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Effect of low maternal vitamin B12 status on fetal growth: A prospective cohort study in a tertiary care hospital of eastern India

Dr. Sandhya Rani Behera
Assoc. Professor, Department of O&G, SCB Medical College & Hospital, Cuttack, Odisha.
Email: Sandhyaranibehera74720@gmail.com

Dr. Anuja Jena
Resident, Department of O&G, SCB Medical College & Hospital, Cuttack, Odisha.
Email: anujajena01@gmail.com

Dr. Ranjita Patnaik
Assistant Professor, Department of O&G, SCB Medical College & Hospital, Cuttack, Odisha.
Email: drranjitapatnaik@gmail.com

Dr Jayashree Jayabharati Moharana
Assistant Professor, Department Of O and G, SCB MCH, Cuttack, Odisha.
Email: jjayabharati220@gmail.com

Dr Satyajit Jena*
Assistant Professor, Department of O&G, SCB Medical College & Hospital, Cuttack, Odisha.
*Corresponding author email: drbapi@gmail.com

Abstract---Background Low birth weight is a key underlying factor in neonatal mortality, which is the leading cause of death i n children under five years of age. The causes of IUGR can be maternal, placental, fetal, genetic cause or combination of these factors. Maternal causes include age, multiparty, nutritional deficiency, medical disorders, medications, substance abuse. According to some recent studies early detection of Maternal Vitamin B12 deficiency in pregnancy and appropriate interventions are likely to reduce incidence of IUGR. Therefore we conduct a prospective observational study in a cohort of pregnant women to investigate the maternal determinant of risk of IUGR and to analyze maternal Vitamin B 12 status and role of its deficiency towards the risk of IUGR. Methods Prospective cohort study. After obtaining ethical clearance study subjects counseled about the study and informed consent obtained. Various information regarding age, detailed history & examination finding, relevant

investigation of mother collected in a structured performa. Serum vitamin B12 levels are measured and recorded in picogram/ml. Pregnant women having serum Vitamin B12 Level below 200 pg/ml were included in study group, while those having levels >/= 200 pg/ml were included in control group. Pregnancy outcome assessed and birth weight of newborn measured and documented. Results In our study we found significant number of preterm birth i.e., 46.7% in low vitamin B12 group, whereas only 10% preterm birth in normal vitamin B12 group. In our study we found low maternal vitamin B12 is directly associated with IUGR & Low birth weight. In our study low APGAR score babies & SNCU admission is significantly higher among mothers with low serum vitamin B12. This may be due to preterm birth& IUGR. Conclusion In this study we concluded that there is strong association of maternal vitamin B12 with IUGR. That suggest better socioeconomic status, improved nutritional status and early detection of vitamin B12 deficiency is likely to play an important role in reducing IUGR. As screening of micronutrient like vitamin B12 is unconventional because of high cost, enriched diet & vitamin supplementation throughout pregnancy should be done to prevent the risk of IUGR.

Keywords---IUGR, Vitamin B12.

Introduction

Low birth weight is a key underlying factor in neonatal mortality, which is the leading cause of death in children under five years of age. According to the World Health Organization (WHO), the global prevalence of low birth weight was 15% in 2014, and it differed by region: Sub-Saharan Africa accounts for 13%, South Asia for 28%, East Asia and the Pacific for 6%, and Latin America and the Caribbean for 9%.[1]In the United Nations-designated Least Developed Countries, the overall prevalence of LBW is 13%. Individually, LBW is a significant predictor of newborn health and survival, as well as a risk factor for infant and childhood mortality.[2] Low birth weight (LBW) is more commonly attributed to intrauterine growth restriction (IUGR) than to prematurity, and India is the world's capital for it. Atypical Indian woman is short and thin, and her infant is also light and thin. Maternal under nutrition is regarded to be a major role in the pathogenesis of IUGR, with insufficient micronutrient intake being the most common cause. The Pune Maternal Nutrition Study (PMNS) found that Indian babies were underweight yet fat (adipose) when compared to European babies, and that maternal intake of micronutrient rich diets was a major predictor of foetal growth. Intra Uterine Growth Retardation (IUGR) is the second most common cause after premature births as a cause for neonate with smaller weight for gestational age.

IUGR refers to poor growth of a fetus while in the mother's womb during pregnancy. The causes may be multi factorial but mostly related to poor maternal nutrition or lack of adequate oxygen supply of the fetus. In poor and middle-income nations, multiple micronutrient (MMN) deficits are common among women of reproductive age. They are accentuated during pregnancy due to the

increasing needs of the developing foetus, which can have adverse implications for both the mother and the infant. [3] Pregnancy is a time period when the foetal body grows and develops, necessitating an increase in nutrients. Nearly all essential nutrients, such as iron, vitamin B12, and folic acid, are required in increased amounts by a pregnant woman. Because IUGR causes the majority of LBW children in India and most poor nations, research into the pathogenesis of IUGR and therapies to prevent foetal growth retardation is critical.

IUGR is the second leading cause of perinatal mortality. There can be fetal or neonatal complications such as still birth, hypoxia or acidosis, congenital anomalies, intellectual disability, mental retardation, seizures, short lifespan. There are broadly 3 patterns of IUGR: asymmetrical IUGR (malnourished babies), symmetrical IUGR (hypo plastic small for date), and mixed IUGR.

The causes of IUGR can be maternal, placental, fetal, genetic cause or combination of these factors. Maternal causes include age, multiparity, nutritional deficiency, medical disorders, medications, substance abuse.

Fetal causes responsible for IUGR include mainly congenital infections, chromosomal abnormalities, metabolic disorders, etc.

Placental causes include abnormal uteroplacental vasculature, placental insufficiency (PIH, Preclampsia), abruptio placentae, partial mole, avascular villi, single umbilical artery.

A compromised maternal nutritional status is a major determinant of IUGR in developing countries. Recently attention turns towards micronutrient deficiency in etiology of IUGR. In randomized studies of various micronutrient supplementation of HIV-infected pregnant women in Tanzania and more recently in expectant moms in Nepal, the efficacy of micronutrients in dramatically lowering the risk of LBW was also proven.[4] Folate deficiency has been shown to contributing factor in IUGR According to some recent studies early detection of Maternal Vitamin B12 deficiency in pregnancy and appropriate interventions are likely to reduce incidence of IUGR.

Therefore we conduct a prospective observational study in a cohort of pregnant women to investigate the maternal determinant of risk of IUGR and to analyze maternal Vitamin B 12 status and role of its deficiency towards the risk of IUGR.

Aim of the Study

To determine whether low maternal serum Vitamin B12 is associated with intrauterine growth retardation.

Objectives of the Study

1. To measure the Maternal serum Vitamin B12 levels during antenatal period and determine the prevalence of low level of serum Vit B12 amongst pregnant women.

2. To measure per abdominal symphisio fundal height in 2nd & 3rd trimester antenatal visit respectively.

3. To measure IUGR by per abdominal examination, Abdominal USG at 3rd trimester antenatal visit.

4. To estimate the anthropometric measurements and determine the prevalence of IUGR amongst babies of pregnant women with low antenatal levels of maternal serum vit B12 levels.

Materials and Methods

Type of study: Prospective cohort study

Place of study: Department of Obstetrics and Gynaecology S.C.B Medical College, Cuttack.

Period of study: September 2020 to August 2021.

University: Utkal University, Vani Vihar, Bhubaneswar.

Sample size: 180

Sampling: Convenient Sampling Technique.

Ethical clearance: Institutional ethical committee, SCB MCH (11.2.21)

Inclusion Criteria

The study includes pregnant women aged 17 to 40 yrs who registered for antenatal screening at the department of obstetrics & gynecology SCB medical college and given consent to participate in study.

Exclusion Criteria

1. Women with multiple pregnancy, those with a chronic illness such as diabetes mellitus, hypertension, heart disease and thyroid disease, those who tested positive for Hepatitis, hepatitis B surface antigen, HIV or Syphilis veneral disease research laborotory (VDRL) test infections.

2. Women unwilling to give proper history and who did not give consent for detailed examination.

3. Women whose fetus was diagnosed with congenital anomalies.

Method of Data Collection

- After obtaining ethical clearance study subjects counselled about the study and informed consent obtained.

- Various information regarding age, detailed history & examination finding, relevant investigation of mother collected in a structured proforma.
- Serum vitamin B12 levels are measured and recorded in picogram/ml.
- Pregnant women having serum Vitamin B12 Level below 200 pg/ml were included in study group, while those having levels >/= 200 pg/ml were included in control group.
- Pregnancy outcome assessed and birth weight of newborn measured and documented.

Observation and Result

Low birth weight was defined as birth weight below 2500 gram and IUGR was defined as birth weight below 10th centile.

Table 1A
Comparison of mean age & mean haemoglobin status of both groups

Serum Vit B12		**N**	**Mean**	**Std. Deviation**
Study Group	Age	90	24.97	3.459
	Hb Status	90	9.200	0.6751
Control Group	Age	90	24.80	2.269
	Hb Status	90	10.940	0.6126

Study Group = Low Maternal Vit B12, Control = Normal Maternal Vit B12

Table shows comparison of mean age & mean hemoglobin status of both groups. In study group mean age of participant is 24.97 with standard deviation of 3.459. In control group mean age of participant is 24.80 & standard deviation of 2.269. In study group mean hemoglobin status of participants is 9.2 &standard deviation 0.67. In control group mean hemoglobin status is 10.94 with standard deviation 0.61.

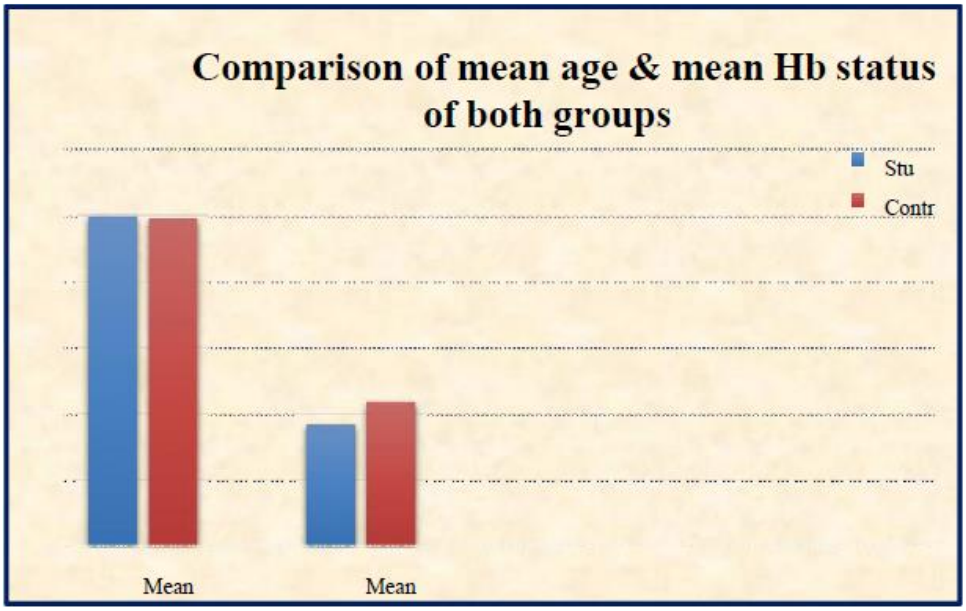


Table 1B
Age group distribution among both groups

Age Group	Study Group		Control Group	
	Frequency	Percentage (%)	Frequency	Percentage (%)
19-24 y	36	40	54	60
25-29 y	45	50	30	33.3
>/=30 y	09	10	06	6.7

Table 1b shows majority of cases in study group belong to 25-29y age group, while in controls most cases belong to 19-24 years age group.

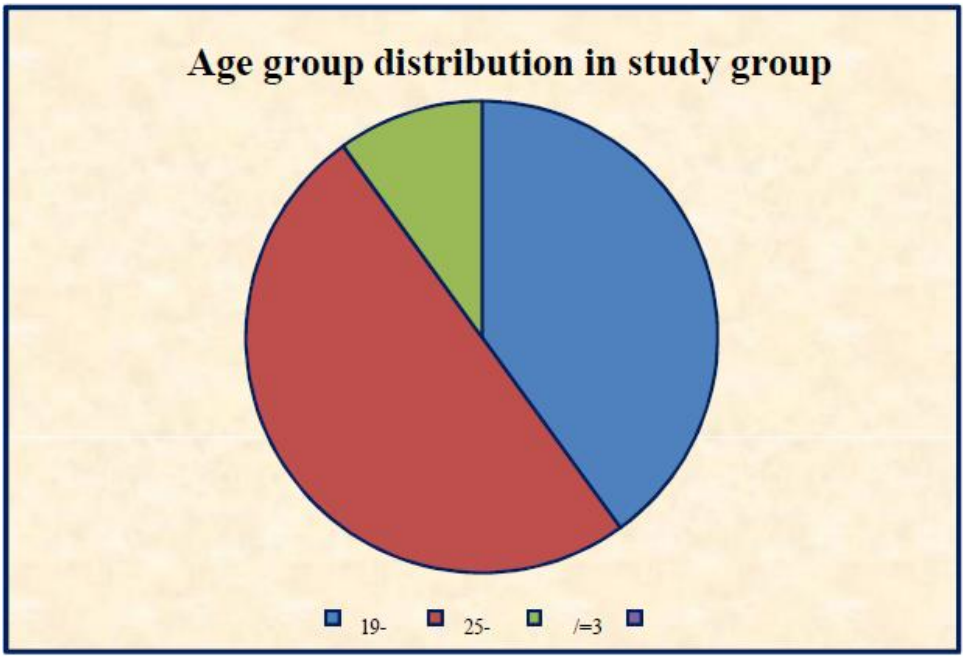


Table 2
Comparison of Parity status of both groups

Serum Vit B12		**Frequency (N)**		**Percentage (%)**
Study Group	Gravida	Multi	51	56.7%
		Primi	39	43.3%
		Total	90	100
Control group	Gravida	Multi	27	30.0
		Primi	63	70.0
		Total	**90**	**100**

This table shows in study group frequency of primi gravida is 43.3% & that of multigravida is 56.7%. Whereas in control group primi & multi gravida are 70% & 30% respectively.

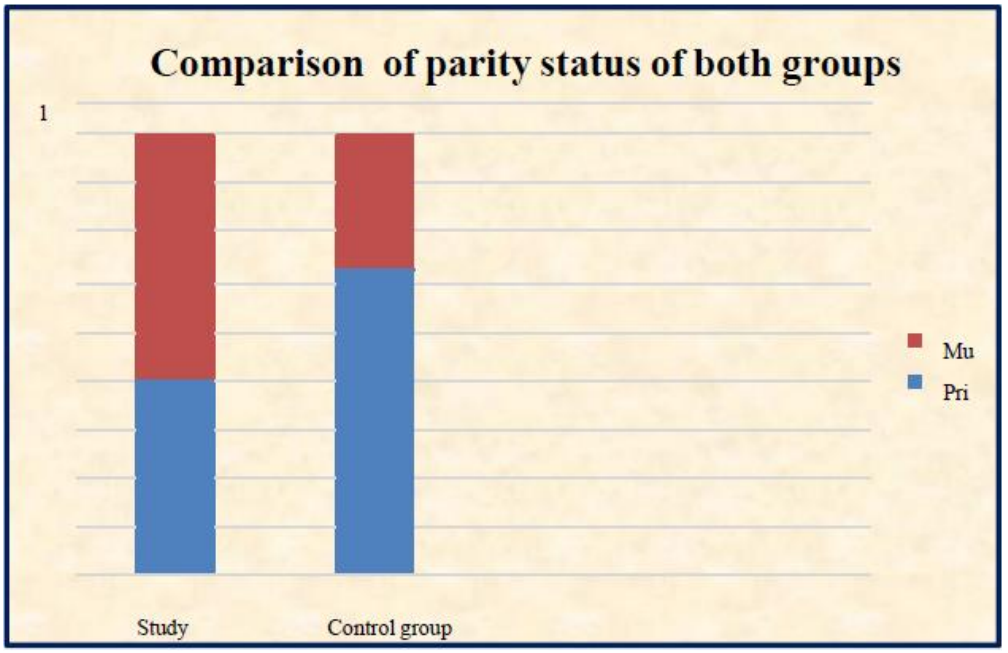


Table 3
Comparison of Socioeconomic status of both groups

Serum Vit B12		**Frequency (N)**	**Percentage (%)**
Group 1	Lower	66	73.3
	Middle	12	13.3
	Higher	12	13.3
	Total	90	100

Serum Vit B12		**Frequency (N)**	**Percentage (%)**
Group 2	**Lower**	**32**	**35.5**
	Middle	10	11.2
	Higher	48	53.3
	Total	**90**	**100**

This table shows comparison of socioeconomic status of both groups. It shows Lower maternal serum vitamin B12 has greater association with lower socioeconomic status of pregnant women.

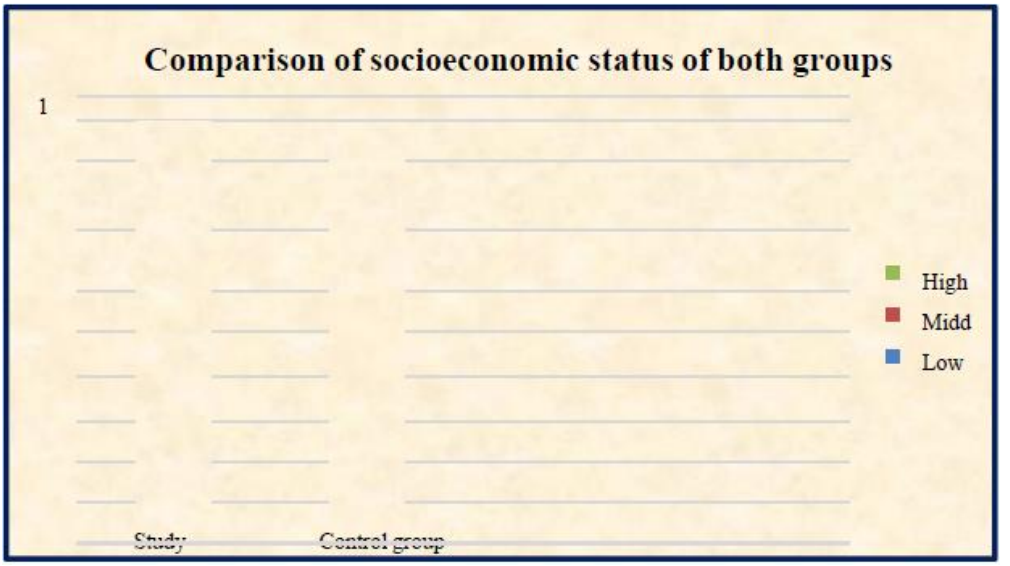


Table 4
Comparison of Symphysio Fundal Height at 28 weeks GA of both groups

Serum Vit B12		**Frequency (N)**	**Percentage (%)**
Study Group	SFH</=24 wks	24	26.7
	SFH>24 wks	66	73.3
	Total	90	100
Control Group	SFH</=24 wks	09	10
	SFH>24 wks	81	90
	Total	**90**	**100**

This table shows comparison of measurements of symphysio fundal height at 28 weeks gestation. In study group 4 weeks or more discrepancy in SFH detected among 26.7% pregnant women which is higher as compared to 10% in control group population.

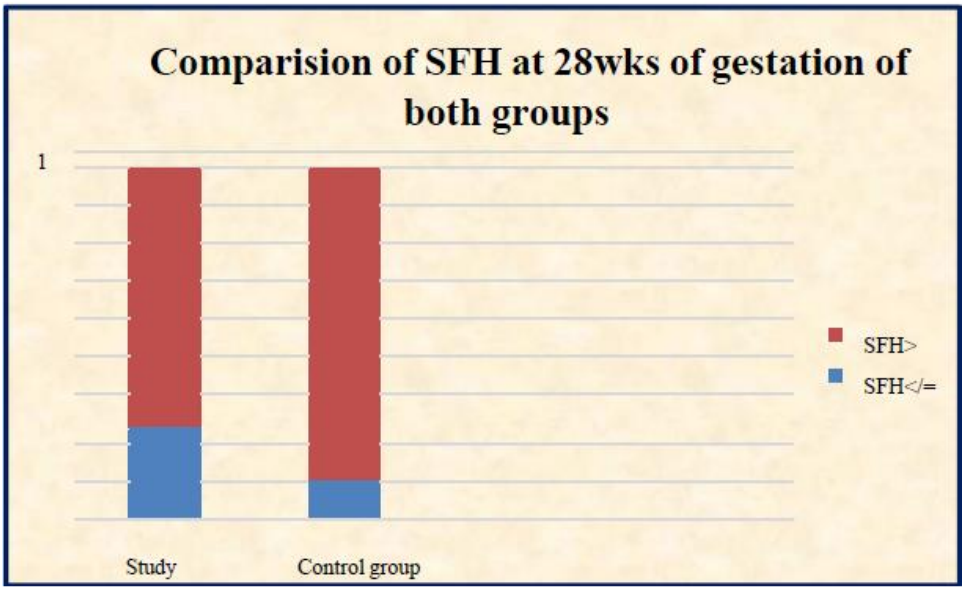


Table 5
Comparison of Symphysio Fundal Height at 36 weeks GA of both groups

Serum Vit B12		**Frequency (N)**	**Percentage (%)**
Study group	SFH</=32 wks	42	46.7
	SFH>32 wks	48	53.3
	Total	**90**	**100**
Control group	SFH</=32 wks	15	16.7
	SFH>32 wks	75	83.3
	Total	**90**	**100**

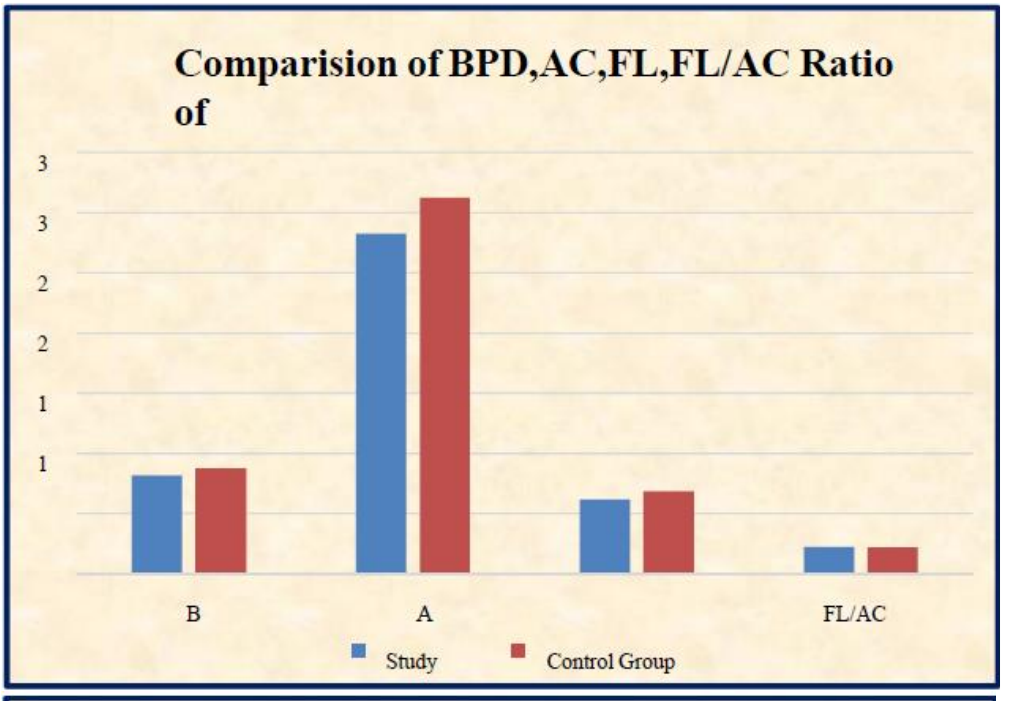
This table shows in study group comparison of measurements of symphysio fundal height at 36 weeks gestation. In study group 4 weeks or more discrepancy in SFH detected among 46.7% pregnant women which is higher as compared to 16.7% in control group population.

Table 6
Comparison EFW, BPD, AC, FL, FL/AC ratio of both groups

Fetal Biometry	**Mean +/- SD**		**P value**
	Study Group	**Control Group**	
BPD (mm)	81.77 +/-6.71	87.60+/-4.72	0.001
AC (mm)	282.70+/-24.66	312.30+/-18.90	0.002
FL (mm)	61.71+/-4.25	68.50+/-4.76	0.001
FL/AC ratio	22.19+/-2.20	21.88+/-1.21	0.245
EFW (Grams)	2043.23+/-512.31	2706.27+/-360.73	0.001

Unpaired T test applied. P value is significant if< 0.05

This table shows in study group fetal biometry measurements as mean EFW (2043.23 grams), BPD (81.77 mm), AC (282.70 mm), FL (61.71 mm), FL/AC ratio (22.19) as compared to mean EFW (2706.27 grams), BPD (87.60 mm), AC (312.30), FL (68.50), FL/AC ratio (21.88) in control group.



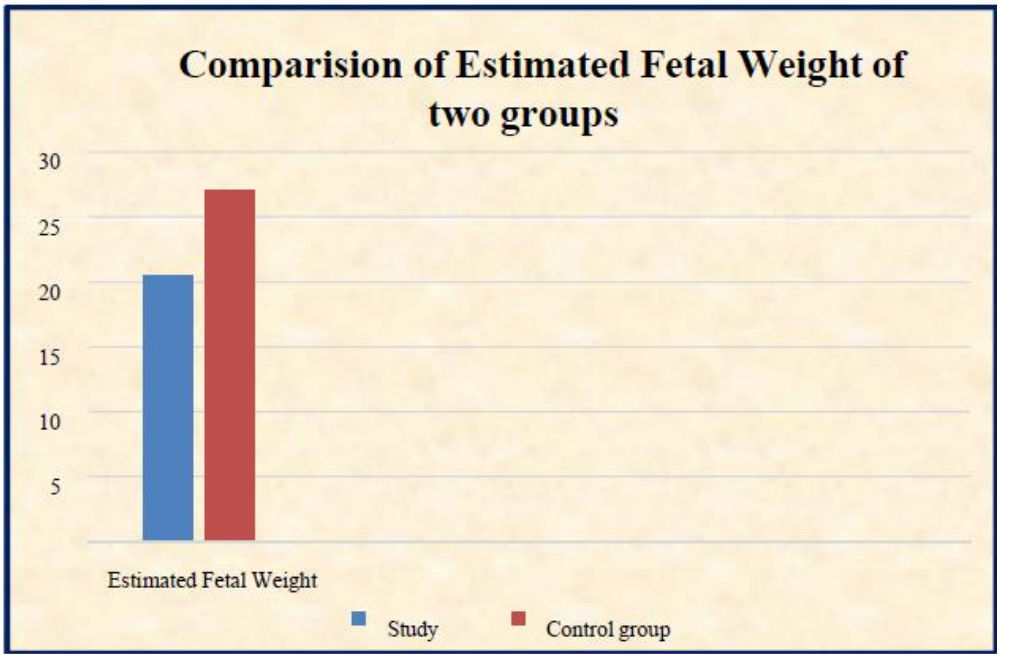


Table 7
Comparison of Term & Preterm delivery of both groups

Variation	**Frequency/Percentage**		**Grand Total**	**P value**
	Study Group	**Control Group**		
Term	48	81	129	0.001
	53.3%	90%		
Preterm	42	09	51	
	46.7%	10%		
Total	**90**	**90**		

Chi Square test is applied. P value is 0.001 which is significant.

The above table shows preterm delivery in study group is 46.7% which is higher as compared to control group i.e., 10%.

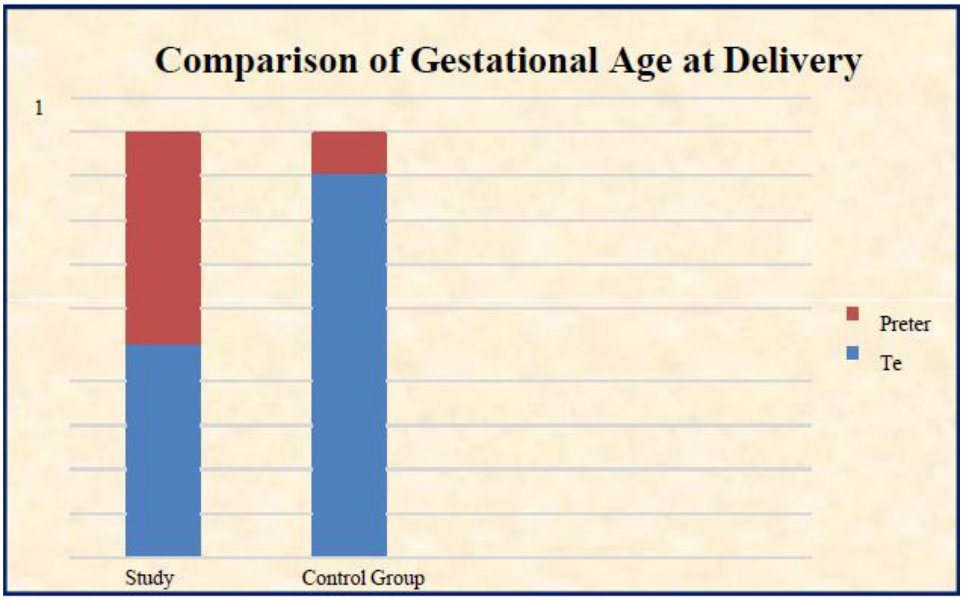


Table 8
Comparison of Mode of Delivery of both groups

Serum Vit B12		**Frequency**	**Percentage**
Study Group	CS	54	60
	VD	36	40
	Total	**90**	**100**
Control Group	CS	42	46.7
	VD	48	53.3
	Total	**90**	**100**

The above table shows comparison of mode of delivery between both groups. In study groups mode of delivery is caesarean section in 60% cases & vaginal delivery in 40% cases. In control groups mode of delivery is caesarean section in 46.7% cases & vaginal delivery in 53.3% cases.

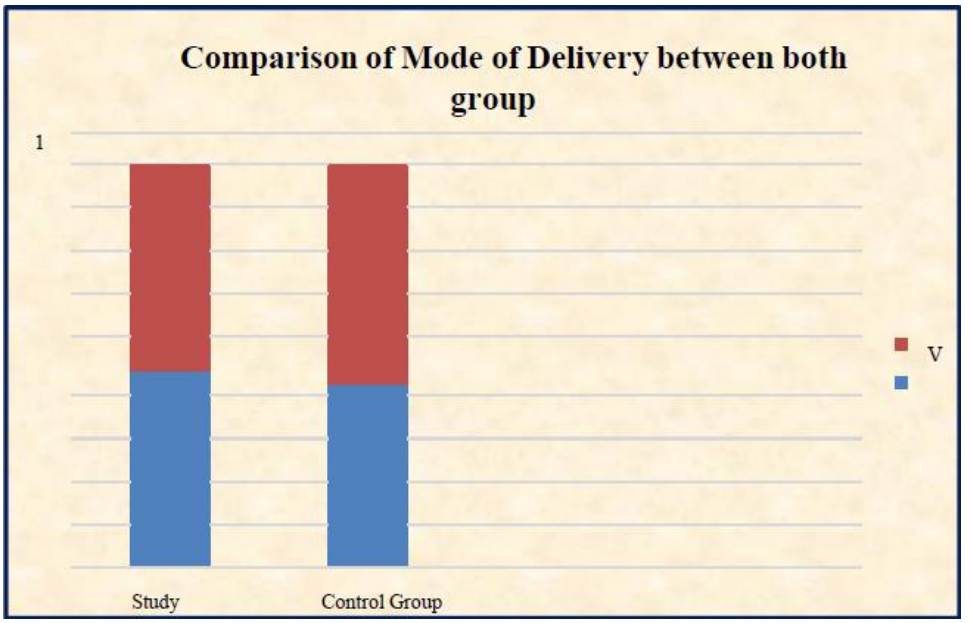


Table 9
Comparison of Newborn SNCU Admission of both groups

SNCU Admission	**Frequency/Percentage**		**Grand Total**	**P value**
	Study Group	**Control Group**		
NO	45	69	114	0.001
	50%	76.7%		
YES	45	21	66	
	50%	23.3%		
Total	**90**	**90**		

C hi square test applied. P value is 0.001, which is significant.

This table shows rate of SNCU admission is higher i.e., in 50% cases among study group as compared to 23.3% among control groups.

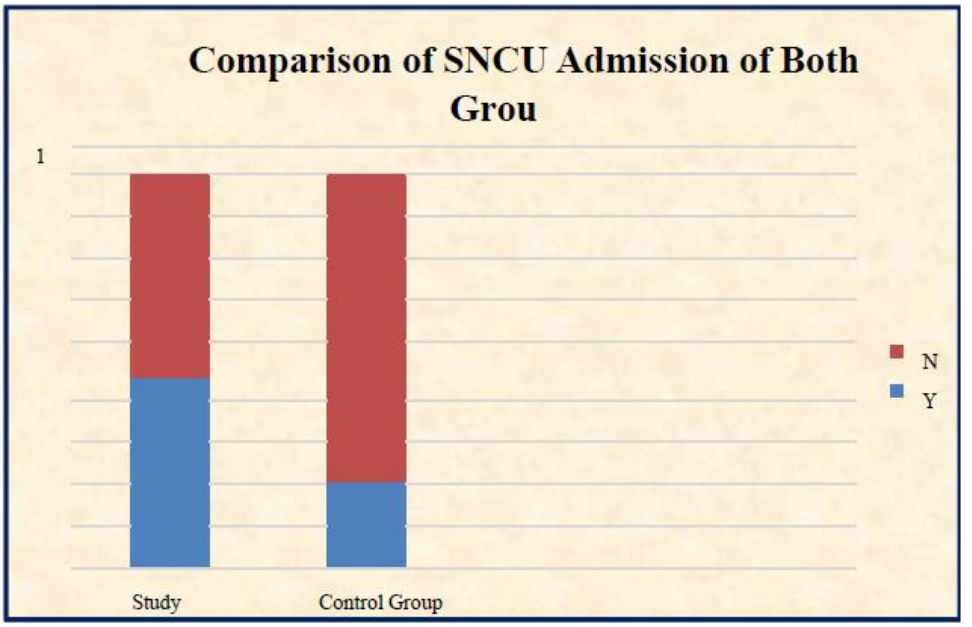


Table 10
Comparison of APGAR Score of both groups

APGAR Score	Frequency/Percentage		Grand Total	P value
	Study Group	Control Group		
< 5	18	03	21	0.001
	20%	3.3%		
>/=5	72	87	159	
	80%	96.7%		
Total	**90**	**90**		

Chi square test applied. P value is 0.001, which is significant.

This table shows frequency of low APGAR score (</=) 5 was found to be higher in study groups i.e., 20% as compared to 3.3% in control groups.

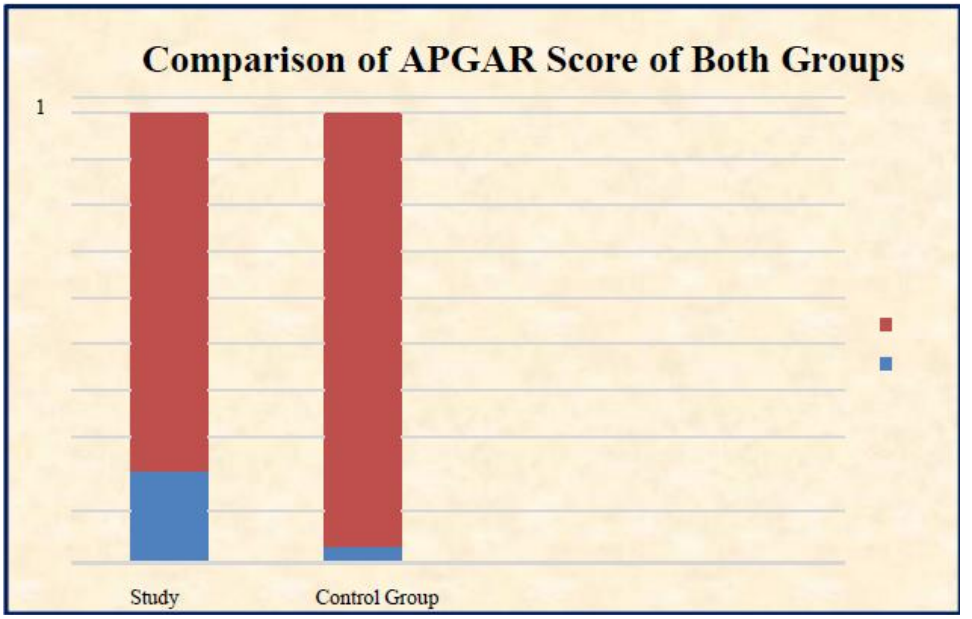


Table 11
Comparison of Birth weight of both groups

Birth Weight	Frequency/Percentage		Grand Total	P value
	Study Group	Control Group		
Low	75	21	96	0.001
	83.3%	23.3%		
Normal	15	69	84	
	16.7%	76.7%		
Total	**90**	**90**		

Chi square test applied. P value is 0.001, which his significant.

The above table shows proportion of LBW new borns is 83.3% in study group which is significantly high eras compared to 23% in control groups.

This prospective study was conducted to evaluate the effect of maternal low serum vitamin B12 on fetal growth. Fetal outcomes were compared among 90 women having low serum Vitamin B 12 (Study group) with those having normal serum vitamin B 12 levels (Controls).

Table 1 shows mean age of study group participants was 24.97 +/-3.4 years which correlates with similar study conducted by **Mutthaya et al.** (2006) including 377 participants; their mean age was reported as 24.6 +/- 4.1 years.

Table 1 also shows mean hemoglobin concentration in study group was 9.2 +/- 0.6 gm/dl as compared to control group where mean hemoglobin level was

10.9+/- 0.61 gm/dl. The lower hemoglobin level in study group may be attributed to lower serum vitamin B12 levels. This correlates with study of Khanna et al. They revealed that a therapeutic follow up approach clearly indicated that vitamin B12 deficiency was fairly common in anemic pregnant women.

Table 2 shows in study group low serum vitamin B12 was more prevalent among multipara (56.7%) in comparison to primigavida (43.3%). This may be due to low birth spacing among low educated Indian lady. Repeated child birth, poor nutritional status may be a cause of low vit B12. This correlates with **Eduardo Villamor et al. (2008)**, who found that Vit B12 was inversely related to mother's parity.

Table 3 shows low maternal serum vitamin B12 is more common finding in pregnant women of low socioeconomic status. Serum Vitamin B 12 level positively associated with amount of money spent on food per person per day. This strongly correlates with study of **Eduardo Villamor et al (2008)** who found Vitamin B12 concentration was strongly associated with in dictators of socioeconomic status including the amount of money spent on food at home & general ranking of household's stratum according to their neighborhood.[5]

Table 4 & 5 shows in study group, rates of 4 week discrepancy of Symphysio fundal height measurements at 28 wks & 36 wks gestation is 26.7 %&46.7 % respectively which is higher than controls.

This indicates that in study group more women reported with lower symphysio fundal height which is a screening measure of IUGR. This finding correlates with **J.PC alvert et al.** (2014) study who found that way of expressing fundal height & an easy and inexpensive screening test for IUGR.

Table 6 shows in study group fetal biometry parameters such as biparietal diameter, abdominal circumference, femur length, estimated fetal weight were reduced. Estimated P value is 0.001 which is significant. This correlates to study of **R. P Patange et al (2014)** they found that biparietal diameter, abdominal circumference, femur length, estimated fetal weight values are significantly reduced in IUGR baby.

Table 7 compares the incidence of preterm birth among the study & control groups. In study group 46.7% delivered preterm in compare to 10% in controls. P value is very significant (0.001). This finding of our study correlates with **Tormod Rogneet et al**. According to their study maternal vitamin B 12 deficiency during pregnancy was associated with increased risk of preterm birth.[6]

A table 8 show in study group mode of delivery is 60% by LSCS & 40% by NVD. In control group baby delivered by LSCS is 46.7% and 53.3% baby delivered by VD. The higher rate of LSCS in study group maybe due to IUGR.

Another study by **BL Lakhkar (2006)** found mode of delivery as 62% & 38% by LSCS &VD respectively.

Table 9 shows more SNCU admission in study group (50%) as compared to control group (23.3%). We calculated P value as 0.001 which indicates high statistical significance. This may be due to high incidence of preterm birth& low birth weight in study group.

Table 10 shows most of babies in study group had low APGAR Score (</=5) that is 20% in comparison to control group i.e., 3.3%. P value calculated to be 0.001 which is statistically significant. It indicates that babies born to mother with low serum vitamin B 12 had low APGAR because of IUGR & prematurity.

Narula et al. (2009) found 25% of IUGR & 6% in control had low APGAR score.
Table 11 shows in study group 83% babies had low birth weight as compared to 23.3% in controls, with P value calculated as 0.001 which is highly significant. This finding correlates with **T Rogne et al. (2017)** study.

T Rogne et al. (2017) found Vitamin B12 deficiency in pregnancy has been associated with higher risk of low birth weight baby.

Muthayya et al. (2006) suggested that low serum vitamin B12 concentration throughout pregnancy are significant determinants of IUGR in urban Indian women[7] of gestational age according to the WHO standards.

Discussion

- Mean age of the study participants with low serum vitamin B 12 in our study is 24.97 years.

- In our study group we found mean hemoglobin Concentration is 9.2 g%, which implies low vitamin B 12 is more prevalent among an aemic women. In our study we found Vitamin B12 level is inversely related to parity.

- Low serum vitamin B 12 is directly related low socioeconomic status. This may be attributed to poor nutrition& poor education status.

- In our study we found significant number of preterm birth i.e., 46.7% in low vitamin B12 group, whereas only 10% preterm birth in normal vitamin B12 group.

- In our study more number of LSCS delivery were observed in study group in comparison to controls. This is because of more chances of IUGR & preterm birth.

- In our study we found low maternal vitamin B12 is directly associated with IUGR & Low birth weight.

- In our study low APGAR score babies & SNCU admission is significantly higher among mothers with low serum vitamin B12. This may be due to preterm birth & IUGR.

Conclusion

In developing countries like India, a compromised maternal nutritional condition is a significant determine a to f intrauterine growth restriction.

Pregnant mothers who are malnourished are unable to provide essential micronutrients to their fetuses, especially in poor socioeconomic groups. Odisha is economically backward state. More women are unaware about their health issues &diet& nutrition. So Vitamin deficient is clearly visible in study participants. In this study we concluded that there are strong association of maternal vitamin B12 with IUGR. That suggest better socioeconomic status, improved nutritional status and early detection of vitamin B12 deficiency is likely to play an important role in reducing IUGR. As screening of micronutrient like vitamin B12 is unconventional because of high cost, enriched diet & vitamin supplementation throughout pregnancy should be done to prevent the risk of IUGR.

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