

# Management of a pregnancy complicated by classical homocysteinaemia

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## Summary

Pregnancy itself increases the risk of venous thrombosis by 4-5 fold. Homocysteinaemia increases this risk as well as the risk of arterial thrombosis which in turn increases the incidence of stroke and myocardial infarction. Therefore, the reduction of thrombotic risk is vital. Therapeutic doses of low-molecular weight heparin (LMWH) may be necessary to prevent thrombosis during and 6 weeks after the pregnancy. The mainstay of controlling homocysteinaemia is dietary management to decrease the amount of methionine, which in turn leads to a decreased amount of homocysteine in the blood. If any interventions during pregnancy becomes necessary, care should be taken to select ones which are associated with lesser risk of thrombosis. Patient should be appropriately counselled about potential implications of future pregnancy and reliable non-hormonal contraception or sterilisation should be offered.

## Background

Management of homocysteinaemia in pregnancy was rarely reported, being such a rare disease itself. It has a high propensity of causing arterial thrombosis which can be lethal. Although many clinical guidelines inform us the best strategies in preventing venous thrombosis

in pregnancy, no such guidance signifies the importance of homocysteinaemia. Hence, the details of the management of a pregnancy complicated by homocysteinaemia could be important to clinicians caring for such. Consideration should be given to include this important thrombotic risk factor in assessing the thrombotic risk in pregnancy.

## Case presentation

A 26 years old, gravida-2, para-1 presented to antenatal clinic at 11 weeks gestation after being referred by the metabolic unit via her general practitioner.

## Medical history

Congenital homocysteinaemia (classical type), initially referred to the metabolic clinic in a tertiary centre from childhood, but poorly engaged, and poor control of homocysteine levels. She was also diagnosed to have vitamin B-12 deficiency, obesity, primary hypertension, (not medicated), depression and possible post-traumatic stress disorder and lens surgery on eyes. However, there was no personal or family history of any venous thrombo-embolic disease or arterial thrombosis.

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## Social history

Patient does not smoke cigarettes. She used to take one unit of alcohol per week pre-pregnancy but nil during pregnancy. She has separated from current partner, who was different from previous partner to her first child.

## Obstetric history

Patient has had an emergency caesarean section at full dilatation due to foetal distress at 40 weeks, in her previous pregnancy. The current partner has had genetic testing and is not a carrier for homocystinaemia which was negative. The cervical screening was up to date and normal. She was deemed low risk at combined first trimester screening. The foetal morphology scans carried out at 18 and repeated at 21 weeks detected no abnormalities. Placenta was positioned normally in the uterus. The blood group was O rhesus positive; no antibodies were detected. Serum infection screening tests for hepatitis-B and C, human immunodeficiency virus and syphilis were negative. She was found to be immune for rubella. Serum electrophoresis was unremarkable.

## Examination

Weight 90kg, Height: 156cm, BMI: 36kgm<sup>-2</sup>, BP: 110/80 mmHg, urinalysis was normal. No signs of varicose veins were seen.

## Investigations

Last serum homocysteine level was 270 micro mol/L 3 years prior to the current pregnancy, 170 in the first trimester, 180 in the third trimester. Coagulation profile was normal (international normalised ratio [INR]=1.2, activated partial thromboplastin time [APTT]=32s and fibrinogen level was 3.9 g/L). The liver, bone, renal and lipid profiles were normal. Iron studies were normal except the serum iron of 8 in the first trimester.

## Differential diagnosis

## Treatment

### Obstetric care plan

This was formulated in conjunction with obstetric physicians. She was advised to continue folic acid 5mg/day and vitamin B6 (pyridoxine) 100 mg/day. She was commenced on low-dose aspirin (100 mg/day) to be continued until 36 weeks with vitamin D supple-

mentation. She was commenced on weight based 60mg of LMWH – enoxaparin (clexane) once daily at initial consultation at 11 weeks which was increased to 90 mg/day. This was planned to continue until 28 weeks and increasing to 60 mg/twice a day until 6 weeks postnatally. Foetal growth scans from 28 weeks were planned. Patient was advised avoid thrombosis-provoking causes such as dehydration and immobility. Thrombo-embolism prevention stockings were offered.

Patient initially wanting vaginal birth after caesarean section (VBAC), but subsequently requested an elective caesarean section with tubal ligation on subsequent visit, booked for 39 weeks.

Patient was insisted to continue taking betaine and cystadane 3g twice a day was prescribed by a specialist endocrinologist at Queensland Lifespan Metabolic Service in Brisbane. She was informed the benefits of following the dietary advice to decrease the amount of methionine.

Patient reported that she has developed an allergy (skin irritation and redness) around clexane injections and that she had discontinued it. Hence, the LMWH was changed to (dalteparin) fragmin 5000 IU/ twice a day from 28 weeks – doubtful compliance, patient admitted not taking aspirin.

## Outcome and follow-up

### Outcome

Although she was booked for elective caesarean section, she opted for VBAC as the cervix was found to be 3cm dilated at 39 weeks. She achieved a successful VBAC, but developed post-partum haemorrhage of 1700 mL, which was treated with uterotonics and a Bakri balloon.

### Follow-up

Ms S was readmitted with purpural sepsis 5 days after, which was successfully treated with IV antibiotics. She was discharged home in 2 days with advice to take fragmin 5000 IU/twice a day for 6 weeks. She was also advised to continue cystadane. She was offered contraception and an appointment to get laparoscopic sterilisation arranged. She has subsequently had an elective, laparoscopic bilateral tubal ligation without a complication.

### Discussion

A PubMed search revealed a successful pregnancy in a patient with homocystinuria who have had a near fatal cavernous sinus thrombosis was reported in 1995<sup>1</sup>. A maternal death was reported in 1987<sup>2</sup>.

### Outcomes of homocysteinaemia

The most common complication is lens dislocation, with 82% of those with classical homocysteinaemia occurring before the age of 10 years old, bone changes, most commonly osteoporosis, occurs in up to 64% of both females and males before the age of 15, and if antiplatelet agents, most commonly aspirin, not commenced early in life, up to 27% will have a major vascular event before the age of 15, this factor is the highest contributing cause of death, and up to 23% will not survive to the age of 30. Varying degrees of intellectual impairment affects up to 50% of those diagnosed<sup>7</sup>.

### Treatment of homocysteinaemia

The mainstay of homocysteinaemia is dietary management to decrease the amount of methionine (an amino acid), which in turn leads to a decreased amount of homocysteine in the blood. The diet is highly specialised and very restrictive.

Early and rigid dietary treatment of homocysteinaemia in infancy may prevent the development of neurological consequences, i.e. developmental delay, but appear to have no effect on ocular and bone disorders.

For reasons unknown, some individuals with classic homocysteinaemia respond well to high doses of Vitamin B6, and others have a limited effect. Those who do not respond to Vitamin B6 should follow a low methionine diet, including the avoidance of fish, eggs, meat, soy, dairy, nuts and beans. Betaine is also routinely used, although its evidence is limited, but is thought to help remove the homocysteine from the blood, by converting homocysteine back to methionine. It would be assumed that patient is responsive to pyridoxine, as she has been commenced on it by the metabolic unit.

Pyridoxine responsiveness should be trialled in early life to categorise those responsive, responsiveness is measured by the levels of rapidly dropping homocysteine levels in the blood after commencement of

high dose pyridoxine. High dose pyridoxine is usually commenced at 300-450mg per day<sup>3</sup>.

### Treatment of homocysteinaemia in pregnancy

Although not studied comprehensively, it is thought that high dose folic acid (5mg per day), reduces the risk of neural tube defects, as it does in other risk factors (anti-epileptic medication and diabetes<sup>4</sup>. Both folate and Vitamin B6 (100mg/day) and B12 (0.4mg per day), has been shown to reduce the homocysteine levels in the blood by 31%. Patient was commenced on high dose folate, 5mg/day, due to the increased risk of neural tube defects associated with homocysteinaemia.

### Risks to the neonate

Maternal homocysteinaemia, if not inherited by the neonate, appears to have no adverse developmental affect<sup>8</sup>. Even though homocysteinaemia is screened for in the neonatal screening program on days 2-3, some forms are not detected, and the diagnoses may not be made until up to 5 years old with the onset of developmental delay, poor eyesight or increased incidence of childhood fractures. The most common form, of which this patient has been diagnosed previously, is usually inherited in an autosomal recessive manner.

### Pregnancy and venous thrombo-embolic disease (VTE)

Although Ms HS does not have a history of previous thromboembolic disease, or any other risk factors for antenatal anticoagulation, her underlying metabolic disorder puts her at very high risk of adverse events secondary to VTE in the pregnant state, thus it was considered imperative to commence anticoagulation in the second trimester. Pregnancy itself increased VTE by 4-5 fold<sup>5</sup> with the combination of increased hypercoagulability, compression of the lower limb venous system by the enlarging uterus and venous stasis.

Incidence wise, VTE is the leading cause of maternal death in the developed world and the risk is highest in the postpartum period<sup>6</sup> thus continuing post-natal anticoagulation for 6 weeks is prudent<sup>5</sup>. Interestingly, it is estimated that 40-60% of antenatal VTE occurs in the first trimester<sup>6</sup> thus an argument could have been made to start Ms HS as soon as pregnancy was detected or planned.

## Pregnancy and arterial thrombosis

Although arterial thrombosis such as stroke and myocardial infarction were reported causes of maternal death, no cases of maternal death due to homocystinaemia were reported in recent reports of confidential inquiry into maternal deaths in the United Kingdom.

## Treatment success

The National Institute for Health and Care Excellence (NICE) estimates that low-molecular-weight heparin reduces VTE risk in medical and surgical patients by 60% and 70% respectively<sup>7</sup>. Extrapolating this data to obstetric patients is difficult with limited evidence, but a Scandinavian study found a relative risk reduction of VTE of 88% in obstetric patients with one previous VTE given LMWH<sup>8</sup>.

## Learning points/take home messages

- Manage the thrombosis risk aggressively
- Early obstetric review and intervention
- Encourage dietary restrictions
- Offer sterilisation

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