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Dr. Lalropuii
Obstetrician and Gynaecologist, Mamit District Hospital, Mamit, Mizoram, India

Dr. Sujatha TL
Professor, Department of OBG, SAT Hospital, Thiruvananthapuram, Kerala, India

Dr. Ayisha Begam
Assistant Professor, Department of OBG, Kanachur Institute of Medical Sciences, Mangalore, Karnataka, India

Corresponding Author:
Dr. Ayisha Begam
Assistant Professor, Department of OBG, Kanachur Institute of Medical Sciences, Mangalore, Karnataka, India

Evaluation of fetal hemodynamic changes and vascular adaptation to moderate and severe anemia in pregnancy

Dr. Lalropuii, Dr. Sujatha TL and Dr. Ayisha Begam

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Abstract
Maternal anemia is associated with poor intrauterine growth, pre maturity and increased risk of preterm births and low birth weight rates, this leads to increase perinatal mortality and morbidity causing poor growth in infants, childhood and adolescence, and ultimately leads to adult low weight and height which in turn is a determinant for birth weight and intrauterine growth. Patients fulfilling inclusion criteria were included in the study after obtaining informed consent. Then they were categorized into moderate and severe anemia depending on their hemoglobin level. All hemoglobin level was estimated by Sahli's method. Moderate anemia was defined as hemoglobin in between 7-10gm% and severe anemia if hemoglobin <7gm%. The MCA PSV was within 50-95th centile for gestational age in 92.9% for group 2,and 42.9% for group 1.while 57.1% group 1 and only 7.1% of group 2 cases were having MCA PSV values in between 5-50th centile for each gestational age. Mean CPR in group 1 was 2.05+/-0.45 and in group 2 was 2.02+/-0.39, the difference of which was not statistically significant.

Keywords: fetal hemodynamic changes, vascular adaptation, anemia in pregnancy

Introduction
Anaemia is the most common nutritional problem during pregnancy. Prevalence of anaemia in India is among the highest in the world [1]. Anaemia is a major public health problem in India accounting for 20% of direct maternal death and another 20% of indirect maternal death [2]. WHO has estimated that the prevalence of anemia in developed country is 14% and 51% in developing country. In India, WHO has estimated the prevalence of 65-75% [3].
National Family Health Survey (NFHS) –II in 1998-99 showed that 54% of women in rural and 46% women in urban are anaemic [4].
NFHS-III statistics reveal that every 2nd of Indian women is anemic and one in every five maternal death is directly related to anemia [5]. Although Kerala has good health indicators in comparison to other states, study of prevalence of anemia among tribal women of reproductive age group in Wayanad district of Kerela conducted by B M Srinivasa et.al in 2014 found that 96.5% of women were anemic [6]. Prevalence among women during pregnancy accounts for approx 57.8% in Kerala (21.3% were of moderate and 2.9% were severe anemia) [7]. As per NFHS-III, prevalence of pregnancy anemia was found to be 84% among 7 selected states including Kerala [8].
There is 8 to 10 fold increase in MMR when maternal hemoglobin falls below 5gm/dl, and a doubling of low birth weight rate, and 2 to 3 fold increase in perinatal mortality rate is seen when the Hb is <8gm/dl. Maternal anemia is associated with poor intrauterine growth, pre maturity and increased risk of preterm births and low birth weight rates, this leads to increase perinatal mortality and morbidity causing poor growth in infants, childhood and adolescence, and ultimately leads to adult low weight and height which in turn is a determinant for birth weight and intrauterine growth. Thus, maternal anaemia contributes to an intergenerational cycle of poor growth in the offspring [1]. The study conducted by Amalia Levy *et al*. in 2005 also concluded maternal anemia during pregnancy is an independent risk factor for low birth weight and preterm delivery.
In anemia during pregnancy, a preplacental chronic anemic hypoxia is believed to be the cause for growth restriction but the at what degree of anemia the fetus is affected and how it affects the fetus hemodynamically and associated cerebrovascular changes has been an area which is not commonly studied, unlike commonly studied growth restriction due to placental insufficiency like gestational hypertension.

Methodology

Inclusion criteria

Antenatal patients with >28weeks of gestation Moderate and severely anaemic pregnant women ieHb<10gm/dl (as per ICMR) Age between 18-40 yrs.

Exclusion criteria

Those antenatal patients with any comorbidities affecting fetal growth and size (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes infection, overt and gestational diabetes, gestational and chronic hypertension, malignancy, hereditary anemia, smoker or alcoholic, hemoglobinopathies, multiple gestation, Diagnosed renal or cardiac illness etc.) and those who are not willing to give consent.

Data collection technique

Patients fulfilling inclusion criteria were included in the study after obtaining informed consent. Then they were categorised into moderate and severe anemia depending on their hemoglobin level. All hemoglobin level was estimated by Sahli's method. Moderate anemia was defined as hemoglobin in between 7-10gm% and severe anemia if hemoglobin <7gm%.

Sahli's method: N/10 of HCL is taken into Sahli'stube, upto 10th level of scale, then 0.02ml of blood is added into it by Sahli's pipette, this will cause lysis of blood cells and hemoglobin will be realeased, which will combine with HCL and form acid hematinin which is tan coloured. This tube is put in hemometer and drop of distilled water is added continuously and is stirred with stirrer until it has exactly the same colour as the comparision standards. Then the reading is taken when colourmatches. Hemoglobin value is expressed as gm/dl or gm%.

After confirming anemia, serum ferritin, peripheral smear study, and RBC indices were sent to confirm iron deficiency anemia. Previous blood reports for glucose tolerance test and thyroid function test, liver and renal function test were checked and sent immediately if not done. If any report came back as abnormal, patient is excluded from the study group.

A pre-structured interview schedule was used to collect information on age, educational qualification, socio-economic status, dietary history, occupation, detailed medical history. A complete clinical examination was done. Clinical evidence of fetal growth restriction and assessment of liquor was done. The previous records of hemoglobin value, obstetric reports ultrasound scan reports reviewed.

Gestational age was corrected according to first trimester dating scan for those who has irregular cycles and gestational age according to last menstrual period was used if patient remembers their date of last menstrual period with previous regular cycles with dating scan corresponding to first trimester scan.

Obstetric ultrasound was done in Department of Radio Diagnosis, with an image point color Doppler machine (Logiq P5) with a convex probe, 3.5 MHz transducer and an electronic caliper system. Patient in recumbent position, fetal biometry and liquor assessment and Doppler study of umbilical and middle cerebral artery was done.

Results

In group 1,there was 76.2% of cases whose UMA PI lies in between 5-50th centile and 23.8% of cases in between 50-95th centile for gestational age. In group 2 it was 78.6% and 21.4%. which was within normal range for each gestational age and the difference between group 1and 2 was not statistically significant.

Table 1: Umbilical Artery PI Distribution

UMA PI	Degree of anemia				Total		χ^2	Df	P
	Group 1		Group 2						
	N	%	N	%	N	%			
5-50th centile	16	76.2	11	78.6	27	77.1	.027	1	.869
50-95 th centile	5	23.8	3	21.4	8	22.9			
Total	21	100.0	14	100.0	35	100.0			

5-50th centile for each gestational age of UMA RI was seen in 52.4% in group 1 and 64.3% in group 2.

50-95th centile for each gestational age in 47.6% in group 2,and 35.7% in group 2

The difference in UMA RI in both the groups is statistically not significant.

Table 2: Umbilical Artery Resistance Index Distribution

UMA RI	Degree of anemia				Total		χ^2	Df	P
	Group 1		Group 2						
	N	%	N	%	N	%			
5-50th centile	11	52.4	9	64.3	20	57.1	.486	1	.486
50-95 th centile	10	47.6	5	35.7	15	42.9			
Total	21	100.0	14	100.0	35	100.0			

Umbilical artery S/D was found to be within normal limit for both groups, with 61.9% of group 2 and 57.1% of group 2 lies in between 5-50th centile and 38.1% of group 1 and 42.9% of group 2 were found to be in between 50-90th centile for each gestational age, which was not statistically significant.

Table 3: Umbilical Artery S/D Distribution

UMA SD	Degree of anemia				Total		χ^2	Df	P
	Moderate		Severe						
	N	%	N	%	N	%			
5-50th centile	13	61.9	8	57.1	21	60.0	.079	1	.778
50-95 th centile	8	38.1	6	42.9	14	40.0			
Total	21	100.0	14	100.0	35	100.0			

In group 1, MCA RI was 5-50th centile in 52.4% and in group 2 it was 85.7%.

Also, in group 1, MCA RI was 50-95th centile in 47.6% and in group 2 it was 14.3%.

This means there was reduction in resistive index of MCA in both severe anemia (ie 5-50th centile in 85.7%) and moderate anemia (52.4%). Although there was reduction in both groups, the reduction was more in group 2, and this was statistically significant.

The mean MCA RI was 0.65+/-0.19 in severe anemia, and 0.75+/-0.07 in moderate anemia.

Table 4: Showing MCA Resistance Index Distribution

MCA RI	Degree of anemia				Total		χ^2	Df	P
	Group 1		Group 2						
	N	%	N	%	N	%			
5-50th centile	11	52.4	12	85.7	23	65.7	4.143	1	. 042
50-95 th centile	10	47.6	2	14.3	12	34.3			
Total	21	100.0	14	100.0	35	100.0			

In group 1, MCA PI was, 5-50th centile in 71.4% and, 78.6% in group 2. In group 1, MCA PI was 50-95th centile in 28.6%, and in it was not found in group 2.

There was no cases wih MCA PI of <5th centile for each gestational age in group 1. While it was seen in 21.4% in group 2. This also indicate that the reduction in MCA PI is more in group 2 (severe anemia) than in group 2.

Table 5: MCA Pulsatility Index Distribution

MCA PI	Degree of anemia				Total		χ^2	Df	P
	Group 1		Group 2						
	N	%	N	%	N	%			
<5th centile	0	0.0	3	21.4	3	8.6	8.558	2	.014
5-50th centile	15	71.4	11	78.6	26	74.3			
50-95 th centile	6	28.6	0	0.0	6	17.1			
Total	21	100.0	14	100.0	35	100.0			

In group 1, the ratio of cerebral and umbilical resistive index was normal ie>1.1 in all the subjects. In group 2, there was 1 case of abnormal C/U resistance (1.09), whose haemoglobin was 5.6gm/dl while all other cases group 2 have normal C/U ratio.
However, there was a reduction in the C/U ratio in both the groups. The mean C/U ratio in group 1 and 2 was 1.39+/-0.19 and 1.16+/-0.05 respectively and this difference is statistically significant

Table 6: C/U ratio distribution

CRI/URI	Degree of anemia				Total		χ^2	Df	P
	Moderate		Severe						
	N	%	N	%	N	%			
Normal	21	100.0	13	92.9	34	97.1	1.544	1	.214
Abnormal	0	0.0	1	7.1	1	2.9			
Total	21	100.0	14	100.0	35	100.0			

The MCA PSV was within 50-95th centile for gestational age in 92.9% for group 2, and 42.9% for group 1.while 57.1% group 1 and only 7.1% of group 2 cases were having MCA PSV values in between 5-50th centile for each gestational age.

Table 7: MCA PSV Distribution

MCA PSV	Degree of anemia				Total		χ^2	Df	P
	Moderate		Severe						
	N	%	N	%	N	%			
5-50th centile	12	57.1	1	7.1	13	37.1	8.995	1	.003
50-95 th centile	9	42.9	13	92.9	22	62.9			
Total	21	100.0	14	100.0	35	100.0			

The CPR was also normal in both the groups.
Mean CPR in group 1 was 2.05+/-0.45 and in group 2 was 2.02+/-0.39, the difference of which was not statistically significant.

Table 8: Mean values with standard deviation of study variables in group 1 and group 2

Variables	Anemia				t	P
	Moderate (N=21)		Severe (N=14)			
	means	Sd	means	sd		
GA in wks	35.57	2.59	37.30	0.98	-1.708	.101
Hb	8.30	1.07	6.25	0.58	6.543	<0.001
AFI	11.35	3.06	9.19	2.34	2.239	.032
SFH cms	33.57	2.34	31.54	3.60	2.004	.054
EFW kg	2320.14	503.40	1860.86	704.06	2.254	.031
MCA RI	0.75	0.07	0.65	0.19	2.199	.035
UA RI	0.57	0.06	0.54	0.04	-1.594	.120
C/U	1.39	0.19	1.16	0.05	4.528	<0.001
UA PI	0.83	0.14	0.75	0.21	1.467	.152
MCA PI	1.72	0.31	1.66	0.39	.512	.612
MCA PSV	2.63	0.51	2.93	0.27	-3.378	.003
MCA SD	4.50	1.03	5.03	1.58	-1.206	.236
MCA S/D	4.45	0.93	4.53	1.21	-.201	.842
UA S/D	2.48	0.35	2.61	0.72	-1.924	.063
PSV	49.25	13.80	60.69	8.97	-2.734	.010
CPR	2.05	0.45	2.02	0.39	.234	.817

Discussion

There was a reduction in amniotic fluid index on severe anemia. The mean amniotic fluid index in severe and moderate anemia was 11.35+/-3.06 cms and 9.19+/-2.3 4cms respectively which was statistically significant (p<0.03). This may indicate the hypoxic environment of fetus in severe anemia, where there is decrease blood flow to kidneys and adrenals leading to decrease in urine output and subsequent oligamnios.
Similarly, Milan Stefanovi'c and colleagues in 2005 also reported the incidence of oligoamnios in severe maternal anemia, where the mean amiotic fluid in severe and moderate anemia was 6.61+/-1.52cms and 11.62+/-19.76cms [9]. In the study by Ghada A the mean AFI in moderate and severe anemia was 13.24 and 12 respectively [10].
Umbilical artery Doppler assessment was found to be within normal values for both the groups. This may show that there is no insult to placental circulation and hence there is no placental insufficiency in anemic hypoxia, unlike the hypoxia induced by placental insufficiency, where there is elevated impedance to blood flow in umbilical artery. In this study, there was no change in placental blood flow, in fact there was a slight reduction in the pulsatility and resistivity index in severe anemia group compare to moderate anemia, but is not significant statistically [6].
Middle Cerebral Artery showed a reduction in RI and PI, with significant reduction in mean RI. Mean MCA RI and PI for moderate and severe anemia was 0.75+/-0.07 and 0.65 +/-0.19 and 1.72+/-0.31 (p<0.03) and 1.66+ /-0.39 (p<0.6) respectively.
There was a reduction in the C/U ratio in both the groups. The mean C/U values in group 1 and 2 was 1.39+/-0.19 and 1.16+/-0.05 respectively. This means there is more reduction in the impedance of cerebral blood flow in severe anemia than in moderate anemia and this difference is statistically significant (p<0.001). In group 1, the C/U values are higher and are within normal values. This means that blood flow distribution between placenta and brain were normal. In group 2, the C/U value was much lower meaning that the fetus has to adapt by increasing its blood supply towards brain by vasodilatation of cerebral vessels.
The similar study by Ghada A *et al*. found the C/U values in moderate and severe anemia as 1.18 and 1.2 respectively, which is almost same to this study. But the study by Milan stefanovic` *et al*. have obtained 1.35+/-0.13 and 1.07+/-0.12 respectively. The lower values in their study may be attributed to the lower mean haemoglobin value ie 4.84+/-3.88gm/dl where in this study, mean hemoglobin value is 6.25+/-0.58gm/dl.
The MCA PSV was found within normal range for each gestational age, with a significant increase in the mean value in severe anemia group. This may be correlated with the hypoxic environment in severe maternal anemia and compensatory increase in cardiac output in hypoxic fetus [4].
This study shows that severe maternal anemia during third trimester has significant effect on fetal growth and well being. 78.8% of severe anemic patients have growth restricted fetus 21% of them have AFI <5th centile for gestational age. There is

significant fetal hypoxia in severe anemia as suggested by significant reduction in C/U ratio and thus vasodilatation as a protective mechanism. Hence, severe anemia should be corrected as soon as possible with blood transfusion as it may lead to fetal distress, and several adverse outcome if not corrected on time as fetal cerebral vasodilatation during a period of several weeks under hypoxia does not protect against cerebral organic damage [5].

There is no significant vasodilatation in moderate anemia, suggesting a satisfactory oxygenation for fetus. Hence, in moderate anemia the physiological adaptation of fetus to extract more hemoglobin from the maternal blood in the placental blood flow is adequate to meet the needs of the fetus, hence immediate correction such as blood transfusion may not be required in case of moderate anemia.

Conclusion

- The CRI/URI (cerebral/umbilical resistance ratio) was also reduced in both the groups with more reduction in severe anemia, and there was significant reduction between the two groups. (p<0.001) but there was no reversal of this ratio in both the groups.
- Cerebroplacental ratio was normal in both groups with slight reduction in severe anemia group, But the difference in reduction between the two group is not significant statistically

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