Pregnancy in multiple endocrine neoplasia type 1 equals multiple complications

Megha Mistry, Manish Gupta and Mandeep Kaler

Abstract

Multiple endocrine neoplasia type 1 (MEN 1) is a rare inherited disorder caused by mutations in the tumour suppressor gene MEN 1. It is characterised by a predisposition towards the development of parathyroid, anterior pituitary and entero-pancreatic tumours. Clinically, MEN 1 is defined following development of two out of these three tumours. There have been no published cases of the management of MEN 1 in pregnancy. We report the first case of a 31-year-old primigravida with a confirmed diagnosis of MEN 1 prior to conception. Due to the rare nature of MEN 1, there are no guidelines on how such women should be managed. The main issues were to assess and manage potential complications, such as hypercalcaemia, diabetes mellitus and the symptoms from a pituitary tumour as well the issues around a gastrinoma and monitor fetal well-being. A Caesarean section was performed at 35 weeks gestation for a growth-restricted fetus with raised umbilical artery Dopplers. The neonate was treated with intravenous calcium secondary to hypocalcaemia. The patient and neonate recovered well. We have demonstrated successful management of a woman with MEN 1 who completed her pregnancy with few complications and a healthy neonate. It is vital for such women to be managed in the context of a multidisciplinary team setting to optimise maternal and fetal outcomes.

Keywords

Endocrinology, high-risk pregnancy, maternal–fetal medicine

Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is a rare disorder, inherited in an autosomal dominant manner. It can affect all age groups and has an estimated incidence of 0.25%. It is caused by mutations in the MEN 1 gene, which disrupt or inactivate production of the protein ‘menin’. Inactivation of menin leads to tumour formation in susceptible tissues, which almost always are endocrine tissues. MEN 1 is characterised by a predisposition towards the development of parathyroid, anterior pituitary and entero-pancreatic (gastrinoma, insulinoma, glucagonoma) tumours. Clinically, MEN 1 is defined following development of two out of these three tumours.¹ In patients with a known first degree relative with MEN 1, the development of a single MEN-associated tumour also constitutes a diagnosis. MEN 1 mutations are also associated with an increased frequency of carcinoid tumours, adrenal adenomas and other non-endocrine features including development of angiofibromas, lipomas and ependymomas.^{1,2}

To our knowledge, there have been no known published cases of the management of MEN 1 in pregnancy. We report a case of a 31-year-old primigravida with a confirmed diagnosis of MEN 1 prior to conception and the subsequent management of her pregnancy.

Case report

Background

A 31-year-old primigravida of South Asian origin with a normal body mass index attended for antenatal booking at nine weeks gestation. Two years prior to conception, investigation with magnetic resonance imaging (MRI) for recurrent migraines identified a pituitary tumour, which was later diagnosed as a macroprolactinoma. Further investigations revealed primary hyperparathyroidism (PHP), secondary hypothyroidism, a pancreatic gastrinoma and a non-functioning adrenal adenoma. An oral glucose tolerance test (GTT) showed marked insulin resistance. MEN 1 was diagnosed, and appropriate treatment was commenced. Her hypothyroidism was treated with daily levothyroxine 100 mcg, control of her insulin resistance was with metformin 500 mg, the gastrinoma was treated with omeprazole 20 mg daily and the macroprolactinoma was managed successfully with cabergoline 0.5 mg three times a week.

Management during pregnancy

Following endocrinology review at nine weeks gestation, the cabergoline was stopped. Serum-corrected calcium and prolactin levels at this stage were noted to be 2.58 mmol/l and 387 mu/l, respectively (normal range (NR) serum-corrected calcium 2.20–2.60 mmol/l and prolactin 0–496 mu/l). At the initial obstetric review (11 weeks gestation), the patient was taking ergocalciferol 800 units with no changes to her other medications. A clinical examination including visual field assessment was unremarkable. HbA1C was 5.82% whilst taking metformin. Repeat serum calcium and thyroid function tests (TFTs) were normal. Her total vitamin D level was 33 nmol/l (50–150 nmol/l) for which she was already taking supplements. A plan was made to review serum electrolytes, corrected calcium and TFTs every four weeks during the pregnancy with serial fetal growth scans. Aspirin was offered due to the risk of pre-eclampsia with hypercalcaemia; however, the patient discontinued it during the second trimester. A routine ultrasound scan at 12 weeks and first trimester screening were both normal.

Between 15 and 20 weeks gestation, the pregnancy was uneventful. An MRI performed at 20 weeks gestation, following a complaint of headaches, showed no growth of the prolactinoma. Following this, the patient remained asymptomatic, and neurological examinations throughout the pregnancy were normal. The anomaly ultrasound at 20 weeks gestation was normal. However, at 22 weeks, raised uterine artery Doppler pulsatility index (PI) was noted.

During the pregnancy, a GTT was performed at 16, 22 and 28 weeks gestation and all were normal. All blood results remained normal throughout the pregnancy, with the exception of serum-corrected calcium, which had increased to 2.70 mmol/l at 24 weeks and 2.87 mmol/l at 32 weeks. The patient remained asymptomatic and was encouraged to increase her oral fluid intake. Repeat serum calcium at 33 weeks was 2.57 mmol/l. Due to the potential risk of neonatal

Department of Obstetrics and Gynaecology, Barts Health, Whipps Cross University Hospital, London, UK

Corresponding author:

Mandeep Kaler, Department of Obstetrics and Gynaecology, Barts Health, Whipps Cross University Hospital, Whipps Cross Road, Leytonstone, London E11 1NR, UK.

Email: Mandeepkk@doctors.org.uk

hypocalcaemia, a plan was made for early involvement of the neonatal team to ensure close serum calcium monitoring of the baby following delivery.

An ultrasound at 28 weeks gestation demonstrated normal fetal growth and umbilical artery Dopplers. At 33 weeks, the liquor volume was normal, but repeat umbilical artery Doppler PI was raised, and the fetal weight was estimated to be 1.599 kg (third centile). The patient was advised to have antenatal steroid injections for fetal lung maturity followed by repeat umbilical artery Doppler ultrasound in three days. The subsequent scan showed a raised umbilical artery Doppler PI, normal middle cerebral artery (MCA) Doppler and normal ductus venosus (DV) flow. Between 34 and 35 weeks gestation, repeat umbilical artery Doppler PI measurements were persistently raised. Liquor volume, MCA and DV Doppler remained normal during this period. The fetal weight was now estimated to be 1.972 kg (fifth centile). In view of the findings of fetal growth restriction (FGR) with no further growth after 34 weeks and a raised umbilical artery Doppler PI, a decision was made for delivery by Caesarean section at 35⁺1 week's gestation.

A baby boy was born in good condition (Apgar score 9 at 1 min, 9 at 5 min, 10 at 10 min) weighing 1.830 kg. The baby was admitted to the Special Care Baby Unit for prematurity and to monitor serum calcium and TFTs. Maternal serum-corrected calcium at delivery was 2.80 mmol/l. Neonatal serum calcium at birth was 2.26 mmol/l (NR: 2.50–2.75 mmol/l), and by day 2 of life, it had dropped to 1.79 mmol/l (NR 2.17–2.66 mmol/l). The neonate was initially treated with intravenous calcium. The neonate was breastfed and was later discharged with cholecalciferol and vitamin D supplements. Forty-eight hours postpartum, the maternal serum-corrected calcium was stable at 2.54 mmol/l. Both mother and baby had an otherwise unremarkable recovery and will be reviewed in the endocrinology clinic as an outpatient.

Discussion

There are published case reports that outline the management of PHP and sporadic pituitary and pancreatic tumours in pregnancy, but there is currently no literature describing the management of a patient with MEN 1 in pregnancy. Our case demonstrated several management issues that arose during pregnancy. These can be attributed to the maternal risks of prolactinoma growth, development of diabetes mellitus, hypercalcaemia and the fetal risks of FGR and neonatal hypocalcaemia.^{3,4}

Hyperparathyroidism is common in MEN 1. For women with PHP, antenatal complications include development of hyperemesis, nephrolithiasis and hypercalcaemic crisis. Maternal and fetal complications include an increased risk of gestational hypertension, pre-eclampsia, FGR, miscarriage and preterm delivery. Healthcare professionals should note the potential intrapartum complications, most importantly maternal arrhythmias secondary to hypercalcaemia. Maternal hypercalcaemia may also cause fetal parathyroid hormone suppression during pregnancy with resultant failure of fetal parathyroid gland development. Subsequently, the neonate is at risk of persistent hypocalcaemia due to permanent hypoparathyroidism and may develop seizures following birth. Outside of pregnancy, hyperparathyroidism secondary to parathyroid adenomas may be treated surgically by parathyroid gland excision or medically with calcimimetics. Asymptomatic patients require no treatment.^{4–6}

Previous case studies of asymptomatic women with PHP in pregnancy have shown that a conservative approach with a eucalcaemic diet, good hydration and regular monitoring of maternal blood tests (serum urea, electrolytes, corrected calcium and phosphate) and fetal growth can produce a good outcome for mother and baby. Surgical resection of a parathyroid adenoma may then take place postpartum. For symptomatic women, careful consideration should be given to the ideal timing for surgery if deemed necessary during pregnancy. Current evidence suggests surgery should be performed preferably in the second

trimester, if serum calcium levels are above 2.75 mmol/L. However, McMullen et al.⁷ suggested that women in early or late pregnancy should not be denied consideration of surgical treatment. Furthermore, it was suggested that surgery should be considered even when calcium levels are only moderately elevated, as the extent of maternal or fetal complications from PHP cannot currently be predicted on serum calcium levels alone.

Minimally invasive surgery with prior ultrasound localisation of parathyroid tissue is thought to be a safe option in pregnancy. If pre-operative localisation with ultrasound fails, radioisotope imaging may be the only option, but careful planning should be undertaken to reduce fetal irradiation.

Although there is currently limited clinical data outlining the safety and efficacy of treatment with calcitonin and calcimimetics such as cinacalcet for PHP in pregnancy, previous case reports have demonstrated good maternal and fetal outcome for their use in the third trimester and puerperium. Their effect in early pregnancy remains to be established.^{7–9}

Our patient had four weekly serum calcium monitoring, with the aim of ensuring a level of less than 2.75 mmol/l. When calcium levels increased at 32 weeks gestation, the patient was encouraged to increase her oral fluid intake. Raised serum calcium was noted for the second time at delivery and was managed with intravenous fluid therapy. On reflection, it may have been useful to measure maternal parathyroid hormone levels and ionised calcium levels to further aid monitoring of her condition.^{4–13}

This patient had been diagnosed with a macroprolactinoma prior to conception, which exhibits accelerated growth during pregnancy. This is thought to be due to hyperoestrogenaemia-induced lactotroph hyperplasia. The main maternal risk of tumour expansion is the potential for development of neurological symptoms such as visual impairment. Prior to pregnancy, our patient was treated with dopamine-agonist therapy to reduce tumour size and normalise serum prolactin. Cabergoline was chosen, but bromocriptine may be a suitable alternative as both medications have shown apparent lack of toxicity in the first trimester. The majority of prolactinomas respond to dopamine-agonist therapy. If medical treatment is unsuccessful or if tumour size exceeds 3 cm, transphenoidal surgery should be considered. This is due to the risk of adenoma growth following discontinuation of medical therapy during pregnancy. Other pituitary tumours are less amenable to pharmacological therapy and often a surgical approach is required.^{13–17}

As per current guidance, our patient was advised to attend regular antenatal appointments to monitor her blood pressure, development of neurological symptoms and assess visual fields, even when asymptomatic. An MRI was performed following development of a headache but should also be performed if any visual field abnormalities are identified. If adenoma enlargement is identified, treatment throughout the remainder of the pregnancy should be with bromocriptine (first-line) or with cabergoline (second-line). Transphenoidal surgery may be considered if medical management has failed. If visual impairment develops in the third trimester and neurosurgical intervention is indicated, it is reasonable to induce delivery of a near-term fetus prior to surgical excision.¹⁸ Our patient did not have any further growth of the prolactinoma on MRI, and visual field examinations remained normal throughout the pregnancy. She therefore did not require dopamine-agonist therapy during the pregnancy.

Of pancreatic/gastrointestinal tumours, the most common cause of symptoms is a result of Zollinger–Ellison (gastrinoma) syndrome. The resultant gastrin overproduction leads to ulceration of the stomach and small bowel. Patients may be treated with proton-pump inhibiting drugs, chemotherapy agents, octreotide and surgical excision.^{10–12} Symptomatic insulinomas may be surgically excised. Glucagonomas may cause diabetes mellitus in 75–95% of patients. However, this is usually controlled with diet modification, oral medications and insulin.¹⁸

Pregnancy is characterised by a state of insulin resistance and hyperinsulinaemia. Therefore, it would be prudent to monitor GTT

in any woman with abnormal GTT or insulin resistance prior to conception. Our patient was known to have insulin resistance secondary to a pancreatic tumour, for which she was already taking metformin. All of her GTT results throughout the pregnancy were normal, and therefore no subsequent change to her treatment was required.¹⁹

Our patient went on to have a preterm delivery secondary to the findings of a growth-restricted fetus with an abnormal umbilical artery Doppler PI. This may have been a secondary complication of PHP due to its known association with FGR or completely unrelated to her medical disorder.³

Conclusion

MEN 1 in pregnancy is rare but requires appropriate management with a multidisciplinary team to prevent maternal and fetal complications. We have demonstrated the first successful management of a woman with MEN 1 who completed her pregnancy with few complications and a healthy neonate. It is vital for such women to be managed by a team including obstetricians specialising in maternal medicine and endocrinologists as these women require close monitoring during their pregnancy.

Declaration of conflicting interests

None declared.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval

Written patient consent has been obtained for this case report.

Guarantor

MG

Contributorship

All authors reviewed, edited and approved the final version of the manuscript.

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