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Endogenous hyperinsulinemic hypoglycemia in pregnancy: Challenges in management and review of literature

Elizabeth Ande, Bhamini Tharmalingam, Abha Govind

ABSTRACT

This case report describes a patient in her early twenties, with postprandial hyperinsulinemic hypoglycemia (HH) in pregnancy. She was diagnosed in childhood and was cared for by a multidisciplinary team in a tertiary facility. She then transferred to a secondary institution, as part of the transition from pediatrics to adult care. Her pregnancy was complicated by multiple episodes of hypoglycemic seizures, warranting multidisciplinary management and in-patient admission. She was commenced on Acarbose and Fortisip, as Cornstarch which she had used in the past, was not effective in controlling the hypoglycemic episodes during the pregnancy. She was delivered via Cesarean section at 34 weeks of gestation. The management of HH can be difficult and this was complicated by the pregnancy. The authors share the challenges of managing this condition in pregnancy together with a review of the literature.

Keywords: Endogenous hyperinsulinemic hypoglycemia, Nesidioblastosis, Octreotide, Pregnancy

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INTRODUCTION

Hyperinsulinemic hypoglycemia (HH) is a rare heterogenous disorder that has so far been reported in 4 pregnancies [1, 2]. Hyperinsulinemic hypoglycemia is characterized by persistently low blood glucose concentrations due to unregulated insulin release [1, 2]. This could be primary (congenital HH) due to variants in about 15 genes responsible for pancreatic development and function [3]. Hyperinsulinemic hypoglycemia could also be secondary to a neoplasm. It may be associated with intrauterine growth restriction (IUGR) in the fetus, birth asphyxia, syndromes (e.g., Beckwith–Wiedemann syndrome and Sotos syndrome) and maternal diabetes or gastrointestinal tract surgery (fundoplication/gastric bypass) [1–3].

Hypoglycemia is a medical emergency, as glucose is the most important fuel for the brain [3, 4]. Lack of blood glucose increases the risk of irreversible brain injury, neurological deficits and sequelae like seizures, cerebral palsy, learning disability, and even death in these patients [3–6].

Congenital HH is quite common in newborns and can be quite severe. This is uncommon in adolescence and adulthood and rare in pregnancy [7]. Hypoglycemia in pregnancy can lead to adverse outcomes for the mother and the baby. Possible outcomes include fetal malformations, growth restriction, being small for gestational age, and poor neuropsychiatric development [1]. Maternal complications include repeated seizures and its potential sequelae such as cognitive and psychiatric impairment, as well as a misdiagnosis of the cause of the seizures [1].

There are various medical and surgical options that have been used to manage HH. There is, however, no specific medication that can be used in pregnancy. The medications that have been reported in the literature in the non-pregnant include Octreotide, Diaxozide, Verapamil, Nifedipine, Glucagon, Sirolimus, and

Acarbose while surgical options include partial or near total pancreatectomy [1, 7, 8].

This case report discusses the challenges of HH in a pregnant patient including diagnosis, management options, and long-term follow-up.

CASE REPORT

A patient in her early twenties, gravida 3 para 0+2 had presented at 10 weeks of gestation for her booking visit. Previously she had 2 first trimester spontaneous miscarriages. Her investigations during pregnancy are listed in Tables 1 and 2. Her booking body mass index (BMI) was 29.1 kg/m^2.

She had a history of hypoglycemic episodes in childhood and she was reviewed and managed by multiple specialists. These episodes were preceded by headaches and blurred vision. There was also dribbling from the mouth, but no urinary or fecal incontinence. She reported being aware of her surroundings and remembering the episode. She also described episodes of exercise induced hypoglycamia. There was no history of seizures or palpitations. She had been investigated from the second decade of life.

She was born at term via Cesarean section, weighing 4.5 kg (9 pounds 10 ounces). Her mother did not develop gestational diabetes mellitus in pregnancy and was not aware of low blood glucose problems at birth. Her mother later developed type 2 diabetes. She gave a family history of fainting/collapsing episodes on her father's side.

Investigations

Pre-pregnancy investigations

The following investigations were undertaken when she reported fainting in the playground in secondary school.

1. Full blood count, liver function test, renal function, lipid profile, and lactate were all normal.
2. Genetic tests for the genes associated with glycogen storage disease and fructose metabolism did not detect any abnormalities.
3. There was preserved pituitary function (morning cortisol 273 mmol/L).
4. Urine tubular proteins *N*-acetyl-β-D-glucosaminidase (NAG) and retinol-binding protein were tested. On the acylcarnitine profile the free carnitine was noted to be low possibly suggesting low dietary intake or renal loss. Blood spot acylcarnitine analysis with paired urinary carnitine analysis was normal.
5. Glucose tests.
6. Imaging studies.
7. Abdominal ultrasound was normal.
8. Magnetic resonance cholangiopancreatography (MRCP) was also normal.

The main conclusion from her childhood investigations showed that she had a reduction in blood glucose; however, still showing measurable insulin. She was diagnosed with post prandial hyperinsulinemic hypoglycemia. This is inappropriate insulin secretion in response to a meal resulting in hypoglycemia [7] (Table 3). This can be autoimmune or due to insulin receptor gene mutation [7].

Treatment

During her pregnancy she could not tolerate cornstarch, and this was compounded with vomiting in pregnancy which resulted in increased frequency of significant hypoglycemic episodes, and she was found unconscious at home with a blood glucose of 2.0 mmmol/L at about 25 weeks of gestation.

She was seen by dieticians, endocrinologists, and maternal medicine physician throughout her pregnancy. The case was also discussed in the obstetric multidisciplinary team meeting.

She was admitted at 28 weeks of gestation with abdominal pain and vaginal spotting. The fetal fibronectin (point of care test for preterm labor) was positive. She had intramuscular steroids to facilitate fetal lung maturity.

She was compliant with the above diet and medications. The FreeStyle Libre sensor® was effective in alerting her to hypoglycemic episodes, the diet and medication also helped to reduce the episodes of hypoglycemic seizures. The subsequent seizure episodes that occurred were mostly at night time when she was fast asleep. These episodes were managed with intravenous (IV) 25–50% Dextrose after checking the blood glucose (Table 4).

She remained in-patient till 34 weeks of gestation when delivery was planned. She had an elective caesarean section at 34 weeks for ongoing seizures and was delivered of a female baby weighing 2.5 kg (birth centile-68.7) with Apgar scores of 8 and 9 in the first and fifth minute.

Outcome and Follow-Up

She was discharged from the maternity unit on the 6th day post-delivery, with a plan to be seen in the endocrine clinic. The baby remained in the neonatal unit. She continued Acarbose 50 mg at night-time, along with cornstarch and the FreeStyle Libre sensors to better monitor her hypoglycemic episodes. The hypoglycemic episodes reduced after childbirth, and she was able to tolerate cornstarch. Her daughter was admitted under the neonatal team during the first few months of life with symptoms of hypoglycemia.

DISCUSSION

Challenges in Management

Pathophysiology

Our patient presented with congenital endogenous HH, a rare condition, characterized by hypoglycemic episodes caused by autonomous insulin secretion in the absence of an insulinoma [1, 2].

Insulin secretion in humans is tightly regulated to ensure that blood glucose remains between 3.5–5.5

Table 1: Blood glucose investigations and results

Prolonged oral glucose tolerance test (OGTT) for 7 hours—half hourly blood glucose monitoring and Insulin/C-peptide levels up to 7 hours	Episodes of hypoglycemia (capillary blood glucose 2.5 mmol/L) at 2.5 hours post-OGTT with detectable Insulin
Prolonged mixed meal test	Episodes of hypoglycemia (capillary blood sugar 2.7 mmol/L at 4.5 hours) with detectable insulin
24 hour Boehringer Mannheim (BM)	3.6–6.1 mmol/L
BM after protein load	BM 3.3–3.7 mmol/L
BM after exercise	BM 3.7–5.6 mmol/L
2 hours post-OGTT	BM 5.2 mmol/L
22 hours fast	No hypoglycemics episodes with BM 3.2 mmol/L at the end of the fast. Insulin levels were detectable during the tests, but markers for fat breakdown (non-esterified fatty acids (NEFA) and 3-hydroxy butyrate (BHOHB) were low. Normal cortisol, ammonia, lactate, and urine organic acids at the end of the fast.

Table 2: Booking investigations in pregnancy

Full blood count (FBC)	Hb 140 g/L, Platelets: 253 × 10^9/L
Blood group	O Rhesus D positive, no antibodies, no haemoglobinopathy
Serology screen	Negative for HBsAg, HIV 1 and 2
Syphilis	Non-reactive
Glycated hemoglobin (HbA1c)	At booking—33 mmol/mol and at 28 weeks 37 mmol/mol
Thyroid function test	T4: 14.9 pmol/L
	TSH: 2.29 mIU/L
Urine MSU	No growth
Combined screening test for Trisomy 13, 18, and 21	Low chance
Pregnancy-associated plasma protein A (PAPP-A)	0.78 MoM

Abbreviations: Hb: hemoglobin; HBsAg: hepatitis B surface antigen; HIV: human immunodeficiency virus; MoM: multiples of the median; MSU: urine midstream specimen; TSH: thyroid-stimulating hormone.

Table 3: Treatment regime in childhood, which greatly improved her blood glucose control

Cornstarch	10 mg three times a day, with the dose to be decreased to 5 mg three times a day if side effects occurred.
Acarbose	12.5 mg three times a day, to be commenced if side effects from cornstarch developed.
Low glycemic index (GI) diet	She was advised to avoid high-sugar or high-carbohydrate foods at any one time and to have snacks between meals and post dinner before bedtime.

Table 4: Treatment regime in pregnancy

Name	Mechanism of action
Acarbose 50 mg oral	Alpha-glucosidase that inhibits postprandial glucose and its insulin response
Fortisip compact protein 125 mL BD	Due to its high protein content
Low glycemic index carbohydrates with protein and fat	At every meal and snack
FreeStyle Libre 2 sensor from about 30 weeks of gestation	For continuous glucose monitoring. The alarm helped in alerting her of low blood glucose levels
Hypoglycemia	Apple juice, snacks. Intravenous Dextrose water for severe episodes
Cyclizine and Ondansetron	Antiemetics
Lactulose	Laxative

mmol/L [7–9]. Insulin drives glucose into the insulin sensitive tissue and stops glucose production, fatty acid release, and ketone synthesis [4, 8]. The presence of insulin prevents fatty acid production and ketogenesis thereby depriving the brain of the primary and secondary source of energy [7].

In HH there is unregulated insulin secretion despite low blood glucose levels [9]. A glucose requirement of more than 8 mg/kg/min is noted in HH and is diagnostic, whereas the normal glucose requirement is 4–6 mg/kg/min [7]. In HH there is also a blunted response to the normal physiological cortisol and glucagon counter regulatory hormone to low blood glucose there by worsening the hypoglycemia [4–6].

Congenital HH has histologically been classified into 3 major groups: diffuse, which is associated with autosomal recessive inheritance; focal, which is typically associated with autosomal dominant inheritance; and atypical forms [5, 7, 8]. Genetic mutations in ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, UCP2, HNF4A, HNF1A, HK1, PGM1, PMM2FOXA2, CACNA1D, and EIF2S3 have been implicated in congenital HH [3, 4, 7–9].

Hyperinsulinemic hypoglycemia could also be secondary or postprandial as in our patient, or due to an insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome, and in patients with insulin receptor mutations [7–9].

By mid-pregnancy there is progressive physiological resistance to the action of insulin, resulting in increase in plasma glucose, though this is below the level than in a non-pregnant woman [10]. Insulin resistance in pregnancy is presumed to be due to the effect of human placental lactogen and cortisol [10]. This glucose crosses the placenta easily and serves as the main energy substrate for the fetus. The glucose level in the mother and fetus are directly correlated to each other [10].

Clinical Presentation

Hyperinsulinemic hypoglycemia usually presents in the neonatal period but can manifest later in infancy, childhood, or rarely in adolescents or adults [7]. The clinical presentation varies in children and can range from irritability, poor feeding and lethargy to severe symptoms with seizures, long-term neurological sequelae (epilepsy, cognitive deficits, and microcephaly), coma and even death [8].

A family history of seizures, diabetes, or consanguinity is very important [7]. Our patient's father had seizures, and she reported her daughter having seizures in infancy. Castillo-López et al. reported 10 of the 17 patients they reviewed with HH, had a history of consanguinity with two affected siblings although this was not so in our patient [12].

Diagnosis

Diagnosis is important to avoid hypoglycemic brain injury to the mother and should be done promptly [7]. Hypoglycemia is diagnosed when blood glucose is ≤3.5 mmol/L. This cutoff is used in patients with HH as ketones as an alternative source of energy for the brain are lacking [7]. There will also be inappropriate insulin and/or C-peptide at the time of hypoglycemia, with a poor response of ketone bodies and plasma non-esterified free fatty acids [7]. To rule out other metabolic conditions, cortisol and growth hormone levels should be tested. Urine organic acids, plasma amino acids, and lactate and carnitines were analyzed in our patient to exclude other metabolic diseases [7, 8]. The diagnostic criteria for HH include a plasma glucose level of <3 mmol/L with detectable serum insulin and C-peptide and suppressed/low serum ketone bodies and fatty acids [8].

Treatment

The aims of treatment are to inhibit insulin secretion, maintain normoglycemia of 3.5–6 mmol/L, establish an appropriate fasting tolerance, and a normal feeding pattern which will prevent recurrent hypoglycemic episodes [8, 9, 11]. Treatment could be acute, with parenteral glucose infusion, frequent feeding, glucagon use, with long-term follow-up. Careful monitoring is important to identify and treat complications [7, 8, 11].

Medications that have been used in the literature include Diazoxide (first line) 2, Octreotide, long-acting somatostatin analogues, Acarbose and Nifedipine [7, 8]. Sirolimus and Exendin are newer agents [6–8]. Surgery is offered where medical management has failed or there is a focal disease identified [7, 8]. Surgical options include partial pancreatectomy or near total pancreatectomy which can however lead to diabetes [2, 7–9].

Diazoxide is a non-diuretic Benzothiadiazine, which inhibits insulin secretion. In such cases of hypoglycemia, it is however associated with alopecia and hypertrichosis which can occur following prolonged use in neonates [7–9, 12].

Octreotide is a somatostatin analog that inhibits insulin secretion and may control blood glucose where Diazoxide is ineffective [1, 12] but has been reported to be associated with intrauterine growth restriction [1, 13].

Acarbose, an alpha-glucosidase inhibitor that inhibits postprandial glucose and its insulin response [1] was used in our patient, and even though she still had hypoglycemic episodes, it was better than the cornstarch. We were not keen to use Diazoxide or Octreotide due to the possible side-effects in pregnancy. However, Damaso et al. reported a 21-year-old primipara with congenital HH [1]. She was managed with Diazoxide and glucocorticoids and was delivered at 35 weeks of gestation, with the baby's birth weight of 2330 g (33rd percentile) [1]. After the delivery she declined a subtotal pancreatectomy. She continued to have increased episodes of hypoglycemia and was commenced on Verapamil which was not effective, she eventually had a subtotal pancreatectomy [1]. Three years later during her second pregnancy she had fewer episodes of hypoglycemia, and she delivered at 39 weeks [1]. This supports the need for surgery where medical options have proved ineffective.

Another case report by Boulanger et al. discussed a 36-year-old with nesidioblastosis (a condition characterized by diffuse islet cell hyperplasia, arising from the ductal epithelium and the formation of ductulo-insular complexes) who was treated with high doses of Octreotide. She was delivered at 32 weeks of gestation and the baby was structurally normal [14]. A 24-year-old smoker was treated with Octreotide for congenital HH, and she had IUGR. As a smoker it was difficult to attribute the IUGR to Octreotide [13]. Barsi et al. also reported a 29-year-old with endogenous HH, who was treated with Octreotide without complications, and she was delivered via Cesarean section at 38 weeks of gestation [2].

Studies have shown that Octreotide can predispose the baby to growth restriction which can be compounded by hypoglycemic episodes in the fetus [13]. Geilswijk et al. reported a patient with familial HH, who had growth restriction as a complication while using Octreotide, and they recommend that dietary modification to manage HH should be instituted before Octreotide [1, 2, 13].

For patients with postprandial hypoglycemia following bariatric surgery, the use of dietary measures and medications such as Acarbose, Diazoxide, Somatostatin/Octreotide, Calcium channel blockers, and glucagon has been used [15, 16]. Halperin et al. showed that glucagon raised the glucose level but also resulted in a corresponding increase in insulin [15]. Avexitide, a glucagon-like peptide antagonist has been shown to prevent hypoglycemia in pilot studies [16].

Wood et al. reported a 28-year-old with postprandial hypoglycemia in pregnancy, this was due to an insulinoma on a background of multiple endocrine neoplasia (MEN-1) causing hypoglycemia [17]. She had used cornstarch and Acarbose, but this was not tolerated as in our patient, and she was given meals with low glycemic index [17]. Postdelivery, she had recurrent episodes of hypoglycemia, and magnetic resonance imaging showed an insulinoma. A distal pancreatectomy was performed, and she had no further episodes of hypoglycemia [17].

CONCLUSION

1. Endogenous HH in pregnancy is worsened by the nausea and vomiting in pregnancy, resulting in more hypoglycemics episodes. It can predispose to malnutrition as sometimes, the estimated nutritional requirement via food alone is not met.
2. The physiological hyperglycemia in pregnancy, caused by human placental lactogen and cortisol, did not improve the hypoglycemic episodes, in our patient, possibly suggesting that the hyperinsulinemia also acted on the glucose produced.
3. The first line treatment for HH is Diazoxide. However, in pregnancy this can result in alopecia and hypertrichosis in the fetus. The second line drug is Octreotide, which is known to or can predispose to IUGR. We managed our patient without it, but she continued to have recurrent episodes of seizures due to hypoglycemia.
4. FreeStyle Libre sensor® was helpful in alerting our patient to the hypoglycemic episodes especially at night. The sensitivity at hypoglycemic levels can be sub-optimal, as it measures glucose levels in the interstitial fluid, compared to finger prick blood glucose levels. Our patient found it useful.
5. Managing congenital HH is complicated and challenging due to the different clinical presentations, genetic background, and responses to treatment. All these are further compounded by pregnancy. Dietary optimization and medical treatment are the management of choice with surgery as a last resort.

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Author Contributions

Elizabeth Ande – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Bhamini Tharmalingam – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Abha Govind – Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.