SICKLE CELL DISEASE IN PREGNANCY

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SUMMARY:

Structural and quantitative changes at the polypeptide chains of haemoglobin lead to defective red blood cells with a life span 1/5th of the normal, a much smaller capacity of oxygen saturation, and a less pliable structure that easily deforms in situations of hypoxia, stress, acidosis, dehydration, cold and prolonged physical effort etc. Multi-organ vaso-occlusion and hypoxia ensues, causing severe bone pains, sequestration, infarction and anaemia. Increased physiologic demands of pregnancy, aggravate falciformation resulting to poor perfusion of the placenta predisposing to preterm pregnancy loss, intrauterine growth retardation, pre-eclampsia, severe anaemia and increased perinatal and maternal morbidity and mortality. Urinary tract, respiratory and bone infections, as well as cardiac and neurologic complications are common. Treatment is preventive and symptomatic. It aims at reducing high risk combinations, and a meticulous follow-up to prevent the woman from developing complications and not dying from these complications. Though vaso-occlusive pain crises and severe anaemia may be fatal they may be remedied by generous use of analgesics, adequate hydration and exchange transfusion. Sickle cell anaemia the most common of the three major haemoglobinopathies is more frequent with individuals of African descent, haemoglobin C is more predominant in the coast of Africa west of the river Niger while alpha thalassemia and beta thalassemia haemoglobin are frequent in the Mediterranean and Southeast Asian countries respectively.


RESUME:

Les modifications qualitatives et quantitatives sur les sous-unités protéiques de l’hémoglobine provoquent plusieurs types d’altérations du globule rouge: la réduction de sa durée de vie d’environ 1/5ème de la normale, la réduction de sa saturation en oxygène, et la déformation et fragilisation des hématies. La vaso-occlusion et l’hypoxie provoquent de graves douleurs osseuses, la séquestration des globules rouges dans les organes, les infarctus et l’anémie. L’augmentation des besoins liés à la grossesse aggrave la falciformation. La réduction de la perfusion placentaire qui en découle prédispose la femme drépanocytaire aux situations de fausses couches, de retard de croissance, de pré-éclampsie ou à des anémies sévères. L’on note également, une augmentation de la morbidité puis de la mortalité périnatale et maternelle. Les infections urinaires respiratoires ou osseuses sont fréquemment retrouvées ainsi que les complications cardiaque et neurologique. Le traitement est préventif et symptomatique; son but étant de décourager les unions entre individus à haut risque et d’assurer à la future mère un suivi méticuleux afin de lui éviter de développer des complications et d’en mourir. La crise vasoocclusive et l’anémie sévère peuvent être fatales. Cependant l’usage des analgésiques, une bonne réhydratation et des transfusions sanguines peuvent remédier à la situation. L’hémoglobine S qui est la plus fréquente des trois types majeurs des ‘hémoglobinopathies est fréquente chez les individus descendant des Africains; l’hémoglobine C se retrouve plus sur la cote africaine à L’Ouest du fleuve Niger. Les thalassémies alpha et beta quant à elles sont fréquentes en méditerranée et au sud –Est asiatique respectivement.


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I- INTRODUCTION

Sickle cell disease (SCD) embraces a variety of combinations in which the sickling gene is present with another abnormal gene affecting haemoglobin production or structure. Normal adult and foetal haemoglobin are called A and F, respectively[1]. Sickle cell haemoglobin is called S; there are many other abnormal haemoglobins of which haemoglobin C [1] and thalassemia are of particular importance in obstetrics when they occur together with S. The normal haemoglobin is composed of four sub units of polypeptide chains (alpha, beta, delta, and gamma chains) each of which carries a haem molecule [2]. The normal haemoglobin contains, 95-98% of adult haemoglobin (HbAorHbA1), 1.5% of haemoglobin A2 (HbA2) and 0.5% of foetal haemoglobin (Hbf) [1]. Most haemoglobinopathies, involve structural changes caused by a single point mutation in amino acids in the haemoglobin molecule as in haemoglobin S and haemoglobin C. In haemoglobin S the amino acid glutamic acid at the sixth position of the N terminal of the beta chain is replaced by valine whereas in haemoglobin C glutamic acid is replaced by lysine instead. Alpha and beta thalassemia haemoglobinopathies are caused by alterations in quantity ( gene deletion) of these haemoglobin chains[3]. The three major haemoglobinopathies are sickle cell anaemia (Hb SS), sickle cell haemoglobin C disease, and sickle cell thalassemia disease. Other less common haemoglobinopathies include , haemoglobin D, haemoglobin E , haemoglobin O-ARAB, haemoglobin Constant-spring, Unstable haemoglobin, and haemoglobin M[1].

II- HISTORY

Sickle cell disease (SCD) had probably existed for long in Africa as many tribes have a local name for it. Research through oral history demonstrated that this disease had existed in nine generations of a Ghanaian family since 1670[3]. The sickling red blood cell was probably first discovered in 1904 when the blood of a black sick student from Grenada was examined under the microscope[4]. From an evolutionary standpoint, haemoglobin S mutation appears to have provided some protection from blood born diseases such as malaria. Patients with haemoglobin AS and haemoglobin SS are less susceptible to infections from falciparum malaria. The significance of a haemoglobin C mutation is less clear, but may represent a similar protection from infectious haemolytic diseases such as malaria [3].

III- EPIDEMIOLOGY

The sickle gene is found more frequently in individuals of African-origin. Approximately one of every 12 African-American has the sickle trait (haemoglobin AS)[5]. Haemoglobin C is more predominant in the west coast of Africa. It has its highest incidence in northern Ghana, Nigeria, and in Burkina Faso haemoglobin C heterozygotes are found in frequencies approaching 30%. On all sides of this zone of high incidence the frequency falls, and to the east it stops abruptly at the Niger river [1]. Alpha-thalassemia and ß-thalassemia genes are found with an increased frequency in individuals of Mediterranean / Arabic descent, and Southeast Asian ancestry, respectively [3]. Haemoglobinopathies are rare among northern Europeans, Japanese, Inuit (Eskimos), Native Americans, and those of Mexican and Korean descent [2 of 2 (6)]. Because of the autosomal recessive pattern of inheritance of these haemoglobinopathies, the risk of an SS offspring of parents with traits of this disease is 1/4. However the incidence of SS disease in pregnancy is less than predicted from the number of births of children with SS, because a high percentage of affected children die prior to reaching reproductive age[5].

IV-PATHOPHYSIOLOGY:

Sickle cell anaemia (HbSS), the most common of the haemoglobinopathies, is an autosomal recessive genetic disease that results from the substitution of valine for glutamic acid at position 6 of the beta-globin gene, leading to production of a defective form of haemoglobin, haemoglobin S (HbS)[7]. Deoxygenation of the haem moiety of HbS leads to hydrophobic interactions between adjacent HbS molecules, which then aggregate into larger polymers, distorting the red blood cell into the classic sickle shape[7]. The major consequence of this sickle shape is that red blood cells become much less deformable; therefore, they obstruct the microcirculation. Tissue hypoxia, which promotes further sickling, results. Sickle-shaped red blood cells are rapidly hemolysed and have a very short life span of only 10-20 days as compared to the life span of 120 days for normal red blood cells [7]. With rapid haemolysis of the red blood cells the bone marrow reacts by stepping up reticulocytosis by about 2%[1]. Certain conditions such as stress, hypoxia, acidosis, dehydration, hyperthermia, cold, prolonged physical effort, pregnancy, labour and puerperium and alcohol intoxication, may precipitate falciformation [1].
Since the earliest description of pregnancy in patients with SCD by Kobak, documentation of complications associated with pregnancy in sickle cell diseases have continued to accumulate [8-10]. Although haemoglobin S trait, haemoglobin C trait, and alpha-thalassemia do not pose significant risks to a pregnant patient, certain complications such as urinary tract infections and anaemia are more common in these patients. Sickle cell disease (haemoglobin SS disease), haemoglobin SC disease, haemoglobin C disease (haemoglobin CC disease), and beta-thalassemia are associated with an increased risk of serious pregnancy morbidity and mortality. The contribution of sickle cell disease to maternal mortality is substantial amongst populations where the disease is common[1]. The principle pregnancy complications encountered with patients with these major haemoglobinopathies include frequent urinary tract infections (cystitis, pyelonephritis), respiratory infections, and vasoocclusive crisis[1,2,3,8]. The complications are at times so severe that it is worth questioning whether patients with these haemoglobinopathies should be counselled against attempting pregnancy.

V-THE EFFECT OF SICKLE CELL DISEASE ON PREGNANCY.

Placental Changes
The placenta shows abnormalities in histopathology, weight, size, location and adherence to uterine wall. Abruptio placenta may be caused by the vasoocclusive process with thrombosis of decidual arterioles, and subsequent venous haemorrhage. Pathological changes in the placenta including fibrosis, infarctions, calcifications, fibrin deposits, and oedema may be enhanced in sickle cell disease[8]. These placental changes may contribute to increased abortions, intrauterine deaths, toxaemia of pregnancy, preterm labour and premature delivery, and the increased perinatal morbidity and mortality associated with SCD in pregnancy.

Abortions
Microvascular damage to the placenta by sickling, the general health of the patient, and the use of alcohol, tobacco and narcotics during pregnancy may increase the frequency of spontaneous abortions. The frequency of abortions in pregnant women with SCD though not very different from the normal population[8], is estimated at 20 to 40% (19% in Yaounde, 26% in Cotonou and 40% in Abidjan) [2].

Intrauterine Growth Retardation
That maternal anaemia and haemoglobin concentration less than 6 gm is associated with growth retardation is controversial[8]. Intrauterine growth retardation may be brought about by hypoperfusion and hypoxia of the placental membranes resulting from occlusion of the arterioles of the decidua of the placenta. The early occurrence in SCD of placental problems such as calcification, infarcts due to direct placental injury, abruptio placenta, placenta praevia and toxæmia also cause IUGR and may explain why prophylactic transfusion started later in pregnancy cannot prevent complications[1,2,8]. Vasospasm of the uterine vasculature and hypoxaemia in the placental bed cause proteinuria and decreased uterine blood flow, resulting in intraterine growth retardation. The nutritional status of patients with sickle cell disease which may be altered by frequent hospitalisation for acute and chronic events, can interfere with appropriate weight gain. Similarly, the prolonged use of narcotics for the treatment of pain may have vasoconstrictive effects on the placental vessels contributing to adverse effect on foetal nutrition[8]. It is estimated that the frequency of foetal hypotrophy is 30%[2].

Pre-Term Labour and Premature Delivery
Both preterm labour and premature delivery have been identified as a common occurrence in sickle cell disease[8-9]. 30% of premature deliveries are related to hyperthemia, infection and anaemia, in particular with SC-thalassemia and S-thalassemia [8]. Increased production of prostaglandin has been implicated along with anaemia, abruptio placenta praevia and toxæmia which are all linked with preterm labour. Multiple gestation, infection, urinary tract infection, intrauterine infection and use of narcotics, smoking, chorioamnionitis and sexually transmitted diseases have also been implicated in the increased perinatal mortality that has been reported[8].

Pre-eclampsia
Toxaemia of pregnancy is a frequent occurrence in patients with SCD. There is a fivefold increase in frequency of pre-eclampsia in sickle cell disease. The mechanism remains unclear, and multiple etiologic factors such as excessive placental mass, placental ischaemia, imbalance of prostaglandins and endothelial injury have been implicated[8]. Nulliparity, lower socioeconomic status, multiple gestation, hypertension, and previous history of pre-eclampsia are factors frequently associated with pre-eclampsia [1,2,8,11].

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NN Nkele et al

55
The blood pressure in non-pregnant individuals with sickle cell anaemia tend to run at lower levels than that of normal controls (90/50 to 110/70).

During normal pregnancy blood pressure falls until 20 weeks of intrauterine pregnancy and thereafter rises to pre-pregnancy levels. Many obstetricians note that blood pressures of 125/75 and higher are associated with increased perinatal morbidity after 36 weeks of gestation. Toxaemia is treated with bed rest; frequent monitoring and hospitalisation is recommended. If toxaemia is mild, delivery of the foetus is recommended if foetal survival is estimated over 95% (gestational age equal to or greater than 32 weeks). When toxaemia is very severe, delivery is recommended after clinical stabilisation of the patient. The management of the pre-eclampsia depends on the severity of the symptoms and the gestational age. In the stable compliant patient mild pre-eclampsia requires close observation with bed rest and maternal surveillance. The goals are to minimise maternal morbidity and to optimize the perinatal outcome. If the patient can be continued on bed rest and delivery can occur after 32 weeks, the outcome is significantly improved. Expedited delivery is recommended for uncontrolled hypertension. Signs of toxaemia, low platelet count, elevated liver enzymes, pulmonary oedema, compromised renal function and headache or visual changes also require a search for differential diagnosis of thrombotic thrombocytopenic purpura (TTP), haemolytic anaemia, elevated liver enzymes and low platelets (HELLP syndrome), haemolytic uremic syndrome (HUS) hypertensive crisis and cerebrovascular accident (CVA) associated with sickle cell disease [8].

Management of sickle cell disease in pregnancy

One in sixteen women in Africa die of complications from pregnancy and childbirth. Pregnant sickle cell women fall in the category of 15% pregnancies that are at high risk of maternal death [7]. Of the estimated 585,000 maternal deaths that occur each year worldwide, over 99 percent occur in the developing world [13]. The main causes of maternal death in sickle cell disease are severe anaemia due to folic acid deficiency, embolism following bone marrow infarction, and acute sequestration of red blood cells [1]. Studies in Ibadan suggested that 1 in 10 pregnant women with sickle cell disease may die as a result of complications of the disease, but the risks can certainly be minimised by special measures [1]. Strategically, there are three fundamental ways in which maternal deaths can be prevented [14]:

1. Through preventing a woman from becoming pregnant.
2. Through preventing a woman from developing a complication that can lead to her death.
3. Through preventing a woman from dying from a pregnancy complication.

Preventing a woman from becoming pregnant or having an affected baby.

Though individuals are at liberty to freely choose their spouses, the burden from high morbidity and mortality of their off springs from SCD is so enormous that proper prenuptial counselling and examination are necessary to avoid high risk combinations. The investigations include [5]:

a) Haemoglobin electrophoresis for the diagnosis of haemoglobins A, S, and C.
b) Solubility testing for observing sickled cells may be negative for individuals with haemoglobin B, C, V, E and thalassemia trait carriers.
c) Investigations for beta thalassemia. Red cell indices, mean corpuscular volume (MCV) less than 80fl when iron deficiency anaemia has been ruled out. An elevated haemoglobin A2 more than 3.5% or haemoglobin F of 1% to 5% signifies beta thalassemia.
d) For alpha thalassemia DNA based testing can detect alpha globin gene deletions that are characteristic of alpha thalassemia.

Perinatal Morbidity and Mortality

There is a wide range of occurrence of perinatal morbidity and mortality in different regions around the world ranging between 10-50 per 1000. In Cameroon perinatal mortality is 75 per 1000 [12] while in the United States it is approximately 18 per 1000 [8]. Neonatal and foetal mortality is observed in 50-80% of cases especially with SC, S-thalassemia and SC-thalassemia [2]. Methods to distinguish foetuses that are at high risk include ultrasound assessment of intrauterine growth retardation performance of biophysical profile, uterine umbilical Doppler blood flow studies and continued monitoring during labour have reduced the incidence. Close monitoring, prompt diagnosis and aggressive treatment of complications during the prenatal and neonatal period by the efforts of multidisciplinary teams have contributed to better outcome [7].
When both parents are carriers of the trait, they have the option of using contraception in order not to have children or run the 25% risk of giving birth to an SS offspring. Oral contraceptives as well as contraceptive agents administered intramuscularly and barrier methods are all acceptable choices for women with SCD [15]. Few studies have evaluated oral contraceptives, but none showed adverse effects [16]. Intrauterine devices are not optimal, since they may be associated with uterine bleeding and infection in any user, regardless of the presence of SCD. Contraception and SCD [15].

Also the pregnant woman could be offered prenatal screening to detect the haemoglobin of the foetuses. She could do: a) Chorionic villus sampling and or b) amniocentesis. The decision to continue or terminate the pregnancy is fraught with many implications of medico-legal, moral and religious considerations. In Cameroon though abortions are allowed in case of risks to a woman’s life, foetal defects or in the case of rape or incest [17], it is not clear if a foetus affected with SS is enough “foetal defect” to be considered a reasonable medical reason for late abortion. Even in the most liberal country like USA where abortion has been legalised for long, only recently (early November 2003) a bill was passed prohibiting late abortions. Abortion is far from meeting the aspirations of patients and the medical team in reducing the burden of sickle cell disease. Fortunately a group of researchers recently devised a new technique of screening called pre-implantation genetic diagnosis (PGD) in which the genetic material of embryos are tested for SS prior to implantation. They reported a successful case of PGD prior to embryo transfer after in vitro fertilisation [18].

Here is how the authors summarise their study [19]:

“In summary, this is the first unaffected pregnancy and delivery after successful PGD for sickle cell anaemia. Our results demonstrate that PGD for the detection of sickle cell anaemia is a powerful diagnostic tool for carrier couples who desire a healthy child but wish to avoid the difficult decision of whether to abort an affected foetus. The procedure, successfully used in this case, may also be applied to other monogenic disorders .... Given the current methods and relatively high cost of the procedure, it is unlikely (however) that PGD will totally replace prenatal testing”. Preventing a woman from developing a complication that can lead to her death.

The SS patient before contemplating pregnancy should be warned of the aggravating effect of SCD crises by pregnancy and the imminent risk of not carrying the pregnancy to term. She runs the risk of developing severe anaemia and toxaemia of pregnancy and as such the likely hood of several blood transfusions and caesarean section should be discussed. The pregnant SS woman is among the 15% of women likely to have complications in pregnancy.

Laboratory investigations.

In addition to routine prenatal laboratory investigations, base line laboratory studies include: Complete blood count, reticulocyte count, haemoglobin electrophoresis, urinalysis, serum iron, ferritin, total iron-binding capacity, and creatinine, screening for red-blood cell antibodies, hepatitis B and C, and the human immunodeficiency virus [5].

Symptoms, laboratory findings, or history suggestive of specific organ involvement should elicit the following work-up [5]: Cardiac: Echocardiography, since these patients can have cardiac dysfunction from ventricular hypertrophy. Renal: 24-hour urine for volume, creatinine, and protein in case of renal papillary necrosis that may lead to haematuria and the inability to concentrate urine, pyelonephrosis. Pulmonary: Pulmonary function tests. They may have infarction, pulmonary hypertension, bone marrow infarction leading to fat embolisation. Cerebral: Head computerised axial tomography (CAT) or magnetic resonance imaging (MRI) because of cerebral vascular accidents.

Treatment

As of date there is no curative treatment for falciformation [2]. The treatment is largely symptomatic and consists of:

1) Good dietary habits [5].
2) Throughout pregnancy prophylactic folic acid (1mg daily) should be given and haemoglobin levels frequently checked [1,5]. Iron supplementation should be given to SC, and S-beta-thalassemia patients but not to SS unless ferritin has been measured [5].
3) When necessary antimalarials should be given [1]. However there is very little evidence to support or refute giving routine chemoprophylaxis in sickle cell disease in areas where malaria is endemic [20].
1) Adequate hydration with isotonic glucose, isotonic bicarbonate and macromolecules when sick or in labour (Dextran) [2].
2) Foetal monitoring. Detection of evidence of placental insufficiency requires prompt Caesarean section.
3) Supplemental oxygen should be given. Hypoxia may compromise cardiac function
4) Adequate hydration is necessary to avoid dehydration.
5) Her BP is monitored constantly. One third of SS pregnant patients have pregnancy induced hypertension.
6) Infection control. Infections are associated with sickle cell crises. Occurring in tissues susceptible to vasoocclusive infarcts (bone, kidney, lung), they manifest as osteomyelitis, urinary tract infections and pneumonia[5]. Evaluating the patient for asymptomatic bacteriuria and treating her, if necessary, is essential[5]. A Cooperative Study of the clinical course of sickle cell disease showed that, neo-natal screening, prophylactic penicillin, and anti-pneumococcal vaccine have had striking effects on survival [8].
7) Oxygenation. Supplemental oxygen is given to increase oxygen tension, which may possibly decrease the intensity of sickling at the capillary level, although its benefits have not yet been proved in clinical studies [5].
8) Transfusion of packed blood cells. Blood transfusion is required when the haemoglobin falls below 6gm %[1]. Straight transfusion in patients with major haemoglobinopathies is usually performed to raise the patients hematocrit to a value between 25% and 30%. Over transfusion may increase blood viscosity and worsen sickling. Packed red blood cells are the blood products of choice, since they reduce the risk of antigen sensitisation. It is common for patients with major haemoglobinopathies to develop positive antibody screens from repetitive blood transfusion[3]. Red blood cell screening for the most common antigens that cause alloantibodies (Kell, C, E, S, Fy and JK) so that phenotypically matched units will be available for future transfusion therapy, can be done at the first visit[5].
9) Exchange transfusion should be carried out if acute sequestration crises occur[1]. When Ricks in 1961 introduced the role of exchange transfusion as treatment, prophylactic transfusion was accepted as treatment for all women with sickle cell disease during pregnancy[8]. However, in the 1980s, a randomised trial carried out by Tuck failed to demonstrate the efficacy of prophylactic transfusion during pregnancy [8].
10) Specific therapeutic trials have been carried out with hydroxyl urea and cyanate of potassium but their efficacy and secondary effects leave much to be desired[2]. The aim of hydroxyurea therapy is to induce production of foetal haemoglobin, and many patients who have used these treatment have presented with less frequent clinical episodes of painful crisis and improved laboratory parameters. However hydroxyurea may have detrimental effects on the foetus. If pregnancy is planned hydroxyurea needs to be discontinued[8].

Measures should be taken to avoid the following:
- a) Uterotonics such as ergometrine which may aggravate vasoocclusive crisis.
- b) Transfusion of cold and whole blood.
- c) Hypertonic solutions such as 10 or 30% bicarbonate and hypertonic glucose. These may increase the viscosity of blood and promote falcification.
- d) Diuretics may cause dehydration.
- e) Betamimetics should be avoided as much as possible in threatened premature delivery; instead natural progesterone should be used[2].

**Intrapartum care**

1) Parturient should be managed in the left lateral recumbent position.
2) Pain crisis should be managed with analgesics and or epidural anaesthesia.
3) Supplemental oxygen should be given. Hypoxia may compromise cardiac function
4) Adequate hydration is necessary to avoid dehydration.
5) Her BP is monitored constantly. One third of SS pregnant patients have pregnancy induced hypertension.
6) Foetal monitoring. Detection of evidence of placental insufficiency requires prompt Caesarean section.
7) Transfusion with packed red blood cells should be considered if hematocrit is less than 20% or if caesarean section is envisaged[21].
8) Vaginal delivery is preferable and caesarean section delivery is performed for obstetrical indications.
9) Blood loss during labour should be evaluated and blood transfusion started if the loss aggravates anaemia.
10) Early ambulation. Anti-embolic stockings and discussion of future pregnancies should be discussed prior to discharge.
11) Results of the cord blood sample screening for sickle cell disease of the infant should be made available to the parents and paediatrician.

**To prevent a woman from dying from a pregnancy complication.**

The follow-up of SCD patients with pregnancy complications requires hospitals equipped with specialised units where basic and comprehensive emergency obstetrical care can be provided. Basic emergency obstetrical care refers to the ability to manage labour, recognise and refer patients with abnormal labour patterns, provide intravenous fluids, medications to stop postpartum haemorrhage, antibiotics, assisted vaginal delivery, manual removal of the placenta, management of incomplete miscarriage and basic neonatal resuscitation. Comprehensive emergency obstetrical care refers to the ability to provide blood transfusions and caesarean sections in addition to providing basic emergency obstetrical care[14]. With modern obstetrical care, a maternal death is a rare event. Where modern obstetrical care is lacking, maternal death rates can be high, paralleling the maternal death rates of Europe and North America in the 1700's and 1800's. In many countries in Africa and several countries in Asia, there are between 1000 and 1700 maternal deaths per 100,000 live births a rate well over 100 times greater than that of the United States[14]. In Cameroon, one out of every 26 women have a life time risk of maternal death [12], the maternal mortality ratio for the year 1995 was 720 per 100,000 live births[22] and by 1999 it was 420 per 100,000 live births[23].

**REFERENCES:**


