A case of severe pyruvate kinase deficiency in a primigravida: successful outcome

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Summary: Pyruvate kinase deficiency (PKD) is a rare non-spherocytic type of haemolytic anaemia. During pregnancy, women with severe PKD are at increased risk of infection, thrombosis, hypertension, fetal growth restriction and anaemia. Management of such cases requires close collaboration between a haematologist and an obstetrician. We report a case of severe PKD in pregnancy with good maternal and fetal outcome.

Keywords: maternal-fetal medicine, high-risk pregnancy, haematology

INTRODUCTION

Pyruvate kinase deficiency is a non-spherocytic type of haemolytic anaemia first described by Valentine *et al.* in 1961.¹ Inheritance is mainly in an autosomal recessive manner but may also be autosomal dominant. The phenotypic variety of the disease is related to the array of 180 mutations on chromosome 1q21.² Homozygote carriers for PKD experience chronic haemolysis from early childhood requiring regular transfusions. Heterozygote carriers are not usually clinically affected, but may experience haemolysis under stress conditions.² Pyruvate kinase (PK) is an enzyme in the rate limiting step of the Embden Myerhoff glycolytic pathway and deficiency results in accumulation of intermediates in the pathway making erythrocytes more susceptible to hypoxic injury. Specific standardized assays for PK are used to diagnose the disease.³

Advances in management of the condition mean that more women of childbearing age are able to become pregnant.⁴

CASE REPORT

A 23-year-old woman who had severe PKD since birth with previous cholecystectomy and splenectomy booked at seven weeks. She required monthly antenatal obstetric and haematology review. Regular medications included penicillin V 250 mg twice daily and folic acid 5 mg once daily. Iron chelation therapy was stopped at this point. She did have severe hepatic siderosis (Table 1), though echocardiography showed a normal left ventricular ejection fraction and cardiac MRI showed no siderosis. Her target Hb was 9 g/dL and her haematologist managed her on a chronic blood transfusion programme (three units every four weeks). This was increased to three weekly transfusions during the antenatal period.

Her twenty-two week anomaly scan showed normal fetal anatomy but uterine artery Doppler notching was noted. Subsequent ultrasounds showed normal growth, amniotic fluid index and dopplers.

Ferritin and haemoglobin remained stable throughout the antenatal period (Table 1).

At 29 weeks she presented with headaches and shortness of breath. She was investigated, reassured and discharged home. At 33 weeks she represented with similar symptoms. In view of her second presentation being unresponsive to antibiotics, a V/Q scan was done to rule out pulmonary embolism, which was negative.

At thirty nine weeks she underwent a successful induction of labour, and had a vaginal delivery. Regular venous gases remained normal throughout labour. She had a healthy female infant weighing 3.6 kg. She remained well during the post partum period and was discharged home on clexane as planned.

DISCUSSION

It is important that specific risk factors associated with PKD and pregnancy are identified from the start. Pre-pregnancy counselling should involve boosting immunity to encapsulated micro-organisms, maternal screening for hepatitis B, C, HIV, CMV. Cardiac investigations should include maternal echocardiography to assess dilated cardiomyopathy secondary to iron overload and MRI to exclude cardiac siderosis.⁴ The carrier status of the partner should be determined to allow proper prenatal counselling.⁶

Antenatal high dose folic acid therapy is required to alleviate folate deficiency due to chronic haemolysis. Iron chelation therapy is stopped antenatally due to potential theoretical teratogenic risk to the fetus extrapolated from animal model studies.^{4,5} However if there is evidence of worsening haemosiderosis or cardiac siderosis then the risks versus benefits of therapy should be discussed.

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Table 1 Levels of Hb and ferritin in pregnancy

Gestational age (weeks)	6	9	13	17	22	25	28	31	34	37	38
Hb (g/dL)	8.1	8.5	9.2	9.1	9.0	8.9	9.5	9.6	10.5	9.7	10.2
Ferritin (ug/L)	n/a	3689	n/a	3848	3200	3433	3254	3102	n/a	3164	n/a

Patients with PKD and previous splenectomy undergoing prophylactic blood transfusion are at increased risk of infection. Increased susceptibility to encapsulated bacteria in splenectomised patients is well known. However siderosis can also contribute to infection risk by impairing T cell, neutrophil and macrophage function resulting in impaired immunity.¹¹

Increased risk of impaired fetal growth has been identified in previous reports of PKD in pregnancy and necessitates the need for regular fetal monitoring.⁷ Potential theories to explain this are abnormal placentation resulting from chronic anaemia or myocardial siderosis leading to reduced cardiac output and a subsequent reduction in uterine blood flow.⁴ Placental dysfunction may also explain the increased risk of hypertensive disorders in these patients described in three previous cases, though only one mild case of pre-eclampsia has been described by Wax *et al.*³ Uterine artery Dopplers may be used as a screening tool to identify those at higher risk.⁸

Pregnancy itself is prothrombotic.¹² When combined with PKD, previous splenectomy and siderosis there is a multiple fold increase in clot formation. Patients with PKD have an increased number of abnormal erythrocytes and erythroid precursors which are thought to be prothrombotic. Loss of haemocatheretic function of the spleen leads to an increase of these cells in the circulation.¹³ Additionally siderosis can lead to endothelial damage and generation of reactive oxygen species which increases risk of thrombus formation.¹⁴ Management of such patients does not require routine antenatal thromboprophylaxis unless there is previous thrombotic history, but post-natal low molecular weight heparin for six weeks should be considered.

It has been postulated that iron toxicity can interfere in oxidative phosphorylation and excess iron can lead to hydrogen ion formation in combination with water causing metabolic acidosis.¹⁰ Our patient was noted to have severe hepatic siderosis and therefore a recommendation was made to avoid prolonged labour and to start iron chelation therapy should acidosis occur.

She continued her pre-conception prophylactic blood transfusions with recommendations to keep her Hb at 9.5–10 g/dL. The use of prophylactic blood transfusion in pregnancy in patients not previously undergoing transfusion has been debated due to the increased risk of iron overload and alloimmunization. Previous studies have recommended limiting transfusions to those who have symptomatic anaemia. Ghidini and Korker reported a successful pregnancy outcome without the use of prophylactic red cell transfusion.⁹

In summary women with severe PKD with iron overload represent a special group who require extra vigilance for

detection of signs of maternal and fetal deterioration. From seven previous cases reviewed since 1980 ours is the only case of severe PKD with no maternal or fetal complications and a normal vaginal delivery.

DECLARATIONS

Competing interests: None declared.

Funding: Not applicable.

Ethical approval: Written consent to publish was received from the patient.

Guarantor: SM.

Contributorship: SM searched the literature and conceived the study. KS wrote the first draft. SM and SC corrected the first draft. SC approved the final version of the manuscript.

Acknowledgements: We would like to thank Mr Richard Howard (consultant obstetrician and gynaecologist) and Dr Khalid Saja (consultant haematologist) for their help in providing care for the patient.

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(Accepted 6 April 2012)