

Case report

Multidisciplinary approach in medicine: successful pregnancy in a patient with hyperinsulinism/hyperammonaemia (HI/HA) syndrome

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SUMMARY

This case illustrates the importance of multidisciplinary counselling and management of pregnancies in women with complex medical conditions, especially concerning women with cognitive impairment. We present a woman with hyperinsulinism/hyperammonaemia (HI/HA) syndrome. This syndrome is characterised by recurrent episodes of hypoglycaemia and elevated ammonia levels, which are potentially harmful to both the patient and a developing fetus. We describe a successful multidisciplinary approach during the pregnancy of a mentally challenged patient with HI/HA syndrome. This case illustrates the importance of personalised counselling during the preconception period and emphasises to include all disciplines involved in the medical and daily care of such a patient. In our case, the extensive multidisciplinary care during the preconception period, pregnancy, delivery and postpartum period resulted in a good maternal and neonatal outcome.

BACKGROUND

Hyperinsulinism/hyperammonaemia (HI/HA) syndrome is a rare autosomal dominant metabolic disease, characterised by life-threatening hypoglycaemia. The gain of function mutations in the *GLUD1* gene, encoding for the mitochondrial enzyme glutamate dehydrogenase (GDH), leads to unrestrained insulin production by the β -cells in the pancreas and increased ammonia levels (figure 1).¹ Clinically, the disease is characterised by recurrent episodes of symptomatic severe hypoglycaemia. Seizures are common and may cause cerebral damage, resulting in cognitive impairment with learning difficulties.²

CASE PRESENTATION

A 29-year-old woman, body mass index 32 kg/m², diagnosed in childhood with HI/HA syndrome, suffers from frequently occurring episodes of severe hypoglycaemia. In addition, a 15q13.3 deletion was detected with psychomotor retardation (IQ 57). She can read and lives independently. She is treated with diazoxide 100 mg two times per day (for detailed information see # in online supplementary file 1), chlorthalidone 25 mg two times per day and a strict diet. Her diet consists of frequent carbohydrate-rich meals, such as regular intake of uncooked cornstarch and avoidance of large protein loads.

After initially limited compliance, several educational sessions resulted in strict medical and dietary management with less hypoglycaemic episodes. This reflected in improved biochemical parameters, as presented in table 1.

The patient had two previous spontaneous miscarriages (6 and 12 weeks of gestational age) while avoiding the healthcare system. After her clinical situation improved, she expressed the wish to conceive again. Therefore, she was referred to the preconception care and counselling team.

Specialised individual preconception care and counselling team

If an increased health risk in pregnancy is known for the mother and/or fetus, then future parents should be referred for specialised preconception counselling. Effective contraception should be prescribed to optimise and ensure proper preconception care (eg, optimise the diet and change in medication). To increase the effect of and compliance with possible interventions, it is important to actively involve the partner in the counselling process. Factors that need consideration during preconception counselling and care in patients with severe conditions in general and in case of the HI/HA syndrome specifically are as follows:

1. Effect of the condition on the pregnancy.
HI/HA \rightarrow maternal hypoglycaemia \rightarrow intrauterine growth restriction and fetal demise.
2. Effect of the pregnancy on the condition.
First trimester: possible deterioration of hypoglycaemia \rightarrow fetal demise.
Second and third trimesters: progressive insulin resistance \rightarrow increasing glucose levels.
Delivery: possible deterioration of hypoglycaemia due to the physical effort of labour.
Post partum: disappearance of insulin resistance \rightarrow maternal hypoglycaemia and uterus involution \rightarrow hyperammonaemia.
3. Risks due to a previous surgical intervention for extrauterine pregnancy or intra-abdominal complications in the case of caesarean section (not applicable to this case).
4. Teratogenic risk evaluation of medication.
Diazoxide \rightarrow maternal hypotension, fetal bradycardia, negative effect on uterus contractions and neonatal hyperglycaemia.



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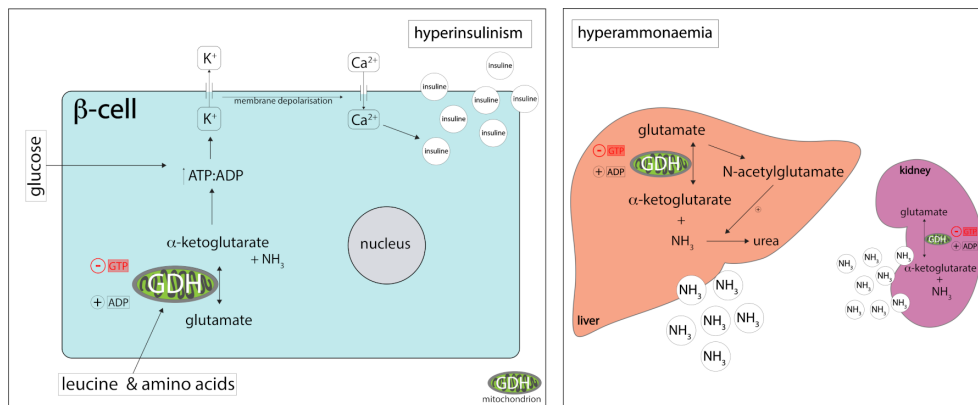


Figure 1 Figure was drawn by Schoenmakers. It shows regulations and interactions by nutrients and drugs (diazoxide and somatostatin) in pancreatic β -cells and hepatocytes on insulin and ammonia (NH_3) production. In HI/HA syndrome, the activity of the mitochondrial enzyme glutamate dehydrogenase (GDH) is increased, which leads to inappropriate high insulin secretion by the β -cells and ammonia production in all body cells. In the β -cell, GDH is activated by leucine to trigger insulin release in response to a protein-rich meal. This figure also shows how increased catabolism of glutamate results in HA, but the 'normal' functioning urea cycle in hepatocytes prevents severe HA. Mild elevations of ammonia due occur in patients with HI/HA, most likely due to a relative deficiency in (urea cycle stimulating) *N*-acetylglutamate (because of low levels of its precursor glutamate), which reduces the urea cycle capacity to metabolise ammonia. It is identified that the molecular dysfunction caused by GDH S445L mutation is responsible for HI/HA.² HI/HA, hyperinsulinism/hyperammonaemia.

- The risks of medication changes/discontinuation necessary for pregnancy.
Stop/lower diazoxide dosage: more severe hypoglycaemia.
Increased need for carbohydrate-rich feeding: maternal weight gain.
- Risks/recurrence of pregnancy complications or adverse pregnancy outcome (referral to a clinical geneticist is sometimes advised).
Fetal growth restriction and a 50% chance for the offspring to inherit the *GLUD1* mutation.

Preconception counselling

After careful consideration, the patient in this case report was advised not to become pregnant considering the following. (1) Due to fetal risks, diazoxide use should ideally be discontinued, with the deterioration of hypoglycaemic episodes as a consequence. (2) Medication change and the changing metabolic demands of pregnancy could lead to maternal as well as fetal hypoglycaemic health risks. (3) The patient has poor disease perception and a small social network to rely on. In addition, lowering or discontinuing the diazoxide would necessitate an increase in carbohydrate intake, leading to accelerated weight gain in an already obese patient.

Regardless of this advice, she became pregnant and presented herself at 9 weeks of gestational age.

TREATMENT

As soon as the pregnancy was known with the treating physicians, a detailed pregnancy and delivery guidance plan was constructed by a multidisciplinary team consisting of a gynaecologist, a metabolic consultant, the diabetic team, a metabolic paediatrician, a neonatologist, an anesthesiologist, a geneticist, a dietician and a social worker.

The diazoxide dosage was reduced by 50% to 100 mg/day because of the association with fetal risks of intra-uterine growth restriction, transient fetal bradycardia and the unknown effect on fetal neurodevelopment (for detailed information see ¥ in online supplementary file 1).³ Her diet was adjusted with an increased intake of slow-release carbohydrate to a total protein intake of 0.71 g/kg (for detailed information see ** in online supplementary file 1). Invasive prenatal diagnostics were offered due to the 50% probability of passing on the *GLUD1* mutation but were declined by the patient and her partner.

Table 1 Overview of biochemical monitoring and treatment before, during and after pregnancy in a patient with hyperinsulinism/hyperammonaemia syndrome

	Normal range	Prepregnancy	Pregnancy trimester			Labour	Post partum
			First	Second	Third		
Glucose (mmol/L)*	4.0–6.1	3.9–5.6	2.6–5.8	4.1–7.0	4.0–6.0	4.6–6.0	5.5–8.3
HbA1c (mmol/mol)	26–42	27	23	26	29	NA	NA
Ammonia ($\mu\text{mol/L}$)	<45	71	64	50	47	55–99	62–92
Diazoxide (mg/day)	–	200	100	100	100	100	200
Chlorthalidone dose	–	0	0	0	0	0	Day 1: 50 mg two times per day
Infusion schedule	–	–	–	–	–	10% Glucose 2L/24 hours	500 mL Tetrastarch† Day 1: 5% glucose 2L/24 hours Day 2: 5% glucose 1L/24 hours Day 3: stop 5% glucose

*Presented as range with lowest and highest value.

†Tetrastarch, 100 mg/mL (10%) hydroxyethyl starch (130/0.4) in isotonic saline.

HbA1c, haemoglobin A1c; NA, not available.

Personalised labour plan

Preparation

To prevent the spontaneous onset of the delivery, the patient will be hospitalised around 39 weeks of gestation. Before labour is induced, an arterial line will be placed to monitor glucose levels every 20 min and ammonia, sodium and potassium levels every 3 hours. A central venous catheter will be inserted to guarantee intravenous access in case of emergencies.

Labour

A glucose infusion with glucose 10%, 2 L/day, will be administered. Patient's diet will be continued. In case of a glucose level <2 mmol/L, an epileptic insult or a hypoglycaemic coma, 50 mL 50% glucose will be administered immediately.

Post partum

Post partum, a quick recovery of insulin sensitivity is expected and glucose levels will be monitored every hour. Plasma ammonia- and potassium levels will be monitored every 4 hours.

Lactation

Breastfeeding is discouraged due to the lack of information on the use of diazoxide during lactation and the need to further increase carbohydrate intake.³

OUTCOME AND FOLLOW-UP

Pregnancy

During the last weeks of the first trimester, the patient presented with lowered glucose levels compared with those during prepregnancy and hypoglycaemia due to vomiting and insufficient intake of food and raw cornstarch (table 1). Because of hypoglycaemic unawareness, a subcutaneous continuous glucose sensor was placed at 11 weeks of gestation. The alert was set to sound when glucose levels were below 4.0 mmol/L to prevent further decrease. Glycaemic control substantially improved by frequent adjustment of the raw cornstarch intake as the pregnancy progressed, although the cognitive impairment of the patient made it difficult at times for her to adequately respond to the glucose monitor alarm.

During the second trimester, no hypoglycaemic events occurred (table 1). As nightly tube feeding was refused by the patient, a dose of cornstarch in the middle of the night (03:00) was added to the regime. The increased intake of carbohydrates resulted in a total weight gain during pregnancy of 19.6 kg. The mild prepregnancy HA of 71 µmol/L normalised during pregnancy (table 1). Fetal growth was evaluated every 2 weeks. The estimated fetal weight at 36 weeks of gestational age was 3092 g (61st percentile).

Labour

The patient was admitted to the obstetric critical care unit at 39 weeks of gestation for the planned induction of labour. Cervical ripening was performed with vaginal administration of misoprostol (E1 prostaglandin analogue). During this phase, hypokalaemia occurred (2.5 mmol/L) and potassium was supplemented. There was one self-limiting episode of HA (99 µmol/L).

Labour was induced by starting oxytocin intravenously and glucose 10% infusion was administered continuously. Because of suspicion of fetal distress (based on the loss of variability and decelerations on fetal heart monitoring) and a failure to progress, a caesarean section with spinal anaesthesia was performed. Glucose levels remained within the normal range during labour

and delivery, and no complications of the caesarean section occurred.

Post partum

Diazoxide 100 mg two times per day and chlorthalidone were restarted directly post partum. Glucose infusion was continued, subsequently decreased to 5% glucose 2L/24 hours for the next day and thereafter to 1L/24 hours for one more day (table 1). Patient's hypokalaemia remained (3.3 mmol/L) and potassium supplementation was continued for the next 2 days. Cardiological and radiological evaluation for an asymptomatic tachycardia of 140 bpm showed no abnormalities. Her plasma glucose levels were still monitored every hour and electrolytes and ammonia levels two times per day. Her ammonia level peaked at 92 µmol/L and decreased to 72 µmol/L the next day. The patient was discharged with her regular prepregnancy cornstarch diet and diazoxide 100 mg two times per day.

Neonatal

A male newborn of 2900 g (13th percentile) was born with Apgar scores of 8/8 (1 min/5 min). The umbilical cord gas showed a pH of 7.33, a base excess of 0, a glucose level of 4.2 mmol/L and an ammonia level of 304 µmol/L (the maximum in neonates is 100 µmol/L). He did not show any signs of neonatal encephalopathy such as lethargy, irritability, poor tone, absent primitive reflexes, seizure activity or feeding difficulties.

Because of respiratory distress and increased C-reactive protein after prolonged rupture of the membranes, he was admitted to the neonatal ward where continuous positive airway pressure (CPAP) was started as well as antibiotics (benzylpenicillin 150 000 IE/kg/day and tobramycin 4 mg/kg/day).

His ammonia level normalised to 96 µmol/L within 12 hours without any further intervention. Glucose levels remained normal except for two short periods of hypoglycaemia (2.8 and 2.9 mmol/L) without any need for glucose infusion. The CPAP was stopped within 24 hours after which no further clinical symptoms were apparent. Antibiotics were continued for 7 days on suspicion of a possible perinatal infection. The patient was discharged in good clinical condition after blood cultures remained negative and his insulin level was 33 pmol/L (normal reference <100 pmol/L). Social care was arranged as to support.

GLUD1 mutation analysis demonstrated that the patient carried the same mutation as his mother, confirming the diagnosis of HI/HA syndrome 2.5 weeks after birth. His insulin level had increased to 272 pmol/L by then, with adequate glucose levels and no clinical signs of hypoglycaemia. Treatment with diazoxide 5 mg/kg/day, hydrochlorothiazide 0.9 mg/kg/day and frequent feeding was started immediately. No clinical signs of hypoglycaemia have been detected after starting this treatment. The patient is now aged 24 months and has shown normal growth and development.

Daily monitoring and attendance are given by the parents with the support of the grandmother and infant welfare.

DISCUSSION

Insulin and insulin-like growth factors are essential for the regulation of energy metabolism, cell proliferation, tissue development and tissue differentiation.

Insulin initiates fetal growth but does not cross the placenta because of its molecular weight, indicating that the developing fetus is completely dependent on its own insulin production, which starts at the end of the first trimester (week 12). Fetal

Rare disease

insulin production is strongly stimulated by maternal glucose, which does cross the placenta into the fetal circulation.⁴

As a result, maternal hypoglycaemia could lead to intrauterine growth restriction in twofold: directly because of a lack of glucose as a nutrient for fetal growth and indirectly because of insufficient fetal insulin production in response to low glucose levels. Even with increased hypoglycaemic episodes, the outcome of neonates is favourable with low perinatal mortality and neonatal morbidity, as long as hypoglycaemic episodes do not recur too often and are of short duration.⁵

During the first trimester in a normal pregnancy, glucose is the most important nutrient for fetal growth and is continuously transferred from the maternal blood to the fetus by the placenta.⁶ The maternal glucose homeostasis in normal pregnancy, therefore, differs from the glucose metabolism before pregnancy; it shows transient hyperglycaemia between meals and at night, in order to provide for the continuous fetal demand. During the first trimester, hyperplasia of the insulin-secreting pancreatic β -cells occurs, with resulting increase of insulin secretion and a simultaneous increase in insulin sensitivity.⁷ Mild hypoglycaemia is a phenomenon seen in a normal pregnancy. Progressive insulin resistance starts to develop in the second trimester, peaking during the third trimester due to increased placental secretion of human chorionic somatomammotropin (hCS).⁸ As a consequence, insulin resistance quickly disappears after the birth of the placenta. With the expulsion of the placenta, the production of hCS ceases and due to its short half-life, its effect quickly disappears. The rapid return of prepregnancy insulin sensitivity can lead to postpartum hypoglycaemia in the situation of uncontrolled insulin production such as HI/HA syndrome or insulinoma.

HA in adults can lead to encephalopathy and brain oedema.

Interestingly, in adults and neonates with HI/HA syndrome, HA-related encephalopathy is not observed and normal protein consumption does not further increase ammonia levels. Ammonia is formed by renal and pancreatic ammoniogenesis due to the enhanced GDH activity. This can be demonstrated

by ammonia-infusing experiments performed in rats. At mildly increased ammonia levels, glutamine synthase activity can be enhanced, directly metabolising ammonia in brain cells preventing brain oedema and encephalopathy. Another explanation for the lack of HA-related encephalopathy in HI/HA syndrome is that the actual additional ammonia production is limited and can be removed by a normal functioning hepatic urea cycle. Therefore glutamine production is not further increased.^{9 10} As ammonia crosses the placenta, maternal HA could contribute to early fetal HA, when the fetal urea cycle is yet to develop.

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Learning points

- ▶ Personalised and multidisciplinary management of pregnancy and labour in patients with complex diseases is indispensable.
- ▶ Lowering the diazoxide dosage and increasing the slow absorbing carbohydrate intake, ideally prepregnancy, is necessary to prevent both severe hypoglycaemia and potential negative effects on fetal growth.
- ▶ This case provides valuable information on managing pregnancies in patients with hyperinsulinaemia and is applicable to other conditions such as insulinoma.

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