

Sickle Cell Disease: Review of Managements in Pregnancy and the Outcome in Ampang Hospital, Selangor

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Abstract—The aim of this study is the review of the management practices of sickle cell disease patients during pregnancy, as well as the maternal and neonatal outcome at Ampang Hospital, Selangor. The study consisted of a review of pregnant patients with sickle cell disease under follow up at the Hematology Clinic, Ampang Hospital over the last seven years to assess their management and maternal-fetal outcome. The results of the review show that Ampang Hospital is considered the public hematology centre for sickle cell disease and had successfully managed three pregnancies throughout the last seven years. Patients' presentations, managements and maternal-fetal outcome were compared and reviewed for academic improvements. All three patients were seen very early in their pregnancy and had been given a regime of folic acid, antibiotics and thromboprophylactic drugs. Close monitoring of maternal and fetal well being was done by the hematologists and obstetricians. Among the patients, there were multiple admissions during the pregnancy for either a painful sickle cell bone crisis, haemolysis following an infection and anemia requiring phenotype- matched blood and exchange transfusions. Broad spectrum antibiotics coverage during and infection, hydration, pain management and venous-thrombolism prophylaxis were mandatory. The pregnancies managed to reach near term in the third trimester but all required emergency caesarean section for obstetric indications. All pregnancies resulted in live births with good fetal outcome. During post partum all were nursed closely in the high dependency units for further complications and were discharged well. Post partum follow up and contraception counseling was comprehensively given for future pregnancies. Sickle cell disease is uncommonly seen in the East, especially in the South East Asian region, yet more cases are seen in the current decade due to improved medical expertise and advance medical laboratory technologies. Pregnancy itself is a risk factor for sickle cell patients as increased thrombosis event and risk of infections can lead to multiple crisis, haemolysis, anemia and vaso-occlusive complications including eclampsia, cerebrovascular accidents and acute bone pain. Patients mostly require multiple blood product transfusions thus phenotype-matched blood is required to reduce the risk of alloimmunization. Emphasizing the risks and complications in preconception counseling and establishing an ultimate pregnancy plan would probably reduce the risk of morbidity and mortality to the mother and unborn child. Early management for risk of infection, thromboembolic events and adequate hydration is mandatory. A

holistic approach involving multidisciplinary team care between the hematologist, obstetricians, anesthetist, neonatologist and close nursing care for both mother and baby would ensure the best outcome. In conclusion, sickle cell disease by itself is a high risk medical condition and pregnancy would further amplify the risk. Thus, close monitoring with combine multidisciplinary care, counseling and educating the patients are crucial in achieving the safe outcome.

Keywords—Anemia, haemoglobinopathies, pregnancy, sickle cell disease.

I. INTRODUCTION

SICKLE cell disease (SCD) is initially found in the Sub-Saharan African continent and the Middle East region. Yet, over the past decades with wide trading and slavery, the disease can be found among those of African descent, in the Caribbean and Middle East regions, India, Mediterranean, including South and Central America [1]. Nowadays, with easily accessible transportation worldwide, intercontinental migration and marriage, it is not uncommon for cases to exist around the globe in other regions with wide phenotypic variations which still need further observation and studies to improve the health care among these patients [2].

SCD is single gene autosomal recessive inheritance disorders where sickled hemoglobin (Hb S) under low oxygen tension and certain stress conditions such as high altitude and ongoing infection, cause the Hb S intracellular molecules to polymerize, reducing its solubility and thus becomes stiff and rigid. The hemoglobin structure changes from disc-like to sickle shaped which exposes its surface membrane to molecules adhesion and adherence to vascular endothelium. This sickling conditions leads to vaso-occlusive events in micro vessels and premature disruption of hemoglobin which leads to chronic anemia. Further complications following vaso-occlusion in various organs especially if it involves vital organs includes acute chest syndrome, cerebrovascular accident, avascular necrosis of the bones, hemolytic anemia, sickle cell crisis, recurrent infection and pain which further contribute to higher morbidity and mortality [3].

SCD is a general term referring to the sickle hemoglobin disorders. There are classifications depending on the genotypes of the patients and usually resemble the severity of clinical presentation. *Sickle cell anemia (HbSS disease)* is homozygote for beta S globin which commonly presents with a severe or moderate severe phenotype. While *HbS/beta0 thalassaemia* is a severe double heterozygote for HbS and

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beta0 thalassaemia, yet the clinical presentation is almost interchangeable from sickle cell anemia itself. Double heterozygote for HbS and HbC are known as HbSC disease where the clinical presentation may be intermediate in severity. *HbS/beta+ thalassaemia* is known to have between mild to moderate severity, but studies have shown that it varies between ethnic groups. The are other genotypes with very mild or subtle presentation include *HbS/hereditary persistence of fetal Hb (S/HPHP)*, *HbS/HbE syndrome* and other rare combinations of HbS genotypes including HbD Los Angeles (Hb SD- Punjab), HbO Arab and G-Philadelphia [4]. Few case reviews reported wide variation among the major SCD due to the genotypic presentation and suggest looking at the detail phenotype presentation, while many focused on the adverse outcomes especially those pregnancy related [3]. Due to its uncommon presentation, most reports were retrospective over a period of years in which the management would differ from one case to another.

The evolving medical technology and advancement in current decades allows early diagnosis, prophylactic treatment and prevention of further complications. Multidisciplinary approach and combined care of these patients' results in better quality of life among SCD patients and longer life expectancy to the mid-50s [5]. Thus, allowing female patients to accomplish their obstetric carrier. Unfortunately, pregnancy itself is a risk factor for SCD patients due to its hypercoagulable state [4]. Physiological changes in pregnancy predisposes SCD patients to multiple maternal complication including recurrent miscarriages, preeclampsia, acute chest syndrome, deep vein thrombosis, recurrent pain crisis, recurrent infection and anemia with risk of blood transfusion [2]. The fetus is at risk of intrauterine growth restriction, intrauterine death, and prematurity which contributes to higher maternal and perinatal morbidity and mortality [1]-[3]. Thus, comprehensive care with multidisciplinary approach throughout gestation is required for reducing the risk to both mother and fetus.

II. OBJECTIVE

The aim of this paper is to review the management practices of SCD patient during pregnancy and the maternal and neonatal outcome in Ampang Hospital, Malaysia over the last seven years. The discussion from this review is meant to improve the care between disciplines managing the patient throughout the gestation and post partum period.

III. METHODS

All Sickle cell patients' records at the Hematology Clinic Ampang Hospital were reviewed retrospectively with their confidentiality preserved. Only pregnant patients with SCD under follow up over the last seven years (2009-2016) were reviewed for antenatal and post partum management practice. The maternal and fetal outcomes were compared and recorded.

IV. REVIEWED RESULTS

A. Case Reviews

Ampang Hospital situated in the state of Selangor, which is just a few blocks away from the capital city of Malaysia, Kuala Lumpur. The distribution of sickle cell patients in Malaysia were sparse and only found in a certain state. Throughout the seven years under review, seven sickle patients were under follow up of the Hematology Clinic, Hospital Ampang with three male and four female patients between the reproductive ages. Only three of the patients were pregnant under our care for the last seven years. Their pregnancies were monitored closely and outcomes were recorded with combine care between hematologist and obstetricians.

B. Genotype and Diagnosis

The first two patients, Indian ethnic in origin, had sickle cell anemia (HbSS disease) which was homozygous. Their diagnoses were made when they were young as they were closely related. The third patient was a young Malay ethnic with compound heterozygous for sickle Beta (β) thalassaemia with heterozygous Constant Spring. All their spouses were screened for haemoglobinopathies and were negative.

C. Antenatal Care

The first two patients were both in their third pregnancy and the third patient was a primigravidae. All three of them were seen early in the first trimester. The first and third patient were on oral hydroxyurea due to a recurrent bone crisis prior to the pregnancy, and the medication was stopped once the pregnancy was confirmed. All patients were given folic acid, penicillin V as prophylactic antibiotic, low dose aspirin and low molecular weight heparin for thromboprophylaxis. The third patient only received low dose aspirin, and they were counseled for adequate hydration and possible worsening pain crisis, risk of infections and worsening anemia throughout the pregnancy. All three of them were noted to be moderately anemic at antenatal booking visit yet clinically asymptomatic. The patients were referred early to the obstetric unit and they were seen frequently between 2 to 4 weekly alternating between obstetricians and hematologist. The maternal and fetal conditions were monitored closely for any possible complications.

The pregnancy in the second trimester for the second and third patients, seem to have progressed well. All of them managed to keep hemoglobin level above 8mg/dL. However, the first patient had a few episodes of painful bone crisis requiring regular opioids during the second trimester and was managed as an outpatient. While only the second patient managed to benefit detail fetal morphological scan as part of a prenatal screening. Otherwise all fetal growth was satisfactory during this gestation without evidence of growth restriction.

A stormier episode for these patients was recorded during the last trimester. The first patient was admitted for community acquired pneumonia with left parotitis at 31 weeks of gestation, followed with worsening haemolysis anemia. She recovered well with broad spectrum antibiotics and

phenotype-matched blood transfusion. Unfortunately, she was readmitted again at 37 weeks of gestation with another episode of worsening hemolytic anemia complicated with symptoms of obstructive jaundice. She was treated with exchange transfusion and subsequently went into labor. An emergency caesarean section was performed in view of two previous caesarean scars in labor and tubal ligation was performed as she completed her family.

The second patient presented with severe bone crisis at 35 weeks of gestation, whereby she was admitted, required an escalating dose of opioid drugs and managed by the anesthetic team. She was planned for exchange transfusion, yet there was no phenotypically compatible blood available. Her thromboprophylaxis was continued together with good hydration. During this admission, fetal well-being was monitored and evidence of distress noted; thus, an emergency caesarean delivery was performed due to fetal compromise. The third patient was admitted at 33 weeks of gestation with a painful sickling bone crisis. During this admission, the patient was given opioid as analgesia, covered with low molecular weight heparin as thromboprophylaxis and broad spectrum antibiotics; she recovered well a few days later and her medications were continued. She presented again at completion of 37 weeks gestation with pre-labor rupture of the membrane, and was subsequently induced with prostaglandins. Unfortunately she did not progress, and therefore, caesarean section for obstetric indication was done. All surgeries were uncomplicated and there was no post partum hemorrhage.

D. Post Partum Care and Outcome

In view of the crisis events preceding the delivery, the first two patients were nursed closely in a high dependency unit for any possible worsening complication with combined care between the obstetricians, hematologist and anesthetic team. The hemoglobin was optimized with phenotype matched blood transfusion. Broad spectrum antibiotics and thromboprophylaxis were given. Adequate pain controls were ensured with opioids together with good hydration. The third patient recovered well post delivery and was discharged with antibiotics, thromboprophylaxis and adequate analgesia. Upon discharge, all patients were extensively counseled regarding contraception and planning for their future pregnancies and associated complications.

All the babies had good weight upon delivery between 2.8 kg to 3.3 kg and their APGAR scores in one minute were 9. The babies were nursed in the neonatal intensive care unit (NICU) as protocol for observation and discharged well. Subsequent hemoglobin screening of the babies revealed both HbSS disease patients had an HbS trait child, while the third patient with compound heterozygous for sickle Beta (β) thalassaemia with heterozygous Constant Spring child showed Beta (β) thalassaemia trait.

V. DISCUSSION

Despite SCD being commonly seen in some parts of the globe, it is still less common in South East Asian region. Yet

more cases were reported and managed with growing expertise and advancement in medical technologies. Although there were few reported cases from Malaysia on sickle cell patients, growing expertise with interest and medical technologies has made the diagnosis possible, made it easily accessible and the management were up to date. Malaysia is unique in a way that it has large diversities and mixture of ethnical origin which may have different sets of inherited haemoglobinopathies [6]. A study by Lie-Injo LE et al. in 1986 revealed that a small population of Indian estate workers in Negeri Sembilan, Malaysia, which originates from Orissa, India had a higher frequency of HbS yet with milder symptoms and had longer life span up to 60 years of age. Among the 12 sickle cell anemia patients screened, all had alpha-thalassemia2 (alpha-thal2), either in the homozygous or heterozygous condition [7].

Pregnancy itself is a risk factor for sickle cell patients as increased thrombosis event and risk of infections due to the immunosuppressive state can lead to increased incidence of crisis, haemolysis, anemia and vaso-occlusive complications including eclampsia, cerebrovascular accidents, renal complications and acute bone pain [8]. The unborn fetus is at risk of recurrent miscarriages, second trimester loss, intrauterine growth restriction and even death due to severe placenta hypoxia following insufficient placenta blood flow. It is a vicious cycle where poor placental blood flow increases the risk of hypertensive disease in pregnancy and preeclampsia. Studies shows that on top of the above mentioned complication, there were increased risk of admission up to 60%, premature delivery, blood transfusions and operative delivery [3], [9].

Good preconception counseling is required for couples, with emphasis on the increased risk of morbidity and mortality to the patient and unborn child. This will ensure good compliance to medication as well as to frequent hospital visits, where medications will be reviewed. Unintended pregnancies among these patients result in increased risks both to the mother and fetus. This is because the maternal health was not optimized and they were unable to benefit the preconception counseling and optimizing their health prior to embarking on a new pregnancy. This is the case for two of the patients in this review, who were having unplanned pregnancies. They only found that they were in early pregnancy while on hydroxyurea and medication, which was subsequently stopped. It is recommended that hydroxyurea treatment be stopped three months prior to conception, due to the teratogenicity found in animal studies, and that the patient be started on folic acid at the same time. A level 3 ultrasonography is recommended to rule out fetal abnormality if exposed, yet termination is not recommended [1], [10], [11]. These patients were subsequently started with a low dose aspirin by 12 weeks gestation as they were considered as in the high risk group for developing preeclampsia in view of the disease pathophysiology; although there was no specific evidence [1], [12].

Yet, there were known increased risk associated with thromboembolic events which increases the risk of maternal

morbidity and mortality [3], [13]. Thus, adequate hydration, the use of appropriate graduated compression stockings and low molecular weight heparin, especially during admission are highly recommended [1], [14]. Pregnancy itself is an immunosuppressive condition and patients are more susceptible to infection than normal populations. Although infections were not the main cause of morbidity among pregnant SCD patients, evidence has shown that sepsis was among the cause of death of young children with SCD in Brazil [15]. For pregnant SCD women the risk of infection is higher and can easily deteriorate; consequently, further worsening the hemolytic anemia, as in our case review. Thus early and prompt management for risk of infection are crucial in reducing morbidity.

All the patients reviewed were anemic from the outset of the pregnancy and required multiple blood product transfusions at the later trimester. Although iron supplementation is generally recommended during pregnancy to reduce the incidence of anemia, it is only recommended for pregnant SCD patients if there is evidence of iron deficiency [1]. SCD patients were usually anemic but the severity and clinical presentation varies depending on their genotypes. Up to 50% of sickle cell anemia patients have received blood transfusions at some stage in their life [16]. Thus, blood transfusion is common and at times requires exchange transfusion due to the severe haemolysis. SCD patients are exposed to various antigens due to multiple blood transfusions. This is the main reason that the use of phenotype-matched blood is mandatory to reduce the risk of alloimmunization and hemolytic transfusion reaction which can increase morbidity and mortality. Studies have shown that a patient who has received more than 10 transfusions throughout their life-time has a higher risk of developing alloimmunization ($p=0.005$) [16]. Although previous studies show a decrease in maternal and perinatal morbidity with prophylactic blood transfusion, but it is now debatable as evidence of alloimmunization, delayed transfusion reactions, and possible transmission of infection and the risk of iron overload were higher [3], [17]. It is recommended to assess the patient clinically together with their hemoglobin levels as a guide, phenotype matched blood for transfusions and cytomegalovirus free infection [1].

A painful crisis is one of the major causes for admission of all SCD patients, similarly with the patients of this study. Studies have revealed that some 27% to 50% of SCD present with a painful crisis [18], [19]. However, it is very important to assess and determine the cause of pain as it could be due to more serious complications such as acute chest syndrome, sign of sepsis or another sickling event. The use of milder analgesia such as paracetamol and weak opioids between 12 weeks and 28 weeks of gestation is recommended on top of rest and adequate hydration [1]. However, in cases of more severe pain, the use of morphines as stronger opioids are recommended with monitoring and combined care between the obstetrician, hematologist and anesthetist. The use of pethidine was strongly discouraged as evidence showed an increased risk of seizures [20].

All three patients delivered via emergency caesarean section due to the obstetric indications with combined care between multidisciplinary team management. Although the findings seem to agree with those of other studies that show increased risk of operative delivery among SCD patients, all the subjects of this study had uncomplicated outcomes. The babies had good birth weight upon delivery and a good APGAR score. Considering the observation number of this study was small, larger multicentered observation is recommended to be conducted. Post partum care is very crucial as patient should be closely monitored for further complications including risk of thromboembolism. Furthermore, these patients underwent a caesarean delivery and were already at risk prior to the delivery itself, and therefore, the use of low molecular weight heparin should be continued till six weeks post partum. Good post natal counseling on adequate hydration, contraception and family planning, compliance to subsequent follow up and medications should be emphasized. Screening for the risk of inheritance of the newborn child should be counseled and conducted between the hematologist and pediatric team. Close monitoring of the maternal and fetal well being with hematologists, obstetricians, anesthetist and neonatologist throughout the antenatal period and continuing to post partum care, and including the patients' family, should be conducted to ensure the best outcome for both mother and baby.

VI. CONCLUSION

Pregnancy with SCD is a high risk medical condition with increased risk of maternal and perinatal morbidity and mortality. However with growing expertise of the disease, good medical technology updates and healthcare services, SCD patients are able to reach live birth pregnancies. Yet, preconception counseling is very important, emphasizing on the increased risk of complications, the need of more frequent hospital visits and medications should be revised. Management throughout the gestation period includes adequate hydration, prompt treatment of infections with antibiotics, thromboprophylaxis coverage, adequate pain control, and phenotype-matched blood to reduce the risk of alloimmunization with combined multidisciplinary care between the hematologist, obstetricians, anesthetist, pediatricians and nursing staff is very crucial in achieving the best outcome. It is hoped that this multicenter review of SCD cases, the current management practices and maternal fetal outcomes will reflect a better picture of the management of this disease, which is uncommon in the region.

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