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PREGNANCY OUTCOME AND LIRAGLUTIDE LEVELS IN SERUM AND UMBILICAL VEIN BLOOD OF A WOMAN WITH TYPE 2 DIABETES. A CASE REPORT

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Case report

Key words: pregnancy, Type 2 diabetes mellitus, liraglutide

Summary. *Background:* According to FDA guidelines, liraglutide should be used on the basis of careful consideration in pregnant women with Type 2 diabetes mellitus. The aim of the present study was to record the concentration of liraglutide in maternal and umbilical vein serum from a pregnant woman treated with liraglutide. *Case report:* The pregnant woman we present in this case report is a 28-year-old diagnosed with Type 2 diabetes mellitus for 7 years. In spite of high insulin dose her glycaemia was poorly controlled, she developed dyslipidaemia and her body weight increased; thus, her diabetologist prescribed liraglutide injections and metformin. At booking, obstetrical ultrasound confirmed intrauterine pregnancy of 8 gestational weeks. The patient was informed about all possible consequences for her foetus that might be caused by liraglutide therapy during pregnancy. She continued her treatment with liraglutide and metformin medication throughout pregnancy. Her pregnancy was terminated by elective Caesarean section at 39 gestational weeks; a healthy newborn male was delivered. The concentration of liraglutide was measured in maternal and umbilical vein serum. *Conclusion:* There was no significant transfer of liraglutide from the circulation of the treated mother to her fetus, at least 3.5 h after the drug application.

Introduction

According to FDA guidelines, liraglutide should be used on the basis of careful consideration, and the physician needs to decide whether the benefit-risk profile is favorable for the specific patient (1).

Liraglutide is an injectable glucose-lowering drug, a glucagon-like peptide-1 (GLP-1) that is used as a long-acting GLP-1 receptor agonist, binding to the same receptors as the endogenous metabolic hormone GLP-1 that stimulates insulin secretion (2,3).

Liraglutide causes a reduction in body weight and fat mass by suppressing energy intake and promoting satiety (4,5). Animal reproductive data have revealed evidence of the negative impact of therapy with liraglutide (1).

Case report

The pregnant woman we present in this case report is a 28-year-old diagnosed with Type 2 diabetes for 7 years. Other significant medical history includes a thyroidectomy (histopathology analysis: Struma diffusa glandulae thyroideae) and cholecystectomy because of gall stones.

During her first pregnancy, her Type 2 diabetes mellitus was treated with insulin analogues (insulin aspart and insulin detemir). She delivered at term, by a Caesarean section (CS), a healthy newborn male (birthweight 3650 grams/49 centimeters long). After delivery, insulin analogues were continued for diabetes treatment. However, her glycaemia was poorly controlled, with average glycaemia at 9.2 mmol/l, HbA1c beyond 7.5% (58 mmol/mol); and she developed dyslipidemia as well. Moreover, her body weight increased; thus, her diabetologist prescribed liraglutide injections at a dose of 1.8 mg once a day, and metformin (3x500 mg daily) from 2014 until today. As a result of the new therapy, her glycaemia was normalized, her body weight stabilized, and her lipid profile values remained moderately above reference values.

This is her second spontaneous pregnancy. Her body height measured before pregnancy was 183 cm, and her body weight was 139 kg. At booking, obstetrical ultrasound revealed intrauterine pregnancy of 8 gestational weeks (GW). A balanced diabetic diet of 1300 Kcal/day was recommended. Her diabetic pharmacotherapy at the time of admission was liraglutide 1.8 mg once daily, metformin 500 mg three times daily and levothyroxin 250 μg once daily throughout the entire pregnancy and after delivery.

Daily mean capillary blood glucose values ranged from 3.5 – 5.6 mmol/l. HbA1c was 6.5% (48 mmol/mol) in the first trimester, and 6.1% (43 mmol/mol) in the second and third trimester. The patient was informed by a diabetologist and signed a patient's consent indicating that she is completely aware of all possible consequences to her foetus that might be caused by liraglutide therapy during pregnancy.

The elective CS was performed with spinal anesthesia at 39 GW. At 7 AM on 21 November 2016, she received liraglutide 1.8 mg, metformin 500 mg, and a 5% glucose 500 ml IV infusion was started. Maternal blood sample was taken at the time of CS. At 10:34 AM, a healthy newborn male weighing 4220 g and 51 cm long was delivered, AS 10/10, and umbilical vein blood was

Table 1. Concentration* of active GLP-1 in maternal and umbilical vein serum from pregnancy complicated with type 2 diabetes mellitus exposed to liraglutide compared to the maternal and umbilical vein serum from the healthy pregnant control and was not exposed to liraglutide

	Sample	pmol/l
Patient exposed to liraglutide	Maternal serum	8.4
	Umbilical vein serum	0.7
Control patient	Maternal serum	1.4
	Umbilical vein serum	0.6

The concentration* of liraglutide was measured with an active GLP-1 ELISA (High Sensitivity GLP-1 Active Chemiluminescent ELISA kit, Millipore Corporation, St. Charles, Missouri, USA).

withdrawn. The concentration of liraglutide was measured with an active GLP-1 ELISA (High Sensitivity GLP-1 Active Chemiluminescent ELISA kit, Millipore Corporation, St. Charles, Missouri, USA). The levels of umbilical vein blood liraglutide, measured with GLP-1 assay after removal of endogenous GLP-1 by thermal degradation (37°C, 4h) were below the limit of assay sensitivity declared by manufacturer (2 pmol/L). Similar result was found in serum of the control pregnant woman, wich was <2 pmol/L and far below reported reference range for GLP-1 in healthy population (12.7 pmol/L (8.0–17.1) (6). Our results indicate that: a) removal of endgenous GLP-1 was succesful and reported results in serum of treated woman indicate indeed liraglutide concentration, and, b) there was no significant transfer of liraglutide from the circulation of the treated mother to her fetus, at least 3.5 h after the drug application as documented in this case. The values of total bilirubin, total calcium, AST, ALT, AF, GGT and LDH in the serum of the umbilical vein did not differ between the pregnant woman taking liraglutide and the healthy pregnant control w/o liraglutide. The child is now 2 years old, healthy and progressing well.

Discussion

In this article, we document the concentration of liraglutide in maternal and umbilical vein serum from a pregnant woman with Type 2 diabetes, treated with liraglutide injections.

According to the accessible literature, this is the first case to our knowledge of a pregnant woman with Type 2 diabetes mellitus who was treated with liraglutide and metformin during pregnancy and childbirth, and who gave birth to a healthy baby. This is the first time the concentrations of liraglutide in the mother's and umbilical vein blood were measured, due to the Type 2 diabetes mellitus treated with liraglutide from preconception throughout pregnancy.

A few years ago, a pregnant woman with diabetes (7) was treated with liraglutide during the first 13 weeks of pregnancy; liraglutide was replaced with insulin, and she gave birth to a healthy baby.

Conclusion

There was no significant transfer of liraglutide from the circulation of the treated mother to her fetus, at least 3.5 h after the drug application as documented in this case.

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KONCENTRACIJA AKTIVNOG GLP-1 U UMBILIKALNOJ VENI TRUDNICE S DIJABETESOM TIPA-2 KOJA JE TIJEKOM TRUDNOĆE LIJEČENA LIRAGLUTIDOM

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Prikaz bolesnice

Klučne riječi: dijabetes tipa 2, trudnoća, liraglutide

Sažetak. Prema FDA kategorizaciji lijekova liraglutide treba koristiti tijekom trudnoće samo ako potencijalna korist opravdava potencijalni rizik za fetus. Cilj je prikazati trudnicu koja je liječena liraglutidom tijekom cijele trudnoće i rodila zdravo dijete. Prikaz trudnice. Uspoređena je koncentracija aktivnog GLP-1 (active GLP-1) u serumu majke i umbilikalne vene trudnice koja je liječena liraglutidom i trudnice koja nije bila na terapiji s liraglutidom. Koncentracija aktivnog GLP-1 u serumu majke neposredno prije porođaja, odnosno nakon 3 sata i 34 minute od davanja 1,8 mg liraglutida, iznosila je 8,4 pmol/l, u umbilikalnom venskom serumu 0,7 pmol/L. U usporedbi sa serumom majke koja nije uzimala liraglutide koncentracija aktivnog GLP-1 iznosila je 1,4 pmol/l, a umbilikanom venskom serumu 0,6 pmol/l. Zaključak. Koncentracija aktivnog GLP-1 seruma umbilikalne vene majke koja je bila na terapiji s liraglutidom se nije razlikovala od koncentracije seruma umbiliklane vene majke koja nije uzimala liraglutid.