CASE REPORT

Methylmalonic acidaemia in pregnancy

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SUMMARY

A 27-year-old woman with vitamin B₁₂ responsive form of methylmalonic acidaemia (MMA) was pregnant with her first child. Treatment was unaltered during pregnancy: a low-protein diet and supplements. Her pregnancy was uncomplicated. She had a spontaneous delivery of a healthy girl with no MMA. The postpartum period was uneventful. MMA is a rare autosomal recessive metabolic disorder caused by a deficiency of methylmalonyl coenzyme A mutase or its vitamin B₁₂-dependent cofactor, leading to a toxic accumulation of methylmalonyl acid in plasma and urine. Clinical presentation involves otherwise unexplained deterioration and neurological dysfunction, recurrent vomiting, dehydration, lethargy, respiratory distress and muscular hypotonia. Long-term sequelae are neurological problems, renal failure, pancreatitis and cardiomyopathy. This is the 11th reported case of pregnancy in a woman with MMA.

BACKGROUND

To the best of our knowledge, this is the 11th published case of pregnancy in a woman with methylmalonic acidaemia (MMA). This case report can be helpful in the management of future patients with MMA considering pregnancy.

CASE PRESENTATION

A 27-year-old primigravid woman visited our outpatient clinic at 11 weeks' gestation. She had been diagnosed with a vitamin B₁₂ responsive form of MMA at age 5 months following excessive vomiting and failure to thrive.

At the age of 1 she had sepsis with *Klebsiella* and an episode of diffuse intravascular coagulation resulting in amputation of several digits and toes because of necrosis. At age 1 she suffered metabolic decompensation with acidaemia following influenza.

In the first decade of her life she had a medical examination every 3 months, the next decade twice a year and then once a year.

She was on a low-protein diet (1.0 g proteins/kg/day) and used zinc sulfate 100 mg once daily, calcium carbonate 500 mg once daily, L-carnitine 500 mg eight times daily, vitamin B₁₂ intramuscularly 1 mg once daily. As the response was always sufficient on oral vitamin B₁₂, injectable B₁₂ was never necessary.

The pregnancy was unplanned and she never had any preconceptional care.

INVESTIGATIONS

A first trimester serum screening test for fetal aneuploidy showed no increased risk for trisomy 21 (pregnancy-associated plasma protein-A multiples

of median (PAPP-A MoM) 1.172; free β -human chorionic gonadotropin MoM 1.859; nuchal translucency 1.9 mm at 13 weeks (1.172 MoM)). At 12, 21, 35 and 39 weeks' gestation, ultrasound investigations showed no structural abnormalities and normal fetal growth in the 50th centile.

Blood tests at 12, 24 and 34 weeks' gestation demonstrated normal values (haemoglobin 10.9, 11.1 and 12.4 g/dL, respectively), at 24 weeks she had a normal glucose tolerance test (fasting 81 mg/dL; 1 h 119 mg/dL; 2 h 132 mg/dL in a 75 g glucose test according to the WHO protocol); serum ionogram was normal (ureum 13 mg/dL, sodium 137 mmol/L, potassium 3.8 mmol/L, calcium 8.6 mg/dL and creatinine 0.63 mg/dL), free serum L-carnitine level at that moment was 25.5 μ mol/L (normal values 24 to 48 μ mol/L).

TREATMENT

The aforementioned diet and supplements were administered unaltered during pregnancy.

OUTCOME AND FOLLOW-UP

At 40 weeks' gestation, she had a spontaneous vaginal delivery of a healthy girl with a birth weight of 3300 g (50th centile), length of 49 cm (40th centile), head circumference of 35 cm (50th centile) and Apgar score of 9 after 1 and 5 min, respectively. Check-up by the paediatrician showed no abnormalities. The postpartum period was uneventful. Six weeks after delivery, her obstetric check-up was normal. Three months after delivery her nephrological follow-up was normal. Follow-up of the baby showed no problems, in particular no MMA.

DISCUSSION

MMA is a rare autosomal recessive metabolic disorder with a reported prevalence ranging between 1:48 000 and 1:169 000.^{1 2} It is caused by a deficiency of methylmalonyl coenzyme A mutase or its vitamin B₁₂-dependent cofactor, leading to a metabolic block in the conversion from valine and isoleucine through methylmalonyl coenzyme A into succinyl coenzyme A and consequently to a toxic accumulation of methylmalonyl acid in plasma and urine. The clinical presentation involves otherwise unexplained deterioration and neurological dysfunction, usually already in early life, due to impairment of energy homeostasis and accumulation of methylmalonyl acid. Other symptoms are lethargy, recurrent vomiting, dehydration, respiratory distress and muscular hypotonia. Treatment is based on a low-protein diet with amino acid mixtures deprived of valine and isoleucine, L-carnitine and (if responsive) vitamin B₁₂ to eliminate toxic intermediates, and repeated courses of antibiotics

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Table 1 An overview of other reported cases of methylmalonic acidemia in a pregnant woman

Reference	Gravidity	Parity	Maternal age (years)	Gestational age (weeks)	Treatment	Birth weight	Fetal outcome	Maternal outcome
van der Meer <i>et al</i> ⁶	1	0	Unknown	40	–	Female, 2900 g (p15)	MMA	Normal
van der Meer <i>et al</i> ⁶ Second pregnancy in same patient	2	1	Unknown	41	Vitamin B ₁₂	Female, 2350 g (<p2.3)	MMA	Normal
Diss <i>et al</i> ⁷	2	0	23	40+4	Protein restriction Carnitine supplements	Female, 3500 g (p25)	Normal	Normal
Wasserstein <i>et al</i> ⁸	1	0	20	36+6	Low protein diet Amoxicillin/metronidazole Bicarbonate, magnesium sulfate	Male, 3220 g (p75)	Normal	Moderate renal insufficiency, chronic pancreatitis, anaemia, optic atrophy (first trimester)
Deodato <i>et al</i> ⁹	1	0	24	38	Low protein diet Hydroxycobalamin intramuscularly Carnitine	Female, 2940 g (p40)	Normal	Increase of urinary MMA
Boneh <i>et al</i> ¹⁰	1	0	Unknown	36	Vitamin B ₁₂ injections	Unknown	Normal	Normal
Adeyemi <i>et al</i> ¹¹	1	0	23	34	Carbamazepine, vitamin B ₁₂ injections, low protein diet, L-carnitine, steroid inhalers, Maxepa, clarithromycin, dexamethasone	Female, 1900 g (p30)	Normal	Normal
Langendonk <i>et al</i> ⁵	1	0	24	38	vitamin B ₁₂ , B9, carnitine, iron, vitamin D, calcium supplements	Female, 2850 g (p10)	Normal	Mild hyperammonaemia in pregnancy
Langendonk <i>et al</i> ⁵	1	0	19	35	Vitamin B ₁₂ , carnitine, amino acid supplement, multivitamin supplement	Female, 1530 g (<p5)	Intrauterine growth restriction	Normal
Lubrano <i>et al</i> ¹²	1	0	29	37	Low protein diet Immunosuppressive treatment B-blocking agent	Female, 2480 g (p25)	Normal	Normal

MMA, methylmalonic acidemia; P, growth percentile.

to reduce microbial propionate production. The prognosis is dependent on the severity and vitamin B₁₂-responsivity of the disease. Long-term sequelae are neurological problems, renal failure, pancreatitis and cardiomyopathy.^{3,4}

Langendonk *et al*⁵ described a series of pregnancies in women with inherited metabolic diseases; two of them were patients with MMA. One woman with MMA had mild episodes of hyperammonaemia during pregnancy, but fetal outcome and postpartum period were normal. The other patient had no metabolic problems despite poor compliance with treatment. Fetal outcome showed intrauterine growth retardation (under 5th centile) but no other problems. For as far as we were able to find this is the 11th reported case of MMA in a pregnant woman; an overview of other reported cases is given in table 1. With the exception of low birth weight, outcomes have been generally favourable, although this impression may be influenced by publication bias (unfavourable cases not being published).

Learning points

- Methylmalonic acidemia (MMA) is a rare autosomal recessive metabolic disorder.
- Reported cases of MMA in pregnancy generally show a good outcome.
- Supplementation with L-carnitine should be continued unaltered in pregnancy.

Contributors MDH wrote the first draft that was further elaborated by YJ and FE.

Competing interests None.

Patient consent Obtained.

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