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INCIDENCE OF INTRAUTERINE GROWTH RETARDATION IN PREGNANCIES WITH AND WITHOUT SICKLE CELL DISORDER : A SINGLE CENTRE STUDY

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ABSTRACT

Objective - This study was to evaluate the difference in incidence of intrauterine growth retardation in pregnancies with and without sickle cell disorder.

Material and methods - This study consisted 44 sickle cell disease (SCD), 95 sickle cell trait (SCT) and 241 normal pregnancy group totalling 380 pregnancies. Study population were matched for age, gravidity and mean blood pressure. Foetal biometric evaluation was done in 2nd or 3rd trimester as and when presented. Estimated fetal weight <10th percentile are considered growth retarded (IUGR).

Result - In 2nd trimester 23.8% of foetuses of SCD group, 6.7% of foetuses in SCT group and 6.1% of control pregnancy group foetuses were growth retarded. In 3rd trimester 33.3% of foetuses of SCD pregnancy group, 17.8% of foetuses in SCT group and 10.5% of foetuses in normal pregnancy group were growth retarded. Significant difference in growth retardation was found between study groups as evaluated during 2nd(p=0 .024) and 3rd trimester (p=0.022).

Conclusion - SCD and SCT pregnancies are associated with increased risk of IUGR which is more prevalent in SCD pregnancies. Early diagnosis of IUGR is possible by ultrasonography in 2nd trimester. With timely management we can improve the fetal growth and its outcome.

KEYWORDS : pregnancy, intrauterine growth retardation, foetal biometry.

Introduction - Sickle cell disease (SCD); an autosomal recessive hemoglobinopathy characterized by "sickle-shaped" appearance of RBC's wherein glutamic acid is replaced by Valine at 6th position in beta-globin chain which is hydrophobic, causing the haemoglobin to collapse on itself and the red blood cells become sickle-shaped1. It was first described in 1910, in a dental student who presented with pulmonary symptoms. In people diagnosed with sickle cell disease, both of the beta-globin subunits is replaced with haemoglobin S (HbS). In milder form only one beta globin chain is replaced by HbS and is known as sickle cell trait or carrier.

SCD is the most common haemoglobinopathy to complicate pregnancy, it affects approximately 100 million pregnancy worldwide2 . In Chhatishgarh state prevalance is very high (9.50%) of which 9.30% are carrier while 0.21% are suffering from sickle cell disease with highest frequency found among the tribal population[3].

Better health facilities has improved survival rate in patients of SCD thus more number of womens reaching to the reproductive age. As with other major organ system; vaso-occlussive process in SCD also affect gravid uterus and placenta which causes risk to both mother and the foetuses[4].

Intra uterine growth retardation (IUGR) is a common diagnosis in obstetrics and carries an increased risk of perinatal mortality and morbidity5. As there is high prevalence of sickling in state of Chhattisgarh; our study aim to evaluate the difference in incidence of IUGR in pregnancies with Sickle cell disease, Sickle cell trait and in normal pregnancies with the help of ultrasound assisted foetal biometric evaluation.

Material and methods – Study was conducted in department of Radiodiagnosis, Pt. JNM medical college Raipur, Chhatishgarh, India for the time period of 20months from February 2016-September 2017. It is a comparative, longitudinal, analytical study consist of total of 180 pregnant women of which 21 are sickle cell disease, 45 are sickle cell trait and 114 are normal pregnant women. Clearance granted from ethical committe of the institution.

Inclusion criteria – 1. Pregnant women 18 to 35yrs of age referred to Department of Radiodiagnosis, Dr. Bhimrao Ambedkar memorial hospital Raipur CG, 2.Pregnant women with sickle cell disease, 3.Pregnant women with sickle cell trait hemoglobinopathy, 4.Normal pregnant women, 5. Singleton pregnancy. 6. 2nd and 3rd trimester pregnancy. Exclusion criteria – 1. Pregnant women below 18 and above 35 yrs, 2.Known foetal congenital anomaly or IUGR caused by condition other then sickling, 3.Patient not willing to take part in study, 4.Multi foetal gestation, 5.Short stature women (height <145 cm). Equipment used - Mindray ultrasound machine with curvilinear transducer of 3.5-5 MHZ.

Head Circumference (HC) -: It is measured in axial plane that traverses through the thalami and cavum septum pellucidum (figure 1a). The transducer is kept perpendicular to the central axis of the head so the calvaria and hemisphere appear symmetrical.

An ellipse is drawn through the outer wall of the calvaria. Alternatively head circumference can be calculated from the biparietal diameter(BPD) and occipitofrontal diameter (OFD) by using the following formula7: $HC = 1.62 X (BPD+OFD)^3$

Biparietal Diameter (BPD) -: It was measured in axial plane that traverses the thalami and cavum septum pellucidum (figure 1a). The transducer is kept perpendicular to the central axis of head so the calvaria and hemisphere appear symmetrical. The callipers are placed at the outer edge of the near calvarial wall and inner edge of far calvarial wall[8].

Abdominal Circumference (AC) -: It is measured in transverse or axial plane which is passing through the upper abdomen including foetal stomach, umbilical vein and portal sinus in single axial plane (figure 1b). Kidneys and insertion of umbilical cord should not be visible and umbilical vein should not be seen upto the skin line9. Callipers are placed on the skin surface.

Femur Length (FL) -: The longest femur measurement (figure 1c) excluding both proximal and distal epiphysis is done[10].

Amniotic Fluid Index (AFI) -: Uterus is divided into four imaginary quadrants with linea nigra and umbilicus acting as the vertical and the

horizontal axis respectively.The deepest pocket devoid of umbilical cord and foetal parts is measured in the vertical dimension (figure 1d). Sum of all the four quadrant measurements is AFI in centimeter. The normal range for amniotic fluid volumes varies with gestational age. Typical values include, sum of the four pockets totalled.

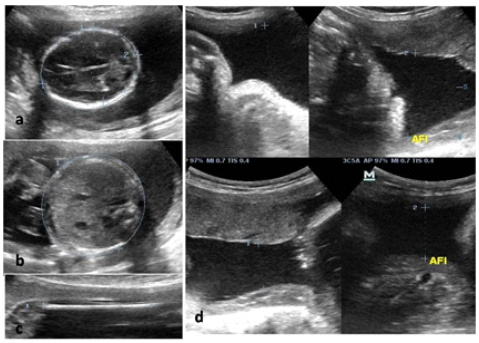

Figure 1-: Axial transthalamic plane for measurement of BPD /HC/OFD (a), axial section through upper abdomen for measurment of AC (b), long axis od femur for measurement of FL (c) and four quadrant measurements of AFI (d).

AFI between 8-18 cm is considered normal; median AFI level is ~14 cm from week 20 to week 35, after which the amniotic fluid volume begins to reduce. AFI <5 cm is considered as oligohydramnios. The value changes with age: the 5th percentile for gestational ages is most often taken as the cut off value, and this around an AFI of 7 cm for second and third trimester pregnancies; and AFI of 5 cm is two standard deviations from the mean. AFI >20-24 cm is considered as polyhydramnios[11]

"Small for date" fetus is defined as foetal weight less than 10th percentile for gestational age. True IUGR defined by the presence of any of the factors associated with a poorer perinatal outcome, including doppler cerebroplacental ratio, uterine artery, ductus venosus and aortic isthmus doppler (figure 2) and a growth centile below the 3rd centile5,6. The gestational age was determined by the first day of last menstrual period and confirmed by the 1st trimester ultrasound. After obtaining well informed written consent, detail obstetric history, family history, present and past history, blood pressure and maternal height was recorded. Foetal ultrasound was performed at 2nd or 3rd trimester. During examination patients were lying supine. Head circumference, biparietal diameter, abdominal circumference and femur length was measured. Foetal heart rate was measured using M-mode and Amniotic fluid index(AFI) was calculated. Comparison of gestational age between study groups at second and third trimester was performed using ANOVA. Hadlocks formula used for calculation of estimated foetal weight and if the foetal weight is less than 10th percentile for gestational age foetus is considered growth retarded. The whole examination did not exceed 15-30 min. Comparison of growth retardation between study groups was performed using Chi-square test.

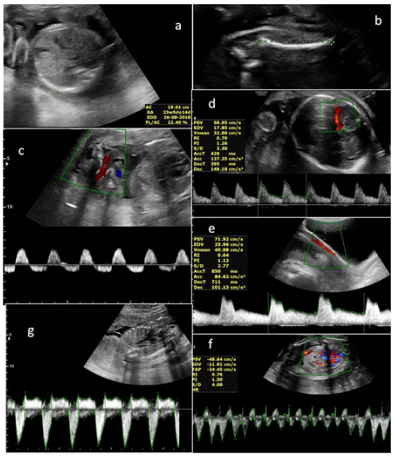

Figure 2-: Ultrasound B-mode & dopplor images in an IUGR pregnancy demonstrating axial section through upper abdomen for AC (a), long axis view of femur FL (b), umbilical artewry waveform display diastolic flow reversal (c), MCA waveform reveal reduced PI with reversed cerebro-placental ratio (d), uterine artery waveform show early diastolic notch with increased S/D ratio (e) & diastolic flow reversal in ductus venosus (f) & aortic isthmus (g) suggestive of uteroplacental insufficinecy with fetal acidosis.

Placental grading (Grannum Classification) -: Based on its maturity placenta grading on ultrasonography done using Grannum classification. An early progression to a grade 3 placenta is concerning and is sometimes associated with placental insufficiency[12,13].

Result – Total 380 patients were selected between the age group of 18-35 years with mean age of 24.1years in SCD group & 23.1years for SCT and normal pregnancy group.

Mean gestational age of fetuses undergone 2nd trimester ultrasound examination was 22.9weeks for both SCD and 22.8weeks for both SCT group and normal pregnancy group. Mean gestational age of fetuses undergone 3rd trimester ultrasound examination was 33.9weeks for both SCD and SCT group and 33.4weeks for normal pregnancy group. No significant difference was noted in gestational age between study groups in 2nd (p=0.994) and 3rd (p=0.663) trimester indicating that the three study groups were matched for gestational age.

Study groups were matched for mean systolic and diastolic blood pressure with comparison done performed using ANOVA.

Incidence of foetal growth retardation was 23.8% in SCD subjects, 6.7% in SCT and 6.1% in normal pregnancy group. Comparison of growth retardation between study groups at 2nd trimester was performed using Chi-square test. P value =0.024 suggest significant difference in incidence of growth retardation between study group (Table 1).

Table 1: Comparison of growth retardation between study groups at 2nd trimester

Growth retardation in 2nd Trimester	Group			Total
	SCD	SCT	Normal	
Normal	16	42	107	165
	(76.2%)	(93.3%)	(93.9%)	(91.7%)
Growth retardation at 2nd trimester	5	3	7	15
	(23.8%)	(6.7%)	(6.1%)	(8.3%)
Total	21	45	45	180

Likewise during 3rd trimester ultrasound examination (Table 2) 33.3% of foetuses of SCD group were growth retarded and 66.7% of foetuses were of normal weight, in SCT group 17.8% of foetuses were growth retarded and 82.2% of foetuses were of normal weight, in normal pregnancy group 10.5% of foetuses were growth retarded an 90.5% of foetuses were of normal weight. Comparison of growth retardation between study groups at 3rd trimester was performed using Chi-square test show significant difference (p=0.022) in incidence of growth retardation among study groups.

Table 2. Comparison of growth retardation between study groups at 3rd trimester

Growth retardation in 3nd Trimester	Group			Total
	SCD	SCT	Normal	
Normal	15 (66.7%)	41 (82.2%)	114 (89.5%)	170 (85.0%)
Growth retardation at 3rd trimester	8 (33.3%)	9 (17.8%)	13 (10.5%)	30 (15.0%)
otal	23	50	127	200

Discussion-

SCD is proposed to be a chronic inflammatory state; wherein endothelial damage secondary to sickled red blood cells and the subsequent release of proinflammatory cytokinesmay contribute to microvascular damage. Physiological adaptations during pregnancy may lead to exacerbation of these pathophysiologic changes. Studies

have shown association between SCD, abnormal mid-trimester uterine artery doppler waveforms, abnormal placental histology (villous sclerosis, intervillous fibrin deposits, and infarction), and subsequent delivery of small for gestational age infants[13].

The effect of sickle cell trait in pregnancy is less clear however the stress of pregnancy modifies the situation, crisis can occur in severe anaemia, dehydration, vigorous exertion and high altitude2 and may complicate the pregnancy and adversely affect the maternal and foetal health.

In a meta-analysis by Oteng-Ntim et al 14; they identified a strong association between SCD and adverse outcome for the mother (including maternal mortality and preeclampsia) and baby (including perinatal death, preterm delivery, and small for gestational age infants).

In our study, among SCD pregnancy group (N=44) 13 (29.5%) patients, among SCT pregnancy group (N=95) 12(12.6%) and among normal pregnancy group (N=241) 20 (8.3%) patients have IUGR.

In study done by Elenga et al15. They found the incidence of IUGR in pregnancies with SCD was 24.2%. This difference in incidence of IUGR may be due to racial difference, nutritional difference, difference in health care facility and number of subjects included in the study.

In a retrospective study done Desai et al16 ; among tribal maternal admissions in the community-based hospital of SEWA Rural (Kasturba Maternity Hospital) in Jhagadia block, Gujarat. 10519 pregnancies were included in the study out of which 131 were SCD, 1645 were SCT and rest were non sickle cell pregnancies. They found that 3 out of 131 SCD pregnancies i.e. 2.3% have IUGR, 31 out of 1645 SCT pregnancies i.e. 1.9% have IUGR and 134 of non Sickle cell pregnancies i.e. 1.6% have IUGR. Among sickle cell deliveries, 70.2% were low birth weight compared to 43.8% of non-sickle cell patient.. This difference in incidence of IUGR from our study may be due to difference in number of subjects included in study, difference in health care facility and regional incidence.

In a study done by Boafor et al17 found that women with SCD have 3 times more chances of having IUGR baby as compared to control group i.e. pregnant women without SCD. Findings are comparable with results in our study.

In a study done by Leticia C et al 18 on abnormal expression of inflammatory genes in placentas of women with sickle cell disease and sickle hemoglobin C; they found that the IUGR was present in 28.6% of sickle cell disease pregnancy while 0%. in HbSC pregnancy and normal pregnancy.

Tan et al19 conducted a retrospective study to assess the incidence of small for gestational age babies in pregnant women with sickle cell trait anemia in St. Thomas hospital London. A total of 16.8% of small for gestational age babies were identified in sickle cell trait pregnancies, while in our study prevalence of IUGR in SCT group is 17.8% which is comparable with this study.

In a study done by ML Kahansim et al20 . Pregnancy outcome among patients with sickle cell disease in Jos, north central Nigeria found that the intra uterine growth restriction was found in 45.7% of pregnancies while in our study IUGR is present in 33.3% of SCD pregnancies, this difference in IUGR may be due to difference in genetics of sickling, difference in number of subjects, difference in health care facility and regional incidence.

Conclusion - In conclusion, normal physiological vascular and hemodynamic adaptations during pregnancy exacerbate the risk of pathophysiological changes associated with SCD. thus sickle cell disease and sickle cell trait pregnancies are associated with increased risk of intrauterine growth retardation and other maternal complications. Early diagnosis of fetal growth retardation is possible by ultrasound examination in 2nd trimester, with proper management we can improve the fetal growth and its outcome.

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