Sickle cell disease in Pregnancy: A new consideration for the Irish Obstetric and Neonatal Service

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INTRODUCTION

Sickle cell disease is a haemoglobinopathy occurring as a consequence of the presence of sickle haemoglobin. It is a recessive disorder in which the sickle haemoglobin molecule is made up of two normal alpha chains bound to two abnormal beta chains (s chains). Several distinct genotypes of the disease process have been described. Homozygous sickle cell (SS) disease and sickle cell haemoglobin C (SC) disease are the most common whereas sickle cell-beta+ (Sβ+) thalassaemia and sickle cell-beta^o (Sβ^o) thalassaemia are uncommon genotypes. Other genotypes are very rare.

The disease causes significant morbidity and mortality in those affected, in the first three years of life and especially in the first year of life. Furthermore, pregnant women with sickle cell disease and the developing fetus are at a higher risk of severe life threatening complications. Early diagnosis is therefore essential and is the cornerstone to implementation of prophylactic programmes and successful management of these patients.

EPIDEMIOLOGY

The disease is endemic in people of African descent as well as in Asians and Indians. It is more especially prevalent in tropical zones of the world such as West Africa, where it is thought to confer some protection against malaria. Homozygous sickle cell anaemia occurs in approximately one in 626 African Americans.[1] A study in Jamaica reported SS disease to occur once in every 300 births and SC disease once in every 7000 births.[1] Since the arrival of the immigrant population in Ireland a significant number of cases of sickle cell anaemia have been managed in Irish hospitals.

GENERAL CLINICAL MANIFESTATIONS

Sickle cell disease is a multisystem disorder which may be complicated by splenic dysfuntion syndromes such as pneumococcal septicaemia, acute splenic sequestration andchronic hypersplenism. Massive haemolysis resulting in aplastic crisis and megaloblastic changes in the blood due to the increased demands for folic acid may also result. Bone pathology such as dactylitis, avascular necrosis of bone, femoral head necrosis and osteomyelitis are recognised complications of the disease. Gastrointestinal manifestastions include painful abdominal crisis characterised by diffuse tenderness, abdominal distention, reduced or absent bowel sounds, ileus, and sometimes fluid levels of radiology. The disease may be further complicated by acute chest syndrome which is the largest single cause of mortality from SS disease at all ages. It is characterised by episodes of pleuritic chest pain and shortness of breath. Other recognised features include leg ulceration, nocturnal enuresis, cerebrovascular accidents occurring predominantly in childhood, proliferative sickle retinopathy secondary to vaso-occlussion in the peripheral retina. Morbidity from the disease is highest in the 6 months to 1 year age group and as such may subsequently result in failure to thrive, delayed puberty or even death.[2]

CLINICAL MANIFESTATIONS PARTICULAR TO PREGNANCY

Maternal Complications

Expectant mothers are at a higher risk of frequent acute splenic sequestration and aplastic crisis resulting in rapid onset of profound anaemia (haemoglobin less than 4 g/dl), megaloblastic changes in the blood (because the accelerated erythropoiesis in SS disease increases demand for folic acid which is also necessary in pregnancy), infections (because of impaired splenic function), and venous thrombosis (following the painful vaso-occlussive crisis).

In a review of 68 cases in Guadelope, there were severe complications especially in homozygous sickle cell disease. Painful vaso-occlusive crisis affected 88% of the SS pregnancies and 27% of the SC pregnancies.[3] The pregnant woman is also at a higher risk of pre-eclampsia, acute chest syndrome and death. The rate of Caesarean section in 'sickle cell pregnancy' is higher than in the general population. In the Guadelope study, it was reported

to be 48% higher.[3]

Fetal Complications

The developing fetus is more predisposed to intrauterine growth restriction as a consequence of placental insufficiency, which results from sickling of erythrocytes and vaso-occlussive episodes in the placental circulation. Megaloblastic red blood cells also inadequately deliver oxygen to the fetus, which is at increased risk of neural tube defects because of the increased consumption of folate. The unfavourable in-utero conditions may further predispose to preterm labour. Twenty-one percent prematurity was reported in the Guadelope study.[3] At the extreme end of the spectrum intrauterine death and abortion may occur.

DIAGNOSIS

Sickle cell disease may be diagnosed antenatally as well as in the neonatal period.

Antenatal diagnosis

The diagnosis of SS disease may be made in the first trimester of pregnancy (first 8 to 10 weeks).[4,5] Diagnostic fetal specimen may be obtained by chorionic villus sampling or by amniocentesis.[6] Chorionic villus sampling involves biopsy of the trophoblast, using a small needle passed via transabdominal route or vaginal route into the placenta. It may be performed as early as 6 to 8 weeks but is usually delayed until 10 weeks. Amniocentesis involves extraction of amniotic fluid using a fine gauge needle under ultrasound guidance. It may be performed as early as 10 weeks gestation. The small amount of DNA obtained is then amplified by polymerase chain reaction (PCR).

It is worth noting that both methods are expensive, require technical expertise and relatively sophisticated DNA technology. Furthermore they carry an inherent risk of miscarriage, chorionic villus sampling more so than amniocentesis.

Neonatal diagnosis

Electrophoresis of fetal blood samples on cellulose acetate followed by confirmation on agar gel is most widely used diagnostic tool.[7] Blood samples may be obtained from the umbilical cord or by heelprick. Dried samples on filter paper may be sent by post to a central laboratory. Repeating the procedure after 2-3 months confirms the diagnosis.

Neonatal diagnosis is cheaper than antenatal diagnosis. It is accurate and is suitable for population screening. Given its timing, it offers the option of early introduction of prophylactic programmes, such as penicillin prophylaxis for pneumococcal septicaemia.[8,9] On the other hand, antenatal diagnosis is expensive and hardly applicable on a population-wide basis though it offers the option of early termination of pregnancy.

MANAGEMENT OF SICKLE CELL DISEASE IN PREGNANCY

General Principles

The pregnancy should be considered 'high risk' and antepartum care should preferably be specialist led, so as to deliver optimal care. Intensive maternal and fetal surveillance should be undertaken. Regular exchange blood transfusions, screening for infection and maintenance of hydration are desirable. Folic acid supplements are necessary while Iron supplements are avoided because of the risk of Iron overload. The high risk fetus should be monitored for early signs of compromise and intervention executed at a clinically calculated time, balancing the risks of in-utero compromise and potential distress to those of intervention and prematurity. During episodes of sickle cell crisis, the patient should be admitted and given specialist care. Anti-D antibodies should be given to Rhesus negative expectant mothers in anticipation of possible preterm labour. Steroids should be administered between 24 and 34 weeks gestation to promote fetal pulmonary maturity. Clinical deterioration will prompt delivery.

Maternal and fetal well-being

Optimal care for the expectant mother includes regular screening for infections by performing full blood count and vigilance for indicators of infection, prophylaxis and treatment of infection when indicated, maintenance of adequate hydration as well as regular exchange blood transfusions in women who are profoundly anaemic.[10] Folic acid supplementation is mandatory to prevent the tendancy to megaloblastic changes in the blood and to prevent the relatively increased risk of neural tube defects in the fetus.

Fetal surveillance includes simple records of fetal movements which give a crude but valuable information on fetal activity, ultrasound assessment of fetal growth where the abdominal circumference and the biparietal diameter are measured at 2 week intervals and plotted on centile charts to assess the rate of growth and to differentiate the healthy small fetus from the 'growth restricted' fetus, ultrasound assessment of the biophysical profile where limb movements, tone, breathing move-

ments and liquor volume are assessed and each scored out of two to a total out of eight.[6] A low score suggests severe fetal compromise. Other measures of fetal surveillance are doppler umbilical artery waveforms which aid to identify the 'small-for-dates' fetuses that are growth restricted, doppler uterine artery waveforms performed at 24 weeks gestation to identify pregnancies which are at risk of adverse neonatal outcome, as well as carditocography where the fetal heart rate is recorded electronically. Abnormalities here represent a late stage in fetal compromise and delivery is indicated.

SUMMARY

With the increasing immigrant population in Ireland, sickle cell disease will become common. Similarly the number of pregnancies and births which will be affected is bound to increase. 'Sickle cell disease pregnancy' is a high risk maternofetal situation which needs multidisciplinary specialist care to deliver optimal care, which is so crucial for both the maternal and fetal well being. Early diagnosis remains essential for prophylaxis against early complications. Development of specialist services dealing with diagnostics, screening procedures, genetic counselling, prenatal diagnosis, education and treatment of various haemoglobin disorders such as sickle cell disease seems to be the likely step in the future, in order to deliver optimal care.

REFERENCES

1. Serjeant GR. Haemoglobin gene frequencies in the Jamaican population: a study in 100,000 newborns. *Br J Haematology* 1986; 64:254-62.
2. Serjeant GR. Recent advances in sickle cell disease. In Recent Advances in Paediatrics 1994; 12:141-54.
3. Leborgue-Samuel Y. Sickle cell anaemia and pregnancy: review of 68 cases in Guadelope. *Journal de Gynaecologie, Obstetrique et Biologie dela Reproduction* 2000; 29(1):86-93.
4. Old JM, Fitches A, Heath C, et al. First trimester fetal diagnosis for haemoglobinopathies: report of 200 cases. *Lancet* 1986; 2(8510):763-8.
5. Old J, Petrou M, Varnavides L, et al. Accuracy of prenatal diagnosis for haemoglobin disorders in the UK: 25 years' experience. *Prenat Diagn* 2000; 20(12):986-91.
6. Impey Laurence. Obstetrics and Gynaecology. Blackwell Science Ltd, Oxford 1999.
7. Chasen ST, Loeb-Zeitlin S, Landsberger EJ. Hemoglobinopathy screening in pregnancy: comparison of two protocols. *Am J Perinatol* 1999; 16(4):175-80/
8. John AB, Ramal A, Jackson H, et al. Prevention of pneumococcal infection in children with homozygous sickle cell disease. *Br Med J* 1984; 288(6430): 1567-1570.
9. Rabb LM, Grandison Y, Mason K, et al. A trial of folate supplementation in children with homozygous sickle cell disease. *Br J Haematol* 1983; 54(4): 589-94
10. Ladwig P, Murray H. Sickle cell Disease in Pregnancy. *Aust N Z J Obstet Gynaecol* 2000; 40(1):97-100.