory Board in 2015 and 2016. LS was a member of the Lilly Advisory Board in 2017. The other authors declare no conflict of interest.

REFERENCES

1. Persson M, Norman M, Hanson U. Obstetric and perinatal outcomes in type 1 diabetic pregnancies: a large, population-based study. *Diabetes Care* 2009; 32: 2005–2009.
2. Rossetti P, Porcellati F, Fanelli CG, *et al*. Superiority of insulin analogues versus human insulin in the treatment of diabetes mellitus. *Arch Physiol Biochem* 2008; 114: 3–10.
3. Associazione Medici Diabetologi (AMD) - Società Italiana di Diabetologia (SID). Standard italiani per la cura del diabete mellito 2016. Available from: http://www.standarditaliani.it/ Accessed March 30, 2017.
4. Russell-Jones D, Gall MA, Niemeyer M, *et al*. Insulin degludec results in lower rates of nocturnal hypoglycaemia and fasting plasma glucose vs. insulin glargine: a meta-analysis of seven clinical trials. *Nutr Metab Cardiovasc Dis* 2015; 25: 898–905.
5. European Medicines Agency (EMA). London: Committee for Medicinal Products for Human Use, 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002498/WC500138940.pdf Accessed March 30, 2017.
6. Plehwe WE, Storey GN, Shearman RP, *et al*. Outcome of pregnancy complicated by diabetes: experience with 232 patients in a 4 year period. *Diabetes Res* 1984; 1: 67–73.
7. Taylor R, Lee C, Kyne-Grzebalski D, *et al*. Clinical outcomes of pregnancy in women with type 1 diabetes(1). *Obstet Gynecol* 2002; 99: 537–541.
8. Marso SP, McGuire DK, Zinman B, *et al*. Efficacy and safety of degludec versus glargine in type 2 diabetes. *N Engl J Med* 2017; 377: 723–732.