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Research Article

ANEMIA DURING PREGNANCY AND ITS ASSOCIATION WITH TERM SGA

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ABSTRACT

Small for gestational age (SGA) refers to an infant whose weight is less than 10th percentile for that particular gestation age. The prevalence of SGA in India is 46.9%. Babies who are small for gestational age have various short term and long term morbidities. Maternal anemia is one of the important risk factor for SGA. According to WHO 40.1% of pregnant women worldwide were anemic in 2016. Association of maternal anemia with SGA has been proven inconclusively and not many studies have looked at term SGA birth as an outcome of maternal anemia, so the present study was conducted.

Aims & objectives: To study the association between anemia during pregnancy and Term SGA.

Materials and methods: It is a hospital based observational study, done in MVJ Medical College and Research Hospital, Bangalore, from November 2017 to October 2019. All term SGA and AGA newborns delivered in MVJ MC & RH or outborn newborns admitted within 24 hours of life who are fulfilling the inclusion criteria were taken as cases and controls respectively. Demographic details of the mothers were taken and antenatal records were looked for presence and absence of anemia and severity of anemia during pregnancy, Hemoglobin cut off for anemia during pregnancy are : 1) ≥11g/dl = Normal, 2)10.9-10g/dl = Mild, 3) 9.9-7g/dl = Moderate, 4) <7g/dl = Severe, 5) <4g/dl = Very severe. All details of mother and baby were recorded in a preformed Performa. Babies were observed in the early neonatal period for immediate outcomes.

Results: Out of 2900 babies admitted, 312(10.75%) babies were SGA, of them 210(67.3%) were term and 102(32.7%) were preterm SGA. 194 Term SGA & AGA babies were included in study. Mothers in SGA group had significantly low levels of mean hemoglobin than AGA mothers (P value<0.0001). Number of mothers who were having anemia in SGA and AGA group were 92.8% and 90.2% respectively. Mild anemia was present in 72.7% of SGA mother and 86.3% of AGA mothers, Moderate anemia in 24.2% of SGA mothers and 13.7% of AGA mothers, severe anemia in 2.2% and very severe anemia in 0.5% of SGA mother, no mother in AGA group had severe anemia or very severe anemia. (P value 0.007). More is the severity of anemia during pregnancy more is the chance of giving birth to an SGA newborn. More number of SGA babies required admission in NICU at birth as compared to AGA babies [155(77%) vs. 50(25%)] with a very significant P value <0.0001. Neonatal morbidities which were significantly more in SGA babies as compared to AGA babies were, Hyperbilirubinemia, Sepsis, Transient Tachyapnea of newborn, Polycythemia, Hypoglycemia, Birth asphyxia, Thrombocytopenia, Leucopenia and Feed intolerance

Conclusion: Anemia is very common during pregnancy (90-93%). As severity of maternal anemia increases risk of delivering term SGA baby also increases. Term SGA babies are prone to develop various morbidities after birth. Early identification and prompt management of moderate to severe anemia during pregnancy can help in reducing the incidence of SGA, and in turn neonatal morbidity and mortality.

***Keywords*:** *Infant, Small for Gestational Age, Anemia*

INTRODUCTION

Small for gestational age (SGA) refers to an infant whose weight is less than 10th percentile for that particular gestation age (Battalglia *et al.*, 1967). In 2012 the highest burden of SGA babies was in South Asia, with the prevalence of 34% and 26% of neonatal deaths were due to small for gestation age (Lee *et al.*, 2017).The incidence of LBW in India is about 30% in contrast to 5–7% in developed countries

(Bhargava *et al.,* 1995). The prevalence of SGA in India is 46.9% (Lee *et al.,* 2013). Babies who are small for gestational age have complications which include: short term complications like perinatal asphyxia, meconium aspiration, persistent pulmonary hypertension, hypothermia, hypoglycemia, hypocalcaemia, polycythemia, jaundice, feeding difficulties, feed intolerance, necrotizing enterocolitis, late-onset sepsis, and pulmonary hemorrhage. Long term complications like poor growth and neurodevelopment outcome occur when they reach the school going age (Sharma *et al.,* 2016), hence reducing the incidence of SGA birth will help in reducing neonatal mortality and morbidity. To reduce the incidence of SGA babies, mothers who are at high risk of delivering SGA babies have to be identified and managed promptly during antenatal period. Various risk factors for delivering SGA babies have been identified (Sharma *et al.,* 2016) out of all these risk factors maternal anemia is the one whose association with SGA has been proven inadequately (Kozuki *et al.,* 2012).

World health organization (WHO)/world health statistics data shows that 40.1% of pregnant women worldwide were anemic in 2016. The condition is prominent in Southeast Asian countries where about half of all global maternal deaths are due to anemia and India contributes to about 80% of the maternal death due to anemia in South Asia. Among the various cause of anemia in women, iron deficiency is most common cause, primarily due to their recurrent menstrual loss and secondarily due to poor supply of iron in diet. During pregnancy anemia is common due to increased demand of iron for growing fetus and placenta; and increased red blood cell mass (with expanded maternal blood volume in the third trimester), which further aggravates with other factors such as childbearing at early age, repeated pregnancies, short interval between pregnancies and poor access to antenatal care and supplementation(Rastogi, 2018). Hemoglobin cut off for anemia during pregnancy are: 1) ≥11g/dl = Normal, 2)10.9-10g/dl = Mild, 3) 9.9-7g/dl = Moderate, 4) <7g/dl = Severe, 5) <4g/dl = Very severe (WHO, 2011). Maternal IDA is associated with adverse health outcomes, including low infant birth weight; inferior health of the newborn (Helmey *et al.,* 2018).

Maternal hemoglobin values during pregnancy are associated with low birth weight and preterm birth in a U-shaped relationship; with high rates of low birth weight at low and high concentrations of maternal hemoglobin (McLean *et al.,* 2009). Various studies have reported an association of anemia during pregnancy and SGA (Ren *et al.,* 2007). A meta-analysis estimated a decreased risk of perinatal mortality by 28% [RR = 0.72 (95% CI: 0.62–0.89)] with each 10-g/L increase in hemoglobin (Stoltzfus *et al.,* 2004). However, a large prospective cohort study involving 163,313 live births found no relationship (Zang *et al.,* 2009)

A separate meta-analysis found maternal anemia determined in the first and second trimesters significantly associated with preterm birth [OR = 1.32 (95%CI: 1.01–1.74)] but not with low birth weight. It found no association between hemoglobin, 100–110 g/L and IUGR; however, it only included 3 studies (Xiong *et al.,* 2000).

As association between maternal anemia and SGA birth is not very conclusive, and not many studies have looked at term SGA birth as an outcome of maternal anemia, so the present study was conducted.

Aims and Objectives

Objective is to study the association between anemia during pregnancy and term SGA.

MATERIALS AND METHODS

It is a hospital base observational study, done in MVJ Medical College and Research Hospital, Bangalore, from November 2017 to October 2019. Weight of all inborn babies was recorded at birth & weight of all outborn babies who were admitted within 24hours of birth was recorded at admission. The infant's gestation age was assessed either by calculating the number of days passed between the first day of mothers last menstrual period (LMP) and her date of delivery, by ultrasound examination done during antenatal period, and by New Ballard score (within 24hrs of birth). Weight of all newborns admitted was plotted on Lubchenco chart. All term newborns whose birth weight was less than 10th centile for gestation age as per Lubchenco chart were classified as Small for gestation age and recruited as subjects

and term newborns whose birth weight was between 10th and 90th centile for the gestational age were classified as AGA and were taken as controls at random after taking informed consent from the mother. Enrolment was done until target sample size was reached. Babies with Major Congenital anomalies, babies whose mothers did not have antenatal record and babies who got discharged before 7 days of life from hospital were excluded from the study. Demographic details of the mothers were taken and antenatal records were looked for presence and absence of anemia and severity of anemia during pregnancy, Hemoglobin cut off for anemia during pregnancy are : 1) ≥11g/dl = Normal, 2)10.9-10g/dl = Mild, 3)9.9-7g/dl = Moderate, 4) <7g/dl = Severe, 5) <4g/dl = Very severe(WHO, 2011). All details of mother and baby were recorded in a preformed Performa. Babies were observed in the early neonatal period for immediate outcomes.

Total sample of 194 SGA babies was calculated based on the prevalence of SGA babies.(Lee *et al.*, 2017) Same number of AGA babies were taken as control (Using formula $n= 4PQ/d^2$, P=prevalence =34%, Q=100-P, d= allowable error=20% of P).General characteristics of the patients were expressed as values of mean and standard deviation for the quantitative variable and percentage for qualitative variables. Statistical analysis was performed using chi-square test for categorical variables, t-test for comparing means between two groups. P value less than 0.05 was considered significant. Data collected was entered into Ms Excel, tables and charts are generated using Ms Word.

RESULTS

Total numbers of babies admitted in our hospital during the study period were 2900, out of which 312(10.75%) were SGA babies. 210(67.3%) were term and 102(32.7%) were preterm. Out of total SGA babies admitted 118 were excluded from our study as they did not meet the inclusion criteria. (102 were preterm SGA, 14 babies were admitted after 24 hours of birth and 1 baby had major congenital anomaly (TGA), 1 discharged before 7 days of life.) 194 SGA babies meeting the inclusion criteria were included in the study as cases & 194 AGA babies selected at random were included as controls in the study (Figure 1).

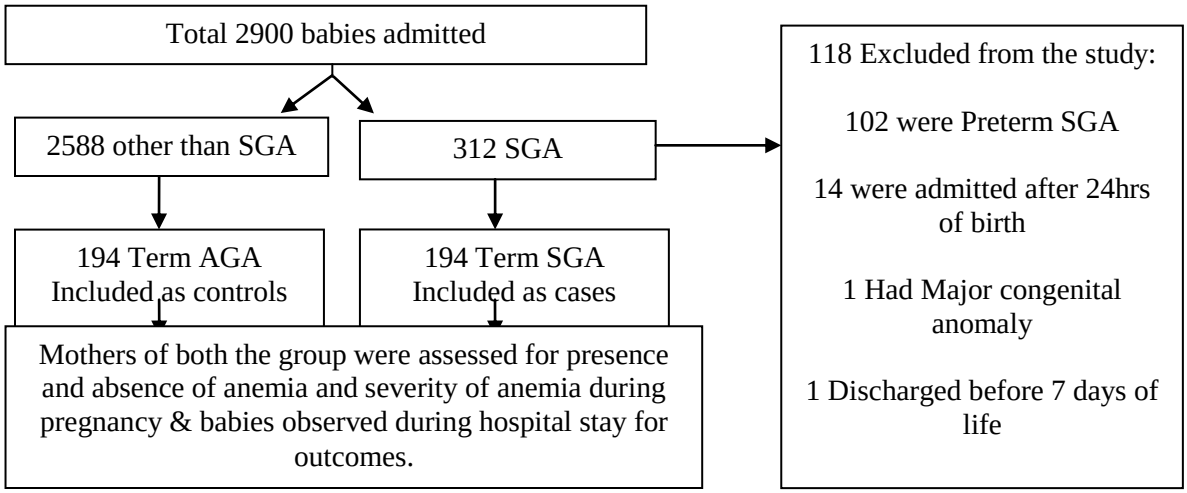

Figure 1: flow chart for subject recruitment and enrolment

Basic characteristics of mothers in SGA and AGA group were comparable in terms of age distribution, socioeconomic status, education, occupation, iron & folic acid supplementation during pregnancy and number of antenatal visits. However there were significantly more number of Primigravida mothers in SGA group as compared to AGA group [125(64.4%) vs. 92(47.5%%)] p value 0.001, and significantly

more numbers of mothers were there with twin gestations in SGA group when compared to mothers of AGA group [19(9.97%) vs. 1(0.5%)] with p value of <0.0001 (Table 1).
The female: male ratio was 1.17:1 in SGA group and 0.76:1 in AGA group, female babies were significantly more in SGA group (P value 0.04). Mean birth weight of SGA babies was 1940 ±240g which was significantly less than the mean birth weight of AGA babies which was 2870±390g (P value <0.0001). Significantly more number of SGA babies were delivered through cesarean section as compared AGA babies [123(63.4% vs. 98(49%)] with P value 0.005. Outborn admissions were 34% in SGA and 25% in AGA, & inborn were 65% in SGA and 74% in AGA(P value 0.08**).** More number of SGA babies required admission in NICU at birth as compared to AGA babies [155(77%) vs. 50(25%)] with a very significant P value <0.0001. The mean duration of hospital stay in SGA group was 8.24(±1.45) days, where as in AGA group was 8.5(±2.18) days, this was not significant (p value 0.07). (Table 2)

Table 1: General characteristics of mothers

VARIABLES	**SGA**	**AGA**	**P value**
Age of mother n (%)			
<20 years	7(3.7)	3(1.5)	0.22
20-35 years	182(93.8)	189(97.4)	
>35 years	5(2.5)	2(1.03)	
Socioeconomic status n (%)			
Upper middle	48(24)	56(29)	0.43
Lower middle	60(31)	50(25)	
Upper lower	36(18)	44(22)	
lower	50(25)	44(22)	
Educational status n (%)			
Educated	175(90.2)	185(95.3)	0.07
Not educated	19(97.8)	9(46.7)	
Gravid status n (%)			
Primigravida	125(64.4)	92(47.5)	0.001*
Multigravida	69(35.6)	102(52.5)	
Single/twin gestation n (%)			
Single gestation	175(90.3)	193(99.5)	<0.0001*
Twin gestation	19(9.97)	1(0.5)	
Iron and folic acid supplementation n (%)			
Taken	172(88.6)	180(92.7)	0.22
Not take	22(11.4)	14(7.3)	
Occupation n (%)			
House wife	109(56.2)	117(60.3)	0.47
Works outside	85(43.8)	77(39.7)	
Number of antenatal visits n (%)			
<4	7(3.7)	7(3.7)	0.79
>4	187(96.3)	187(96.3)	

**significant p value*

Table 2: General characteristics of Newborns

VARIABLES	SGA	AGA	P value
Gender distribution n (%) Male Female	 89(45.8) 105(54.1)	 110(56.7) 84(43.3)	0.04*
Mean Birth weight ,g, mean (SD)	1940±240	2870±390	<0.0001*
Mode of delivery n (%) Cesarean section Normal vaginal	 123(63.4) 71(36.5)	 98(49%) 99(51%)	0.005*
Place of delivery n (%) Inborn Outborn	 127(65) 66(34)	 144(74) 50(25)	0.08
****NICU admission** n (%) Yes No	 151(77) 45(23)	 50(25) 144(74)	<0.0001*
Duration of hospital stay, days, mean (SD)	8.24(±1.45)	8.15(±2.18)	0.07

significant p value Neonatal Intensive Care Unit*

Table 3: Anemia during pregnancy and SGA

ANEMIA	SGA (%)	AGA (%)	P VALUE
PRESENT	180(92.8)	175(90.2)	0.46
ABSENT	14(7.2)	19(97.8)	
TOTAL	194	194	

Table 4: Mean hemoglobin during pregnancy and association with SGA

VARIABLE	SGA	AGA	P VALUE
	MEAN (±SD)	MEAN (±SD)	
HEMOGLOBIN (g/dl)	9.1 ±1.46	9.73 ±0.95	<0.0001*

**significant p value*

Table 5: Severity of maternal anemia and association with SGA

ANEMIA	SGA (%)	AGA (%)	P VALUE
MILD (10.9-10g/dl)	131(72.7)	151(86.3)	0.007*
MODERATE (9.9-7g/dl)	44(24.4)	24(13.7)	
SEVERE (<7g/dl)	4(2.2)	0(0)	
VERY SEVERE(<4g/dl)	1(0.5)	0(0)	
TOTAL	180	175	

**significant p value*

Number of mothers who were having anemia in SGA (92.8%) and AGA (90.2%) group were same.(Table 3) this suggests that anemia is common in mothers of both SGA and AGA groups. Mothers in SGA group had significantly low levels of hemoglobin than AGA mothers (P value<0.0001). (Table 4) Mild anemia was present in 72.7% of SGA mother and 86.3% of AGA mothers, Moderate anemia in 24.2% of SGA mothers and 13.7% of AGA mothers ,severe anemia in 2.2% and very severe anemia in 0.5% of SGA

mother, no mother in AGA group had severe anemia or very severe anemia(P value 0.007) (Table 5). More is the severity of anemia during pregnancy more is the chance of giving birth to an SGA newborn
In our study neonatal morbidities which were significantly more in SGA babies as compared to AGA babies were, Hyperbilirubinemia (85.5% vs. 30.9%, P value <0.0001), Sepsis (33% vs. 14.5% , P value <0.0001), Transient Tachyapnea of newborn (24.2% vs. 10.3%, P value 0.0003), Polycythemia (23.7% vs. 4.6% , P value <0.0001) Hypoglycemia (18.5% vs. 5.15%, P value <0.0001), Birth asphyxia (16% vs. 8.7%, P value 0.04), Thrombocytopenia (11.8% vs. 4.6%, P value 0.016), Leucopenia (11.8% vs. 3%, P value 0.002) and Feed intolerance (9.2% vs. 2%, P value 0.004). (Table 6) No baby died during the hospital stay.

Table 6: Outcomes of SGA babies

MORBIDITIES	**SGA (%)**	**AGA (%)**	**P VALUE**
HYPERBILLIRUBENEMIA	116(85.50)	60(30.9)	<0.0001*
SEPSIS	64(33)	29(14.5)	<0.0001
TRANSIENT TACHYAPNEA OF NEWBORN	47(24.2)	20(10.3)	0.0003*
POLYCYTHEMIA	46(23.7)	9(4.6)	<0.0001*
HYPOGLYCEMIA	36(18.5)	10(5.15)	<0.0001*
BIRTH ASPHYXIA	31(16)	17(8.7)	0.04*
ACUTE KIDNEY INJURY	25(12.80)	14(7.20)	0.09
THROMBOCYTOPENIA	23(11.8)	9(4.6)	0.016*
LEUCOPENIA	23(11.8)	6(3)	0.002*
MECONIUM ASPIRATION SYNDROME	19(9.8)	10(5.1)	0.12
SEIZURES	18(9.2)	12(6.1)	0.34
FEED INTOLERANCE	18(9.20)	4(2)	0.004*
HYPOCALCEMIA	10(5.1)	3(1.5)	0.09
CONGENITAL PNEUMONIA	5(2.5)	12(6.1)	0.13
HYPERGLYCEMIA	3(1.5)	5(2.5)	0.72

**significant p value*

DISCUSSION

This study was conducted in a rural tertiary care hospital in Bangalore, from November 2017 to October 2019, in term SGA newborns.10.75% of babies admitted in our hospital were SGA, out of which term SGA were 67.3% and preterm SGA were 37.4%.Kushwah et al studied 750 hospital deliveries (term singleton neonates) and found that 28.4% were SGA (Kushwah *et al.,* 2004). Mehta et al studied 637 hospital deliveries and reported 25% were SGA (including term & preterm) (Mehta *et al.,* 1998). As compared to other Indian studies percentage of SGA newborns was less in our study. Narang et al reported 3.53% of SGA babies delivered in their hospital; with 68.9% being term SGA and 31% were preterm SGA (Narang *et al.,* 1997).
Most characteristics of mothers in SGA and AGA group were comparable, except Primigravida being significantly more than multigravida in SGA group and significantly more number of mothers with twin gestation who delivered SGA baby as compared to AGA mothers. It is well accepted that nulliparity increases the risk of SGA infants when compared to multiparity (MaCowan and Horgan , 2009) as shown by a study in hospitals of Auckland, New Zealand (Thompson *et al.,* 2001). This is explained by the fact

that in first pregnancy there is immaturity of uterine structures and vascular structures which make them more sensitive to gestational stimuli, as local conditions improve in subsequent pregnancy there is a greater development of placenta and more improved fetal nutrition (Bernabe *et al.,* 2004). Twin gestation significantly increases the risk of delivering an SGA baby has been shown in many studies (Narang A *et al.,* 1997; Okogho and Funitusi, 1997; Hanoudi and Rabab, 2006). The main reason for this is the decreased availability of substances for each fetus (Bernabe *et al.,* 2004).

Female newborns were significantly more in SGA group as compared AGA group. Another study reported female newborns had (1.38) times risk to get SGA birth (Hameed *et al.,* 2011), whereas other studies from India did not show any difference in sex distribution (Dey *et al.,* 2007; Narang A *et al.,* 1997). Male babies having more birth weight than female babies in our study may be explained by the fact that Y chromosome has influence on the birth weight: term male infants weigh between 150 and 200 g more than females (Bernabe *et al.,* 2004). Significant difference was noted in birth weight of SGA babies as compared to AGA babies which is expected as SGA babies have intrauterine growth restriction.

Significantly more number of SGA babies were delivered through cesarean section than AGA babies in our study. Number of SGA babies admitted in NICU after birth were significantly more than AGA babies. This result suggests that SGA babies are having more morbidity at birth hence requires ICU care as compared to their AGA counterpart. This fact has been proven in many studies (Muhammad *et al.,* 2009; Hasthi *et al.,* 2017; Narang *et al.,* 1997). Morbid outcomes which were significantly more in SGA babies in our study were: Hyperbilirubinemia, Sepsis, Transient Tachyapnea of newborn, Hypoglycemia, Birth Asphyxia, polycythemia, Thrombocytopenia, Leucopenia and Feed intolerance. Similar outcomes have been reported by other studies (Sharma *et al.,* 2016).

Number of mothers who were having anemia in both SGA and AGA group were similar. This suggests that anemia is very common during pregnancy. It is evident from our study that as the severity of anemia during pregnancy increases the risk of delivering SGA baby also increases. So mother who is having very severe anemia has most risk, followed by mother with severe anemia, then moderate anemia and then mother with mild anemia for delivering SGA baby. The association between severity of anemia and SGA as shown in our study was also confirmed in a meta-analysis done in year 2012 which showed that hemoglobin <90- or <80-g/L range was associated with a 53% increase in risk of the newborn being SGA, hence moderate to severe, but not mild, maternal anemia appears to have an association with SGA outcomes (Katz, 2012). Study done in Assam has reported that maternal anemia was associated with increased risks of low birth weight and small-for-gestational age babies.(Nair et al,2016). However a recent meta-analysis showed that the overall relationship between maternal anemia during pregnancy and SGA was not significant, but the relationship between anemia during pregnancy and SGA based on pregnancy trimester showed that maternal anemia was significant in the first trimester, and this relationship was not significant in the second trimester (Badfer *et al.,* 2019). However in our study we have not looked at trimester wise association of anemia and risk of SGA. Another study done by Nair et al showed that Anemia during pregnancy is a risk factor for low birth weight and SGA, independent of the trimester (Nair *et al.,* 2018).

There are some plausible biological mechanisms linking maternal anemia to SGA. Low hemoglobin levels restrict oxygen circulation in the body, creating an environment of oxidative stress or chronic hypoxia, which could then cause fetal growth restriction. Another possible mechanism with iron deficiency anemia is that iron deficiency leads to an increased production of nor epinephrine, which then stimulates production of corticotrophin-releasing hormone and in turn possibly restricts fetal growth (Kozuki *et al.,* 2012).

CONCLUSION

Anemia is very common during pregnancy. As severity of maternal anemia increases risk of delivering term SGA baby also increase.

Term SGA newborn are not like term AGA newborn, due to intrauterine growth restriction, they are more prone for requiring ICU care, Hyperbilirubinemia, Sepsis, Transient Tachyapnea of newborn, Hypoglycemia, Birth Asphyxia, Polycythemia, Thrombocytopenia, Leucopenia and Feed intolerance. Hence special attention should be given to such babies after birth.

Early identification and prompt management of moderate to severe anemia during pregnancy can help in reducing the incidence of SGA, and in turn neonatal morbidity and mortality.

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