Octreotide therapy and restricted fetal growth: pregnancy in familial hyperinsulinemic hypoglycemia

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Summary

Hypoglycemia during pregnancy can have serious health implications for both mother and fetus. Although not generally recommended in pregnancy, synthetic somatostatin analogues are used for the management of blood glucose levels in expectant hyperinsulinemic mothers. Recent reports suggest that octreotide treatment in pregnancy, as well as hypoglycemia in itself, may pose a risk of fetal growth restriction. During pregnancy, management of blood glucose levels in familial hyperinsulinemic hypoglycemia thus forms a medical dilemma. We report on pregnancy outcomes in a woman with symptomatic familial hyperinsulinemic hypoglycemia, type 3. During the patient's first pregnancy with a viable fetus octreotide treatment was instituted in gestational age 23 weeks to prevent severe hypoglycemic incidences. Fetal growth velocity declined, and at 37 weeks of gestation, intrauterine growth retardation was evident. During the second pregnancy with a viable fetus, blood glucose levels were managed through dietary intervention alone. Thus, the patient was advised to take small but frequent meals high in fiber and low in carbohydrates. Throughout pregnancy, no incidences of severe hypoglycemia occurred and fetal growth velocity was normal. We conclude that octreotide treatment during pregnancy may pose a risk of fetal growth restriction and warrants careful consideration. In some cases of familial hyperinsulinemic hypoglycemia, blood glucose levels can be successfully managed through diet only, also during pregnancy.

Learning points:

- Gain-of-function mutations in *GCK* cause familial hyperinsulinemic hypoglycemia.
- Hypoglycemia during pregnancy may have serious health implications for mother and fetus.
- Pregnancy with hyperinsulinism represents a medical dilemma as hypoglycemia as well as octreotide treatment may pose a risk of fetal growth restriction.
- In some cases of familial hyperinsulinemic hypoglycemia, blood glucose levels can be successfully managed through diet only.

Background

Familial hyperinsulinemic hypoglycemia type 3 (HHF3, OMIM #602485) is caused by gain-of-function mutations in *GCK*, the gene encoding glucokinase. In the pancreatic beta cell, glucokinase catalyzes the phosphorylation of glucose to glucose-6-phosphate, which in turn stimulates insulin secretion. Although loss-of-function

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GCK mutations cause impaired insulin secretion and mild hyperglycemia, i.e., maturity onset diabetes of young, type 2 (MODY2), activating *GCK* mutations lead to hyperinsulinism and subsequently hypoglycemia (1). HHF3 is inherited in an autosomal dominant manner and characterized by marked phenotypic variation even within families. In accordance, some heterozygous mutation carriers may only present postprandial hypoglycemia, whereas others experience repeated admissions to hospital due to hypoglycemic convulsions and coma (2, 3).

Animal studies have shown that maternal hyperinsulinism and hypoglycemia during pregnancy increases the risk of fetal malformation and fetal growth restriction (4). Further, it has been hypothesized that incidences of severe maternal hypoglycemia may have damaging impact on the fetal neurological development (5). Although somatostatin analogues may lower insulin secretion and reduce the risk of hyperinsulinemic hypoglycemia, administration of these drugs during pregnancy is generally not recommended due to inadequate data on potential effects on the fetus. Some reports suggest that somatostatin analogues can be used without deleterious effects to the fetus, but recently reservations have been made upon the possible risk of severe fetal growth retardation and likely association to neonatal necrotizing enterocolitis (6, 7, 8).

Hyperinsulinemic hypoglycemia in pregnancy thus forms a medical dilemma as hypoglycemia as well as treatment with somatostatin analogues may cause intrauterine growth retardation. To our knowledge, only two previous publications have addressed this topic (6, 7).

We present pregnancy outcomes in a woman with symptomatic HHF3 treated with octreotide injections in one pregnancy and with a low carbohydrate diet only in a subsequent pregnancy. During the first pregnancy with a viable fetus intrauterine growth retardation (IUGR) developed whilst in the second pregnancy with a viable fetus, fetal growth velocity was normal.

Case presentation

The patient, a thirty-four-year old Caucasian woman, was diagnosed with HHF3 at twenty-three years of age. She was obese with BMI of 34 and smoked 20 cigarettes per day but was otherwise healthy. The patient had no history of severe hypoglycemic episodes, defined as having low blood glucose levels that requires assistance from another person to treat. Yet, she reported intermittent light-headedness, headache and hunger, especially during exercise and when trying to lose weight. In 2004, at the time of diagnosis,

pre-prandial blood glucose ranged 1.9–2.7 mmol/L, and during oral glucose tolerance test, the blood glucose level was 1.6 mmol/L after 3.5 h with the patient experiencing cold sweat and pronounced discomfort. A 72-h fasting test was initiated but disrupted after only six hours, as blood glucose dropped to 1.9 mmol/L. HbA1c was 4.2% corresponding to 22.4 mmol/mol, and levels of plasma C-peptide (1014 pmol/L) and plasma insulin (88 pmol/L) were increased, whereas plasma pro-insulin was normal (11 pmol/L), suggesting hyperinsulinemic hypoglycemia. Molecular genetic screening identified a heterozygous gain-of-function *GCK* mutation, c.1367C > T, p.Ala456Val, which had previously been reported in a symptomatic second-degree relative. The patient was recommended a daily calorie intake of 6000–7000 kJ dispersed on 6 meals, high in fiber and with a low glycemic index. Diazoxide therapy was suggested, but the patient declined, as she was unable to accept the possible side effects. Instead, since 2005, she was treated successfully with intramuscular injections of octreotide acetate 10 mg every fourth week to prevent severe hypoglycemia. After treatment was instituted, the patient reported no hypoglycemic symptoms or side effects.

In 2007, she conceived spontaneously but had a missed abortion in gestational week 10. There was no apparent increase in incidences of hypoglycemia leading up to the miscarriage and no conclusions were made upon the cause.

The patient became pregnant for a second time later the same year, and on her request, octreotide was discontinued from gestational age (GA) 11 weeks. Pre-pregnancy BMI was 39, and she smoked 5 cigarettes per day. She was closely followed every fourth week by a dedicated obstetric-endocrine team with self-monitoring of blood glucose profiles and monitoring of fetal growth. At GA 19 weeks, fetal growth was normal and no malformations were identified on ultrasound. From GA 20 weeks, blood glucose dropped below 3.0 mmol/L with increasing frequency and at GA 23 weeks, octreotide therapy was reinstituted as the risk of severe hypoglycemia with serious health implications for both patient and fetus was considered significant. Again, the drug was administered as intramuscular injections every fourth week. The initial dosage was octreotide acetate 10 mg with an increase to 20 mg every fourth week from GA 27 weeks. After reinstatement of octreotide acetate injections, the pre-prandial blood glucose levels stabilized >3.0 mmol/L. Fetal ultrasound measurements showed decreasing growth velocity, and at GA 37 weeks, IUGR was diagnosed with fetal biometrics 26% below normal (Fig. 1A). The patient

delivered spontaneously in GA 37 + 5 weeks after stripping membranes two days earlier. The child had Apgar scores 10 at 1 min and 10 at 5 min, and birth weight and length were 2200 g and 47 cm, respectively. Post-natal molecular genetic testing revealed that the child had not inherited the familial *GCK* mutation. The patient decided not to breast-feed and octreotide therapy was continued. Data regarding the child's post-natal growth is unfortunately not available.

In 2012, the patient conceived for the third time. An injection of octreotide had been administrated two weeks prior to estimated conception and further administration was discontinued due to the possible risk of impaired fetal growth. A routine sonographic evaluation for nuchal translucency identified a missed abortion corresponding to GA 8 + 3 years. Octreotide therapy was not reinstituted, and the patient managed blood glucose levels through diet only.

In 2013, the patient conceived the fourth time. Her weight was 108 kg, corresponding to a BMI of 40, and she did no longer smoke. At the first visit in the obstetric clinic at GA 8 weeks, she was advised to take small and frequent meals 6 times a day, high in fiber and low in simple carbohydrates. Again, the patient was followed every fourth week to evaluate blood glucose measurements, including blood glucose profiles and HbA1c, and fetal growth. Blood glucose levels were stable between 3.0 and 5.0 mmol/L throughout the first and second trimester (Table 1). In GA 29 weeks, pre-prandial blood glucose dropped below 3 mmol/L, and the diet was adjusted to meals every two hours with 10–12 g of complex carbohydrates and a high content of fiber and fat. During the third trimester, blood glucose levels were predominantly 3.0–4.4 mmol/L with only a few measurements of 2.5–2.9 mmol/L and no
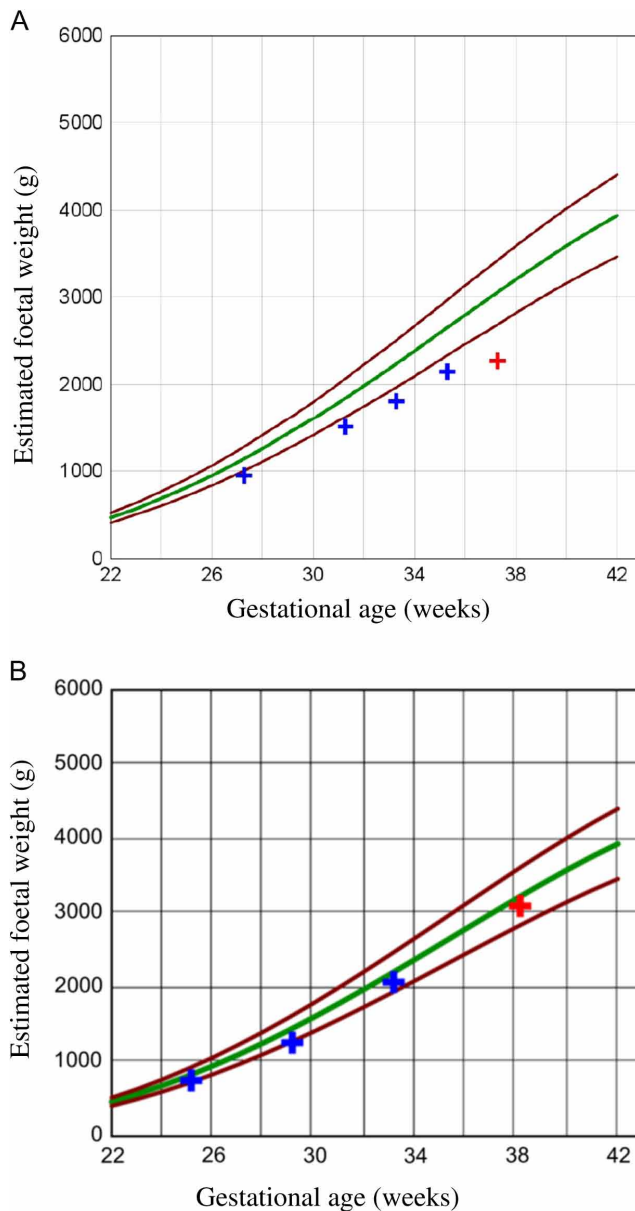

Figure 1
(A) Fetal weight, first pregnancy. Upper and lower red lines marking 97th and third percentiles respectively. (B) Fetal weight, second pregnancy. Upper and lower red line marking 97th and third percentiles respectively.

Table 1 Blood glucose profiles during the fourth pregnancy, first trimester.

Day	Breakfast		Lunch		Dinner	
	Pre	Post	Pre	Post	Pre	Post
	3.6	4.5	4.1	4.9	3.6	4.8
	3.6	4.6	4.4	4.5	3.2	4.2
	3.5	4.4	3.6	3.9	3.0	4.9
	3.3	4.6	3.5	4.0	3.4	4.2
	3.6	4.4	3.6	4.2	3.5	4.4
	3.5	4.3	3.3	4.0	3.2	4.0
	3.6	4.6	3.6	4.1	3.3	4.1
	3.4	4.5	3.4	3.9	3.3	4.2
	3.6	4.4	3.5	4.0	3.5	4.4
	3.7	4.5	3.5	4.0	3.3	4.2
	4.0	4.6	3.7	4.0	3.4	4.4
	3.9	4.2	3.6	4.1	3.5	4.0
	3.4	4.0	3.5	4.0	3.6	4.6
	4.0	4.6	3.5	4.0	3.3	4.4
	4.2	4.8	3.8	4.4	3.4	4.2
	3.4	4.0	3.6	4.0	3.5	4.4
	3.8	4.2	3.7	4.2	3.6	4.1
	3.3	3.9	3.4	4.0	3.1	3.9
	3.1	3.8	3.3	3.9	3.0	3.7
	3.0	3.7	3.2	4.0	3.5	3.9
	3.1	3.6	3.3	3.9	3.4	3.8

Pre: Pre-prandial blood glucose, mmol/l. Post: Post-prandial blood glucose, mmol/l, 1½ hours after meals.

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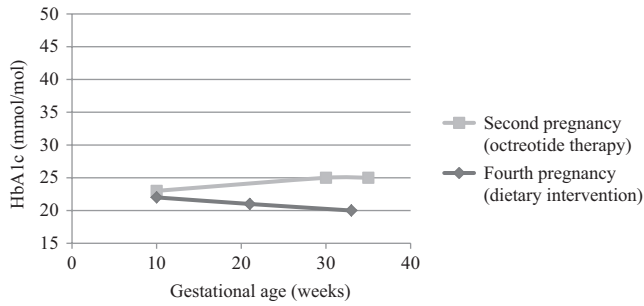DOI: 10.1530/EDM-16-0126

Figure 2

HbA1c during pregnancies. Normal range (non-pregnant women):
31–44 mmol/mol. Normal range during the second and third trimester of
pregnancy: 21–40 mmol/mol (9).

symptoms of severe hypoglycemia. The fetus showed
no signs of IUGR, and fetal growth velocity was normal
throughout the second and third trimester (Fig. 1B). After
spontaneous labor in GA 39+6 weeks, the patient gave
birth to a healthy child with Apgar scores 10 at 1 min
and 10 at 10 min, and birth weight and length at 2890 g
and 48 cm, respectively. Post-natal molecular genetic
testing showed that the child did not carry the familial
GCK mutation. Data regarding post-natal growth are
unfortunately not available.

Discussion

Here, we present pregnancy outcomes in a woman with
symptomatic HHF3 treated with octreotide injections in
the first pregnancy and with a low carbohydrate diet only
in a subsequent pregnancy. Two additional pregnancies
during octreotide treatment resulted in the 1st trimester
spontaneous abortions. During the first pregnancy with
a viable fetus, octreotide injections were instituted from
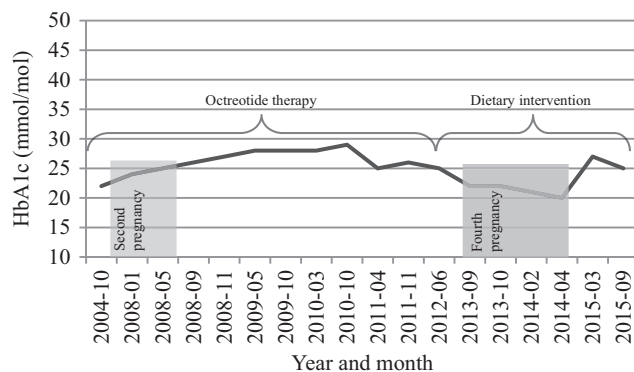GA 23 weeks to maintain blood glucose levels in a normal

Figure 3

HbA1c measurements over time. Grey boxes indicating second and fourth
pregnancy, respectively.

range and prevent severe hypoglycemic events. A decline
in fetal growth velocity was observed from GA 27 weeks,
and IUGR was evident at 37 weeks of gestation. In the
second pregnancy with a viable fetus blood glucose levels
were managed on a low carbohydrate diet only. The fetal
growth velocity was normal throughout the pregnancy.
The patient did not experience incidences of severe
hypoglycemia in any of the pregnancies and HbA1c levels
were in the normal range for the second and third trimester
pregnancy (Figs 2 and 3) (9). No fetal or umbilical cord
malformations were noticed and neither of the children
carried the familial gain-of-function *GCK* mutation.
Though the patient smoked up to five cigarettes per day
during the first pregnancy, this is unlikely to explain the
abrupt decline in fetal growth velocity from the 23rd week
of gestation. Instead, the intrauterine growth retardation
observed in the first pregnancy may be ascribed to
octreotide administration; this factor being the single
most important difference between the two pregnancies.

Previous reports on the use of octreotide during
pregnancy are scarce and conflicting. Uneventful
pregnancies with normal outcomes have been observed
in acromegalic women and in one case of unspecified
nesidioblastosis (6, 10). Other investigators report on
fetal growth retardation and a possible risk of NEC in
the neonate after intrauterine octreotide exposure (7, 8).
Animal studies on prenatal development report reduced
fetal growth and maturation after intrauterine exposure to
octreotide. Based on these findings, the drug is generally
not recommended for pregnant women (http://www.
ema.europa.eu/docs/en_GB/document_library/Referrals_
document/Sandostatin_LAR_30/WC500169358.pdf.
Accessed 27th of March, 2016). Octreotide passes the
placental barrier and influence the fetus in the same way
as human somatostatin by decreasing levels of insulin and
insulin-like growth factor 1 among others (11).

In the present case, the possible damaging effects of
octreotide may have been further aggravated as familial
hyperinsulinism in itself may increase the risk of IUGR.
Skajaa and coworkers proposed that fetal growth in a
HHF pregnancy could be influenced by the genetic state
of the fetus, analogously to what is seen in MODY2. Our
case cannot elucidate this issue, as none of the children
were carrying the familial GCK mutation and the genetic
status of the aborted fetuses is unknown. Instead, our case
indicates that non-carrier fetuses are at risk of growth
restriction when exposed to octreotide.

In cases of familial hyperinsulinism, octreotide is
used during pregnancy to prevent severe hypoglycemia
with the inherent risk of coma and death. Though

hypoglycemia has been associated with both congenital malformations and impaired fetal growth in animal studies, there is no evidence to confirm a similar teratogenic effect of hypoglycemia in pregnancy in humans (4, 5, 12). In adults, recurrent hypoglycemia is associated to a significant decline in cognitive function. Similar findings have not been reported in offspring of diabetic mothers with recurrent hypoglycemic episodes in pregnancy (13). It is speculative whether the more or less constant hypoglycemic state seen in HHF3 affects fetal cognitive development.

Conclusion

Octreotide administration during pregnancy in hyperinsulinism may pose a risk of fetal growth retardation. Other dietary interventions with low carbohydrate content should be considered before octreotide therapy is instituted. Close follow-up of at-risk pregnancies is warranted as hypoglycemia in itself may lead to fetal growth impairment.

Patient consent

The patient gave written informed consent for publication of this article.

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