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Study of placental maturity by ultrasound in pregnancy with sickle cell disease/trait & correlation with normal pregnancy

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Abstract
Aims and Objectives: The aim of the study is to evaluate the effect of sickle cell disease/trait on the maturation of placenta and further correlation with maturation of placenta in normal individuals.
Material and Methods: Antenatal ultrasound of 45 pregnant patients from each three different categories (i.e., sickle cell disease; sickle cell trait and normal) was done. Sickle cell disease (SCD) and Sickle cell trait (SCT) patients were diagnosed on the basis of serum electrophoresis test. The degree of placental maturation, thickness and location of the placenta evaluated. The data collected from the subjects then further compared for any difference between the degree of maturity between three study groups.
Results: The correlation between placental grading and gestational age in all three categories was not statistically significant (P value > 0.05).
Conclusion: There is no significant difference noted among all the three categories in term of placental maturation and fetal weight measures.

Keywords: sickle cell disease, sickle cell trait, serum electrophoresis, antenatal ultrasound, placental grading

1. Introduction
Sickle cell disease is a genetic disease of autosomal recessive inheritance. [1] In individuals with sickle cell disease, both of the beta-globin subunits are replaced with hemoglobin S. In milder form only one beta-globin chain is replaced by Hemoglobin S and is known as sickle cell trait or carrier [2]. The SCD causes anemia and acute Vaso-occlusive crisis involving the major organ systems i.e., the heart, lungs, kidneys, brain, spleen, liver, intestinal tract, and long bones [3, 4].
Pregnant women affected with SCD experience these medical as well as vascular effects to the gravid uterus and placenta, which create additional risk for both women and their fetuses. [5] Yet data on pregnancy outcomes for Indian women with SCD and their offspring are limited [6]. The effect of SCT on pregnancy is less clear with conflicting evidence in the literature however, the stress of pregnancy modifies the situation. The sickling crisis in SCT women may occur in cases of extreme anemia, dehydration, acidosis, vigorous exertion and at high altitude. Sickle cell disease affects fetus in the form of Intra uterine growth retardation (IUGR), premature birth, Intra uterine fetal demise, fetal distress in labour and increased perinatal mortality and mother in the form of severe anemia, sickle cell crisis, pulmonary disease and infections etc. [7].
The Ultrasound evaluation of placenta can describe subsequent progressive sonographic changes in the placenta. The placenta undergoes series of progressive changes that relate to gestational age and fetal maturity. Remarkable changes are seen on gross and microscopic examination of placenta of patients with sickle cell disorders, hence the present study was undertaken to find out the pathological changes seen in the placenta of sickle cell disorders (trait and disease), as compared to normal pregnancy.

2. Materials and methods
This is an observational cross sectional descriptive study. This study was conducted from

March 2018-September 2019 at Department of Radio-diagnosis, Pt J.N.M. Medical College & Dr. B.R.A.M. Hospital, Raipur. Equal number of subjects (i.e., 45) from all three categories fulfilling selection criteria (Table. 1) included into the study and informed consent taken. Ultrasound evaluation was done with SAMSUNG RS80A ultrasound machine (Model no: USS- RS8CF4U/IN) with curvilinear probe of 3.5MHZ. The diagnosis of Sickle cell disease and Sickle cell trait patients were confirmed by serum electrophoresis test.

The placental grading, Head circumference, bi-parietal diameter, abdominal circumference and femur length was measured, fetal heart rate was measured using M-mode, Amniotic fluid index calculated and anomaly scan was done.

Ethical clearance: Taken from Ethics Committee, Pt. Jawaharlal Nehru Memorial Medical College and associated Dr. BRAM Hospital Raipur and head were contacted and informed before purpose of study.

Statistical analysis: Chi square test is used to analyze the significance of difference between distributions of the data. One way ANOVA test was used to compare the mean difference between different groups. P value <0.05 is considered as statistically significant.

3. Results

Data of 45 pregnant women from each three different categories i.e., sickle cell trait, disease and normal; are collected. The age wise distribution of study subjects reveals that in each study group maximum study subjects were between 20-25 years of age group i.e. (45.45%), (51.06%) and (48.88%) in Sickle cell trait, sickle cell disease and normal pregnant women respectively (figure 1).

In sickle cell disease patient maximum 23 study subjects with gestational age of 32-37 weeks, of that (56.52%) 13 had their placenta grade III and 18 with gestational age of 26-32 weeks, (44.44%) 8 had placenta grade III. Association between placenta grading and gestational age in sickle cell disease patient was not statistically significant (P value > 0.05) (figure 2A).

In sickle cell trait cases maximum 24 study subjects with gestational age of 32-37 weeks, of that (57.7%) 15 had their placenta grade II and 16 with gestational age of 26-32 weeks, (37.5%) 6 had placenta grade II. Association between placenta grading and gestational age in sickle cell trait cases was not statistically significant (P value > 0.05) (figure 2B).

In normal study subject's maximum 19 with gestational age of 32-37 weeks, of that (52.6%) 10 had their placenta grade II and 21 with gestational age of 26-32 weeks, (52.9%) 9 had placenta grade III. Association between placenta grading and gestational age in normal pregnant cases was not statistically significant (P value > 0.05) (figure 2C).

The placental grading correlation with estimated fetal weight (EFW) in sickle cell disease patient reveals maximum 24 cases has placenta grade-III of that (41.7%) 10 were between 2-2.5kg, 13 patients have placenta Grade-II of that (46.2%) 6 cases were between 2-2.5kg ,5 patients have placenta Grade-I of that (60%) 3 cases were between 2-2.5kg and 3 cases has placenta grade-0. Association between placenta grading and EFW in sickle cell disease patient was not statistically significant (P value > 0.05) (figure 3A).

In sickle cell trait cases maximum 22 cases have placenta grade-II of that (36.4%) 8 cases were >2.5kg, 11 cases have placenta grade-III of that (45.5%) 5 cases were >2.5kg, 8 cases have placenta Grade-I of that (37.5%) 3 cases were each between 1-1.5kg and 1.5-2 kg respectively. Association between placenta grading and fetal weight in sickle cell trait cases was statistically significant (P value < 0.05) (figure 3B).

In normal pregnant cases maximum 18 cases have placenta grade-III of that (33.3%) 6 cases were between 1.5-2kg, 17 cases have placenta grade-II of that (29.4%) 5 cases were between 2- 2.5kg and 9 cases has placenta Grade-I of that (44.4%) 4 cases were each between 1-1.5kg. Association between placenta grading and estimated fetal weight in normal pregnant cases was not statistically significant (P value > 0.05) (figure 3C).

In sickle cell disease patient, maximum 24 cases have placenta grade-III of that (41.7%) 10 cases had placenta thickness between 3-3.5 cm, 13 cases have placenta grade-II of that (38.5%) 5 cases each had placenta thickness between 3-3.5 cm and 3.5-4 cm respectively. Association between placenta grading and placental thickness in sickle cell disease patient was not statistically significant (P value > 0.05) (figure 4A)

In sickle cell trait cases, maximum 22 cases have placenta grade-II of that (36.4%), 11 cases have placenta grade-III of that (36.4%) 4 cases each had placenta thickness between 3.5-4. Association between placenta grading and placental thickness in sickle trait cases was not statistically significant (P value > 0.05) (figure 4B).

In normal pregnant mothers, maximum 18 cases have placenta grade-III of that (27.8%) 5 cases each had placenta thickness <3 cm and between 3.5-4 cm respectively, 17 cases have placenta grade-II of that (35.3%) 6 cases had placenta thickness between 3-3.5 cm. Association between placenta grading and placental thickness in normal pregnant cases was not statistically significant (P value > 0.05) (figure 4C).

4. Discussion

The cross-sectional study was used to evaluate the placental maturity of pregnant females with sickle cell disease, sickle cell trait & in normal pregnancies. The study included total 135 pregnant subjects.

The association between grading of placenta with gestational age in sickle cell disease, sickle cell trait and normal subjects is not statistically significant (P value > 0.05). The grading system is as follows:

Placental Grading (Grannum Classification)

- **grade 0:** <18 weeks
  - Uniform echogenicity.
  - Smooth chorionic plate.
- **grade I:** 18-29 weeks

1. Occasional parenchymal calcification/hyperechoic areas.
2. Subtle indentations of chorionic plate.

- **grade II:** 30-38 weeks
  - Occasional basal calcification/hyperechoic areas.
  - Deeper indentations of the chorionic plate (does not reach up to the basal plate) seen as comma type densities at the chorionic plate.

- **grade III:** ≥ 39 weeks
  - Significant basal plate calcification.
  - Chorionic plate interrupted by indentations (frequently calcified) that reach up to the basal plate cotyledons.

Our study demonstrated that the predominant placental grading is grade III in sickle cell disease patients 24/45 (figure 5). The predominant placental grading is grade II in sickle cell trait patients 22/45 (figure 6). The predominant placental grading is grade II & grade III in normal subjects 17/45 & 18/45 respectively.

A similar study by Das L *et al*. (2017) reported that there is a definite correlation between the grades of placenta and fetal outcome. In our study grade III placenta was seen mostly (35%) at 32-37weeks of gestation. A definite correlation is found between the advanced maturity of placenta and high-risk pregnancies like PIH, Intra uterine growth retardation (IUGR) and sickle cell anemia but a delayed maturity of placenta is seen in diabetes and Rh-negative pregnancies [8].

In our study the placental grading correlation with EFW in sickle cell disease patient is not statistically significant (P value > 0.05). Whereas, association between placenta grading and fetal weight in 45 sickle cell trait cases was statistically significant (P value < 0.05).

Hopper *et al*. (1984) noted that if the placenta appeared to be grade I prior to 27 weeks; grade II prior to 32 weeks and grade III prior to 34 weeks of gestation, the pregnancy would likely to be complicated with intrauterine growth retardation and preeclampsia [9].

Kazzi *et al*. (1983) also reported the association of grade III placenta with small for gestational age infants [10].

Mckenna *et al*. in (2005***)*** noted that ultrasound detection of a grade III placenta at 36 weeks gestation in a low- risk population helps to predict subsequent development of pregnancy induced hypertension and may help in identifying the growth- restricted baby [11].

Proud and Grant (1987) observed in a study of 2000 unselected pregnant women the development of mature placental appearance (grade 3) on USG by 34- 36 weeks' gestation in high risk (HT and APH) cases was associated with increased risk of low birth weight and perinatal death [12].

In our study placental grading correlation with placental thickness in sickle cell disease patient showed that association between placenta grading and placental thickness in sickle cell disease & trait patient was not statistically significant (P value > 0.05).

5. Tables and Graph

Table 1: Selection criteria

A. **Inclusion criteria**.
B. All diagnosed sickle cell disease /trait pregnant with gestational age 26 weeks to 40 weeks.
C. **B. Exclusion criteria**
1. Pregnancy with other hemoglobinopathy (Thalassemia, HbC, HbE).
2. Twin pregnancy,
3. Pregnancy with other complication i.e., hypertension, diabetes mellitus, Rh negative, smokers, oligo-hydramnios etc.
4. Pregnancy less than 26 weeks,
5. Not willing to give consent for study.

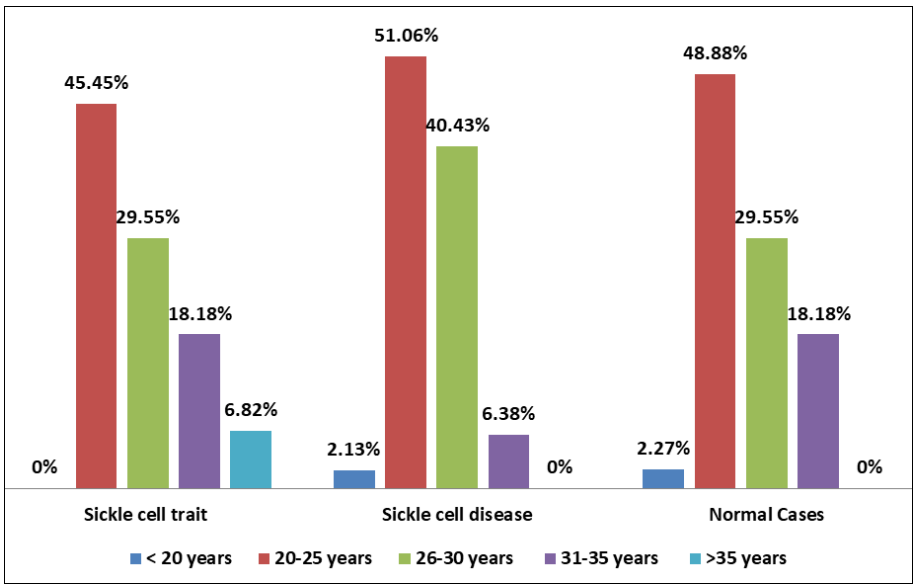

Fig 1: Age wise distribution of study subjects

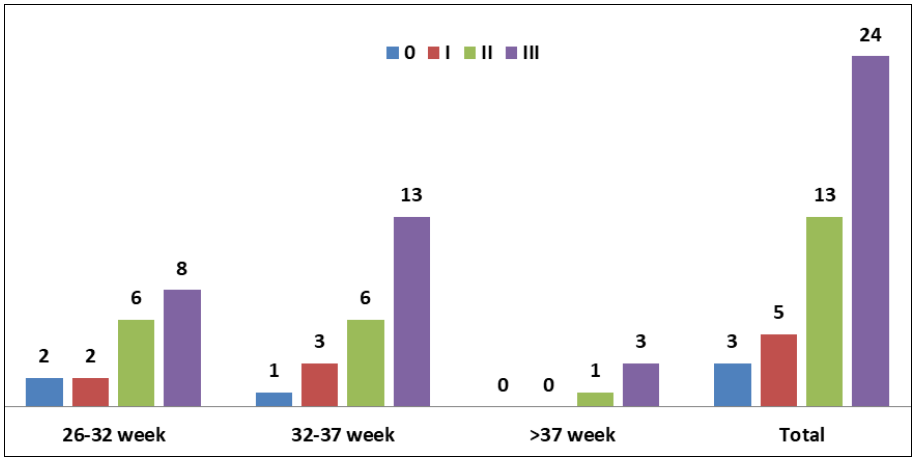

Fig 2A: Placental grading correlation with gestational age in sickle cell disease women

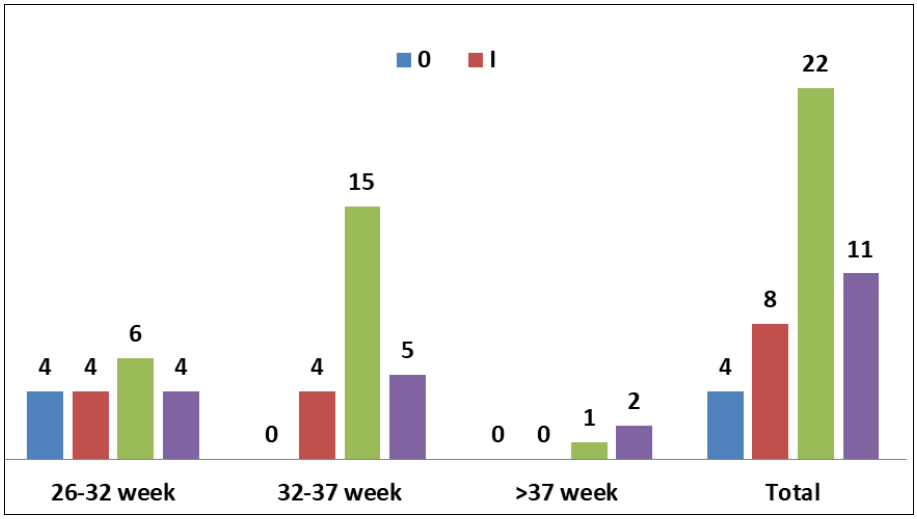

Fig 2B: Placental grading correlation with gestational age in sickle cell trait patient (N=45)

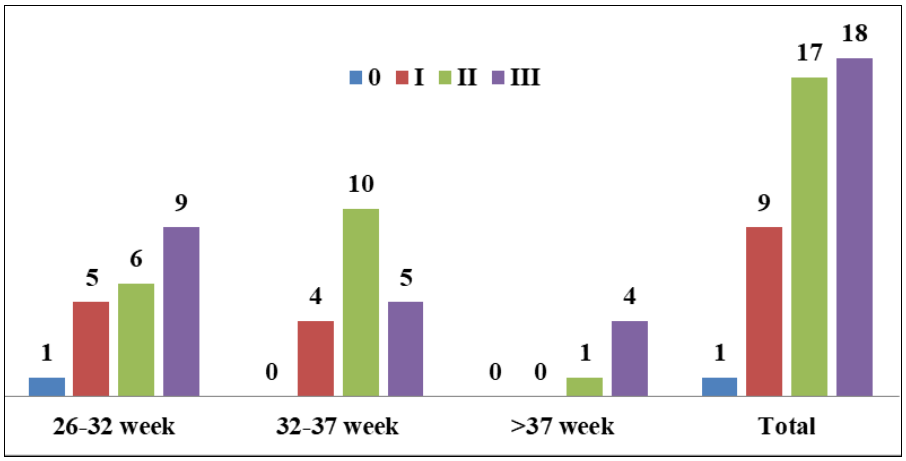

Fig 2C: Placental grading correlation with gestational age in normal pregnant patients (N=45)

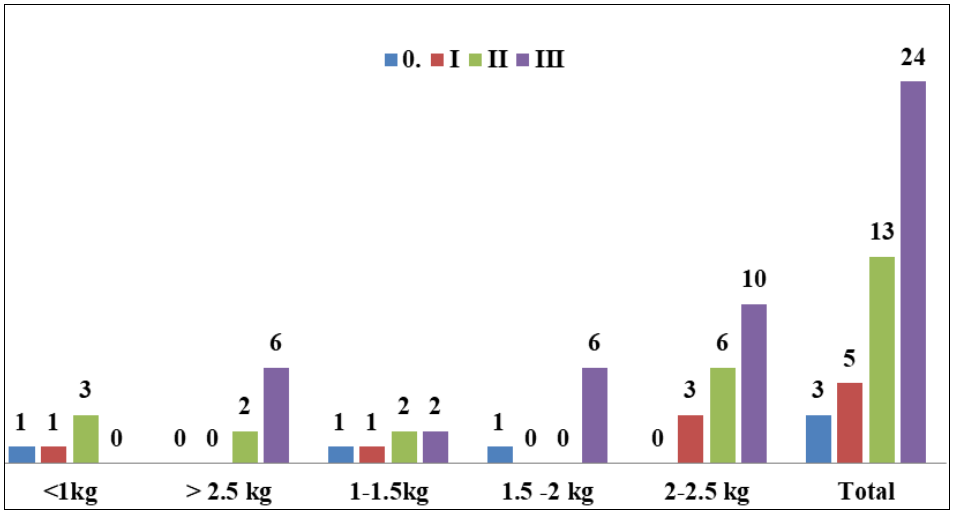

Fig 3A: Placental grading correlation with estimated fetal weight in sickle cell disease patient (N=45)

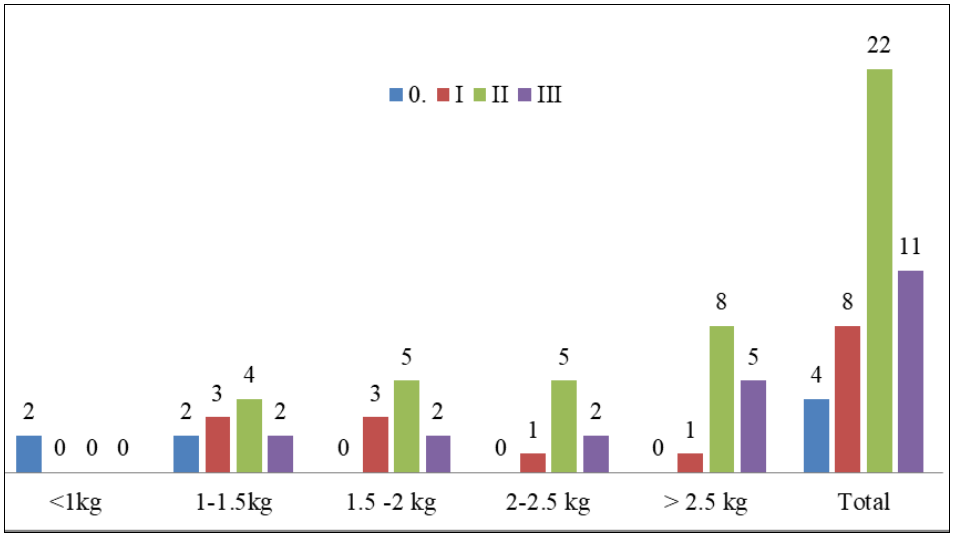

Fig 3B: Placental grading correlation with estimated fetal weight in sickle cell trait patient (N=45)

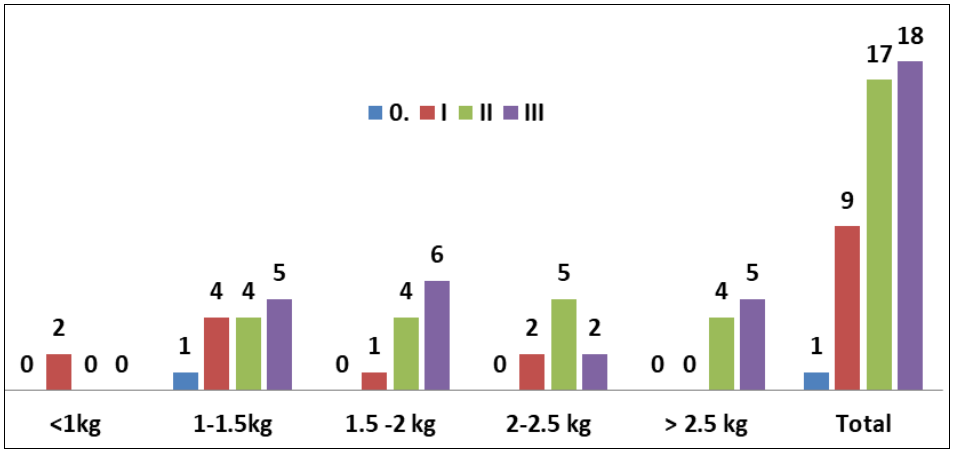

Fig 3C: Placental grading correlation with estimated fetal weight in normal pregnant patient (N=45)

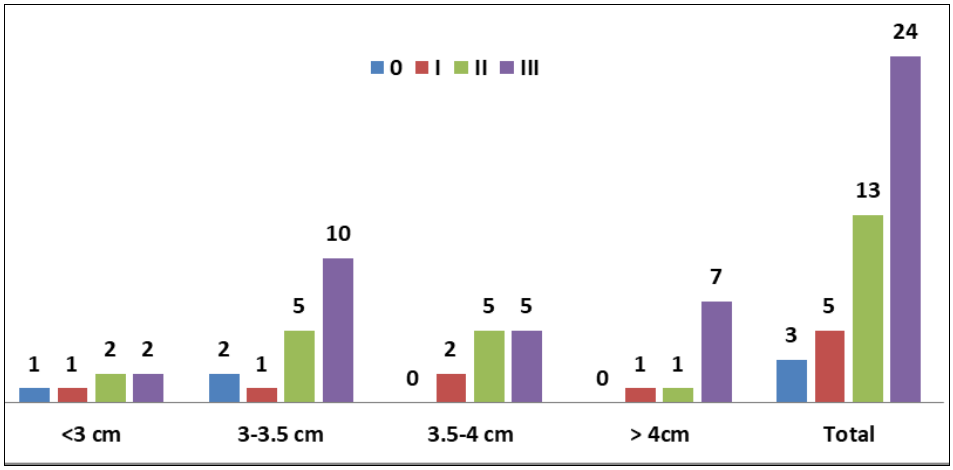

Fig 4A: Placental grading correlation with placental thickness sickle cell disease patient (N=45)

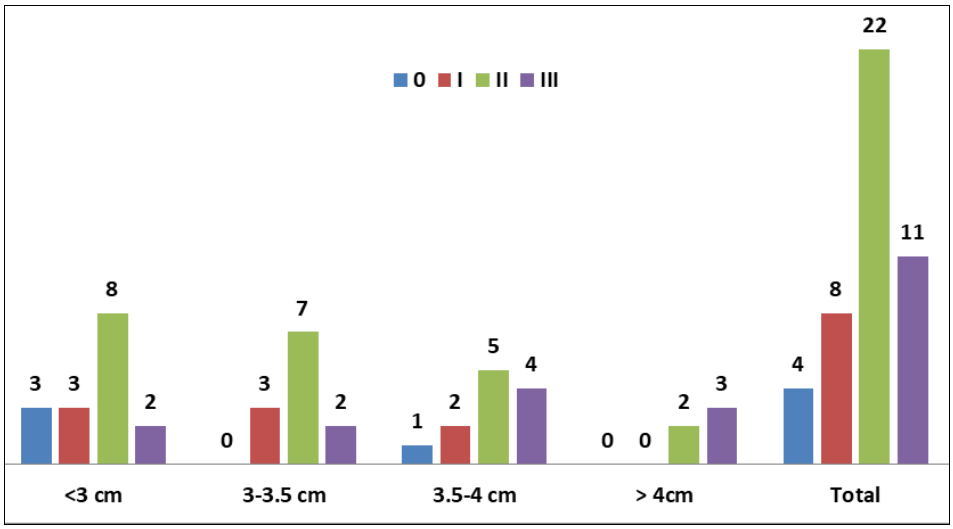

Fig 4B: Placental grading correlation with placental thickness sickle cell trait patient (N=45**)**

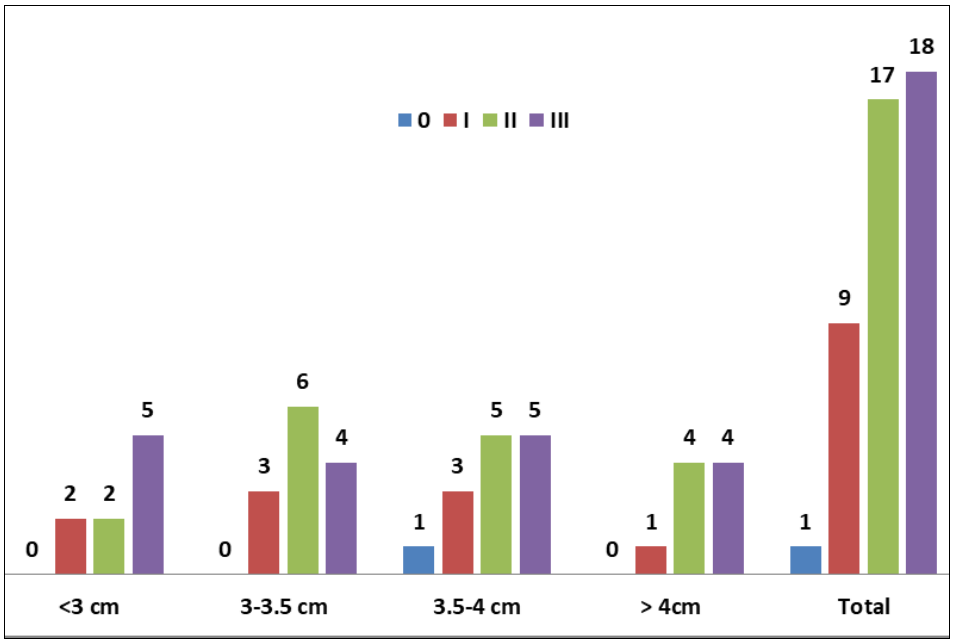

Fig 4C: Placental grading correlation with placental thickness normal pregnant patient (N=45)

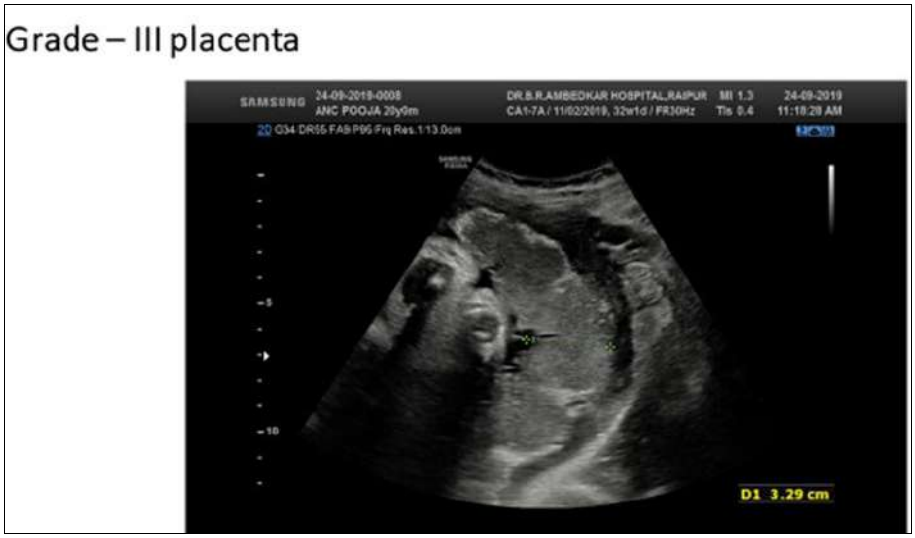

Fig 5: Grade III placenta**.**

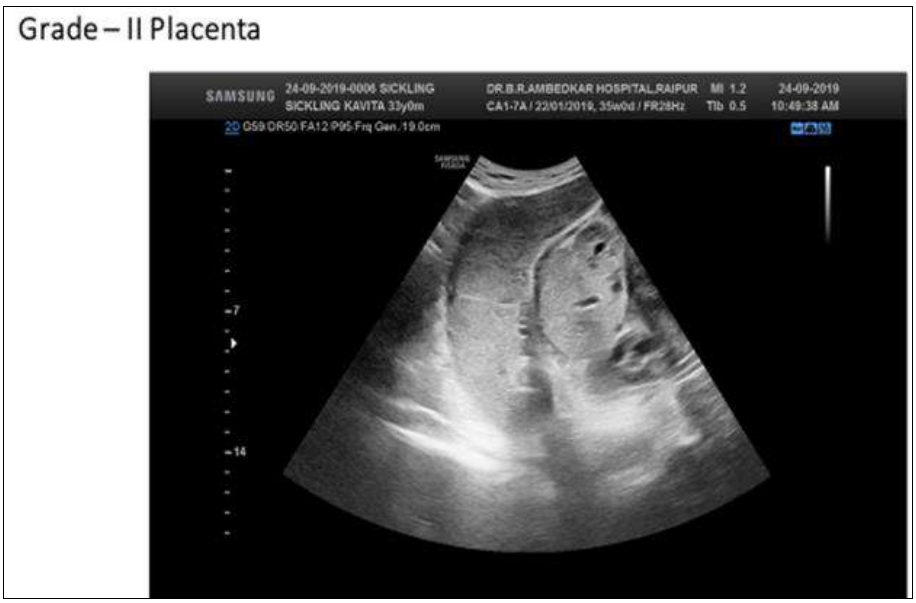

Fig 6: Grade II placenta

8. Conclusions

It is concluded that there is no positive correlation noted in sickle cell disease, sickle cell trait and normal pregnancy in term of placental calcification which determine the placental maturity. In term of fetal weight, no positive correlation seen in sickle cell disease, sickle cell trait and normal pregnancy.

9. Limitations

Placental grading can be correlated with AFI, maternal anemia & basal calcifications in further future studies.

10. Acknowledgments

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