LUPINE PUBLISHERS

Journal of Clinical & Community Medicine

DOI: 10.32474/JCCM.2020.02.000134

ISSN: 2690-5760

Research Article

Hemoglobin Disorders and Scenario of Reproductive Medicine in Central India: Need for Family Planning, Antenatal-Pediatric Health Care and Amelioration

RS Balgir*

Department of Biochemistry, ICMR - National Institute for Research in Tribal Health, Madhya Pradesh, India

***Corresponding author:** RS Balgir, Ex-Scientist F/Deputy Director (Senior Grade) & Head, Department of Biochemistry, ICMR-National Institute for Research in Tribal Health, Jabalpur, Madhya Pradesh, India

Received: June 25, 2020 **Published:** July 07, 2020

Abstract

Background: Hemoglobin disorders are autosomal recessively inherited, genetically transmitted monogenic blood defects, world-wide highly prevalent in tropical regions, and causing the major public health challenges in central India. In view of credit for the 2nd highest infant mortality rate (IMR) in Madhya Pradesh (70 per thousand live-births in the year 2010), it seems, therefore, carrier couples of the hemoglobinopathies might be one of the contributing factors for the high IMR in central India.

Objectives: The aim of this study is to investigate actual reproductive (antenatal and postnatal) scenario pertaining to fertility and mortality in couples afflicted with hemoglobin disorders. Methods: Couples (parents) including their offsprings with at least one affected/suspected case of hemoglobinopathies, referred to ICMR - National Institute for Research in Tribal Health, Jabalpur from the local NSCB Medical College and Hospital, were consecutively studied as matched case controls. A total of 171 couples was referred during the period from March through December 2010.

Results and Discussion: Out 171 couples, 80 were found normal and 91 couples had different hemoglobin disorders. It was observed that the number of conceptions (2.187 vs 1.800), livebirths (1.934 vs 1.562), surviving offsprings (1.802 vs 1.437), stillbirths (0.121 vs 0.062), neonatal deaths (0.132 vs 0.100), deaths under one year (0.153 vs 0.112), and deaths under 10 year (0.220 vs 0.125) per couple at the time of investigations was higher in couples with hemoglobinopathies than the normal controls. The number of stillbirths (0.121 vs 0.062) per couple was almost two times higher in couples with different hemoglobin disorders than in the controls. Carrier and affected families were imparted genetic/marriage counseling.

Conclusions: This study indicated that afflicted couples with these hereditary (genetic) disorders are increasing the affected offsprings. The increased production of abnormal offspring leads to increased morbidity and mortality and may be contributing towards increased neonatal/infant (antenatal and postnatal) mortality or reproductive wastage in the state of Madhya Pradesh. These couples are in urgent need of family planning, antenatal/postnatal health care and family welfare.

Keywords: β-thalassemia syndrome; Sickle cell anemia; Defective genetic endowments; Reproductive medicine; Family Planning; Antenatal health care; Genetic counseling

Introduction

Hemoglobin disorders are, autosomal recessively inherited, genetically transmitted monogenic blood defects, world-wide highly prevalent in tropical and sub-tropical regions, and causing the major public health challenges in India. The β-thalassemia syndrome and sickle cell disorders are the major genetic, public/community health care and devastating challenges in tropical central India. The victims include the infants, growing children, adolescent girls, pregnant women and a large number of ignorant and vulnerable people. Inherited disorders of hemoglobin cause high degree of hemolytic anemia, clinical jaundice, frequent infections, painful crises, splenomegaly, retardation of development and growth [1-3] and are responsible for high infant morbidity, mortality and antenatal (fetal) wastage in India [4-12]. In sickle cell disease, the distorted red blood cells lead to increased viscosity and hemolytic anemia; and further decreased oxygenation. When sickling occurs within small blood vessels, it can cause logjams (clogging) that

can interrupt blood supply to vital organs (vaso-occlusive crisis). Repeated vaso-occlusive crises result in widespread microvascular obstruction with interruption of normal perfusion and function of several organs, including the spleen, lungs, kidneys, heart, and brain. Adults with sickle cell disease are functionally asplenic, having undergone auto-splenectomy and contribute to the increased incidences of severity of infections. A great deal of literature is available regarding the clinical and hematological aspects of these disorders, but the details regarding the reproductive outcome in affected couples are scanty in India [13-16].

The neonatal (NMR) and infant mortality rates (IMR) are the most important indicators of socio-economic status of a community/country. Early detection and effective clinical management of anemia in pregnancy may contribute substantially to the reduction in undernutrition in childhood, adolescence and improvement in maternal health and reduction in maternal mortality. Maternal anemia is associated with poor intrauterine growth and increased risk of preterm births and low birth weight babies. This, in turn, results in higher perinatal morbidity and mortality, and higher infant and antenatal mortality rate [14, 17-19]. A doubling of low birth weight rate and 2 to 3 fold increase in the perinatal mortality rates is seen when the hemoglobin is less than 8g/dl [18, 19]. Intrauterine growth retardation and low birth weight inevitably lead to poor growth trajectory in infancy, childhood and adolescence and contribute to low adult height [18, 19]. Parental height and maternal weight are determinants of intrauterine growth and birth weight [18]. Thus, maternal anemia contributes significantly to the intergenerational cycle of poor growth and development in the offspring [17-19].

In view of the credit of the 2nd highest infant mortality rate (IMR) in the state of Madhya Pradesh (70 per thousand live-births in 2010) in comparison to other states and the average of India (53) and the high prevalence of hemoglobin disorders, it was presumed that -thalassemia syndrome and hemoglobinopathies, apart from poor nutrition and unhygienic conditions and meager medical health care facilities, might be one of the significantly contributing factors for the infant/neonatal mortality or antenatal (fetal) wastage in carrier couples of hemoglobinopathies in the state of Madhya Pradesh. The study was designed keeping in mind the poor health scenario in central India to find the fertility and mortality among the couples in relation to hemoglobin disorders and to suggest remedial measures for amelioration of the affected population, in general, in India.

Materials and Methods

In the present study, a total of 171 native couples (families) were screened for β-thalassemia and other hemoglobinopathies during the period between March through December 2010, irrespective of age, sex, religion, caste, and community. Matched couples who were free from any kind of β-thalassemia syndrome and hemoglobinopathies, served as case controls for the present study. The couples (parents) including their offsprings with at least one suspected/confirmed case of homozygous β-thalassemia/hemoglobin E/Sickle cell anemia or compound heterozygosity, attending the Netaji Subhash Chandra Bose (NSCB) Medical College & Hospital, Jabalpur, Madhya Pradesh, were included in the study. The study was carried out according to the ethical guidelines for biomedical research on human subjects. Each subject was requested to provide the background information such as name, age, residential address, reproductive history (abortion, miscarriage, stillbirth, etc) if any, month of gestation, history of hospitalization if any, blood transfusion or pregnancy related complications, if any, etc. In addition, the suspected cases of hemoglobinopathies routinely referred to ICMR – National Institute for Research in Tribal Health, Jabalpur were also included in the study. Those cases with only iron deficiency anemia, induced abortion or accidental deaths were excluded from the study.

For the present study, the neonatal mortality rate (NMR) is defined as the number of deaths within 28 days of life per thousand livebirths in a particular area, whereas, the infant mortality rate (IMR) is defined as the number of deaths within one year per thousand livebirths in a particular area.

There are several relevant co-confounding and concomitant non-genetic variables that are known to affect reproductive outcome in terms of neonatal and infant mortality and enhance reproductive wastage in both normal controls and carrier cases of hemoglobinopathies [6, 18]. For inclusion criteria, the factors like lack of tetanus toxoid immunization, malnutrition (nutritional deficiencies), neonatal infection, prematurity (low birth weight), acute respiratory infection, abnormal condition of placenta and cord, anemia and jaundice, hand and foot syndrome, retarded growth and development, diarrhea, malaria, lack of basic health care, prevalent unhygienic conditions, poverty, illogical socio-cultural traditions and taboos, single parenthood, were covered. The neonatal period constitutes almost two-third of the deaths of IMR. The causes of death during neonatal period are: sepsis, birth asphyxia (when a baby does not breathe or cry immediately after birth), prematurity (born before 37 weeks of gestation) and low birth weight (less than 2.5 Kg), birth injury and congenital anomaly (cleft lip and cleft palate, heart disease) including genetic defects (hemolytic anemia or jaundice). Exclusion criteria for this study include birth asphyxia, birth injury, HIV infection, sexually transmitted diseases (syphilis, etc.), aplastic anemia and other hematological disorders, congenital anomalies, measles, accidental death, etc.

Intravenous 2 ml of blood samples were taken under aseptical conditions from each individual after taking informed/written consent for screening of hemoglobinopathies and β-thalassemia syndrome. All the adopted techniques and procedures standardized

in the laboratory were followed as described elsewhere [6-12, 20]. For quality control, results were cross-checked periodically.

The genotypes of couples like AA X AA stands for normal husband and normal wife (control); AA X AS denotes for normal husband and sickle cell trait wife or normal wife and sickle cell trait husband; AA X SS for normal husband and sickle cell disease wife or vice versa; AS X AS denotes that both husband and wife are carrier for sickle cell disease; AS X SS means one partner is carrier for sickle cell disease and other partner is suffering from sickle cell disease; AS X β–Thal. Trait stands for one partner being carrier for sickle cell disease and the other counterpart is beta-thalassemia trait (or carrier of Thalassemia major); the genotype AS X S-β–Thal stands for one partner being carrier of sickle cell disease and the other partner is sickle cell-beta-thalassemia (having compound disease, i.e. sickle cell and beta-thalassemia); sickle cell disorders mean here all the above diagnostic categories (genotypes) combined except the normal controls. Out 171 couples, 80 were found normal and 91 couples had different hemoglobin disorders. Results of analysis were given to parents for treatment and further clinical management by the concerned referring doctor. It was envisaged to bring awareness among these couples through genetic counseling about the genetic disorders and their causal effects on health. Their eradication is necessary because they are not curable but preventable through prenatal diagnosis for carrier detection, education and genetic counseling.

Results

It is emphasized that both normal controls (vs = versus) and abnormal subgroups (combined hemoglobinopathies) had similar characteristics with respect to the concomitant factors and the present observations of reproductive outcome are attributable to different genotypes of hemoglobinopathies in the state of Madhya Pradesh from Central India. The reproductive history of normal controls as well as different combinations of genotypes of hemoglobinopathies in carrier couples is presented in Table 1 and 2. It is interesting to note that the number of conceptions (2.187 vs 1.800), livebirths (1.934 vs 1.562), surviving offspring's (1.802 vs 1.437), stillbirths (0.121 vs 0.062), neonatal deaths (0.132 vs 0.100), deaths under one year (0.153 vs 0.112), and deaths under 10 year (0.220 vs 0.125) per couple at the time of investigations was higher in couples with hemoglobinopathies (combined) as compared to normal controls (Tables 1- 4). The number of stillbirths (0.121 vs 0.062) per couple was almost two times higher in couples with different hemoglobin disorders (combined) than in the controls (Tables 1,2).

Further, it is noteworthy that the fertility or the number of conceptions per abnormal (combined hemoglobinopathies) couple is higher than in the normal controls (Tables 1, 2). This implies that the abnormal couples produce more children than the normal couples to ensure the survival of at least some of them.

Table 1: Reproductive history (figures in absolute numbers) of couples with different hemoglobinopathies.

Diagnosis	No. of Couples	Conceptions	Abortions	Stillbirths	Neonatal Deaths●	<1year Deaths■	<10 years
Hb AA X Hb AA (Normal controls)	80	144	14	5	8	9	10
Hb AA X Hb AS	24	53	6	4	2	2	2
Hb AA X Hb SS	4	7	0	3	1	1	1
Hb AS X Hb AS	17	45	3	0	5	6	9
Hb AS X Hb SS	5	9	0	0	2	3	4
Hb AS X Hb AE	1	3	1	0	0	0	0
Hb AE X -Thal.T	1	7	0	0	0	0	0
Hb AS X -Thal.T	7	21	1	0	0	0	1
Hb AA X S- -Thal	2	2	0	0	0	0	0
Hb AS X S- -Thal	5	11	0	1	1	1	1
-Thal.T X S- -Thal	2	3	0	0	0	0	0
Hb AA X -Thal.T	13	22	0	3	1	1	1
Thal.T X -Thal.T	10	22	1	0	0	0	1
Hemoglobinopathies (Combined)	91	199	12	11	12	14	20

●Birth to 28 days. ■Birth to 365 days or within 1 year.

Table 2: Reproductive history of couples with hemoglobinopathies.

Diagnosis	No. of Couples	Conceptions	Abortions	Still-births	Neonatal Deaths●	<1year deaths ■	<10 yrs Deaths
Normal (Hb AA X Hb AA)	80	144	14	5	8	9	10
Per Couple	-	1.8	0.175	0.062	0.1	0.112	0.125
Per 1000 Livebirths	-	125/144	112	40	64	72	80
Hemoglobinopathies (Combined)	91	199	12	11	12	14	20
Per Couple	-	2.187	0.131	0.121	0.132	0.153	0.22
Per 1000 Livebirths	-	176/199	68	63	68	79	113

●Birth to 28 days. ■Birth to 365 days or within 1 year

Table 3: Surviving children (offsprings) with hemoglobinopathies.

Diagnosis	No. of Couples	Concep-tions	Total Survivals	Hb AA		Hb AS		Hb SS		S- -Thal.		-Thal. T		Thal. Major		Hb SE		Hb E-Thal	
				M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Hb AA X Hb AA(Normal)	80	144	115	53	62														
Hb AA X Hb AS	24	53	41	20	8	9	4												
Hb AA X Hb SS	4	7	3	2	0	0	1												
Hb AS X Hb AS	17	45	33	4	6	5	5	7	7										
Hb AS X Hb SS	5	9	5			2	2	0	1										
Hb AS X Hb AE	1	3	2	0	1											1	0		
Hb AS X b-Thal. T	7	21	19	1	1	0	3			5	1	3	5						
Hb AS X S-b-Thal.	5	5	10	0	1	1	1	1	1	2	1	0	2						
Hb AA X S-b-Thal.	2	2	2	0	1							0	1						
Hb AA X b-Thal T	13	22	19	8	6							0	4						
b-Thal T X b-Thal T	10	22	20	3	9							3	2	1	2				
b-Thal T X S-b-Thal	2	3	3			2	0			1	0								
Hb AE X b-Thal T	1	7	7	1	4							1	0					0	1
Hemoglobinopathies (Combined)	91	199	164	39	37	19	16	8	9	8	2	7	14	1	2	1	0	0	1

Table 4: Surviving offsprings (sexes combined) with hemoglobinopathies.

	No. of Couples	Conceptions	Livebirths	Surviving	HbAA M+F	HbAS M+F	HbSS M+F	S- - Thal M+F	- Thal.T M+F	-Thal. Major M+F	HbSE M+F	HbE Thal M+F
Normal Control	80	144	125	115	115	-	-	-	-	-	-	-
Per Couple	-	1.8	1.8	1.56	1.44	-	-	-	-	-	-	-
Per 1000 Livebirths	-	-	-	920	920	-	-	-	-	-	-	-
Hemoglobinopathie (Combined)	91	199	176	164	76	35	17	10	21	3	1	1
Per Couple	-	2.19	1.93	1.8	0.84	0.38	0.19	0.11	0.23	0.03	0.01	0.01
Per 1000 Livebirths	-	-	-	933	432	199	97	57	119	17	6	6

Discussion

Hemodynamics in Pregnancy

In normal pregnancy, a large number of physiological modifications in the hemodynamic, cardiovascular, and coagulation-fibrinolysis systems occur that are designed by nature to prevent blood loss during delivery. During the first trimester, there is an increase in blood volume [21, 22]. The volume of blood continues to expand rapidly during the 2nd trimester (30-50%) before it reaches the stable level in the last three months. In parallel, the amount of red blood cells (RBC) increases but to a lesser extent (20%), leading to relatively anemia due to hemodilution [21, 23], and this reaches

to its maximum level by 30-32 weeks of pregnancy. Dilutional decrease of hemoglobin is, therefore, a common physiological process of pregnancy, especially between 28 and 34 weeks, when hemoglobin concentrations are the lowest. In the first month of pregnancy, the red blood cell mass increases about 18-25%, followed by a drop after childbirth due to peripartal hemorrhage [21, 24-26]. The increase in RBC mass ensures enough oxygen for the increased demands from both mother and fetus. These physiological changes lead to decrease in ~thrombosis, and an adequate blood supply is ensured despite the bleeding that occurs with childbirth [27-29]. Uterine artery blood flow increases during pregnancy (ten times) and reaches 450-750ml/min at term [30].

In parallel, there is a substantial increase in clotting capacity with an increase of coagulation factors I (fibrinogen), VII, VIII, IX, X, XII and von Willer brand factor. In summary, hemodynamic and hemostatic changes represent adaptation of nature to the challenges of reproduction and are prerequisite for a successful pregnancy outcome of mother and her child.

Iron Deficiency/Hemolytic Anemia in Pregnancy

In general, anemia occurs frequently in pregnant women and is associated with iron deficiency or rapid hemolysis of red blood cells. Others causes include hemoglobinopathies (β-thalassemia, sickle cell anemia), infections (hookworms, malaria), vitamin B12 deficiency, or chronic inflammations. In most cases, it is possible to find the reason of anemia and treat it correctly during pregnancy, thereby improving the outcome of mother and child.

The primary reason of anemia in pregnancy is iron deficiency. Iron need increases considerably during pregnancy. Most of time, the iron stores are insufficient to fulfill this increase, which is the consequence of physiological changes (erythrocyte mass ~ 450 mg, placenta ~80 mg, bleeding during vaginal delivery of birth ~250 mg, and fetus ~225 mg). The iron needs during pregnancy are estimated to one gram of additional iron. If the woman breastfeeds her child, she will need an extra one gram iron per day [31]. If anemia is diagnosed during pregnancy, the following hematological investigations [a mean cell volume (MCV) can elucidate and support the cause of anemia] and can advocate: (a) microcytic anemia due to iron deficiency or hemoglobinopathy; (b) microcytic anemia related to deficiency in vitamin B12 or folate; and (c) normocytic anemia related to maternal diseases/infections.

Iron deficiency can, therefore, not be excluded if the MCV is normal. Hemoglobinopathies should always be suspected in case of severe hypochromic microcytic anemia. Red cell distribution width (RDW) may to help differentiate iron deficiency from other microcytic anemias, e.g., hemoglobinopathies. Thus, if mean corpuscular hemoglobin is below 26 pecogram (pg), it is important to screen for hemoglobinopathies in case of normal iron stores. Regarding iron stores, serum ferritin seems to be the best and most reliable and practical marker.

Hereditary or Genetic Contributions

The present study strongly supports the contention that hereditary hemoglobin disorders including -thalassemia syndrome and sickle cell disease (anemia) contribute significantly to the reproductive and antenatal wastage and high neonatal, infant and childhood (pediatric) morbidity and mortality in the state of Madhya Pradesh in Central India. There are several high risk vulnerable communities that practice territorial endogamy and frequently marry among blood relatives (consanguinity) because of economic/property benefits leading to inbreeding due to small effective community size. There have emerged several independent breeding isolates of a community with the passage of time which had a common stock in the distant past. These findings are in agreement with our previous studies carried out in the state of Orissa [5, 14-16]. Moreover, hemoglobin disorders are, autosomal recessively inherited, genetically transmitted monogenic blood defects, and world-wide highly prevalent public health challenges in tropical and sub-tropical regions in India and also elsewhere too. Thus, globally as well as locally, they are posing a major genetic and health care problem for prudently tackling them.

This study has revealed that hereditary causes, apart from other concomitant nongenetic factors, could also be responsible for the higher neonatal/infant mortality in Madhya Pradesh. It is apparent that the reproductive wastage stillbirths, neonatal deaths, and childhood (pediatric) deaths per couple with hemoglobinopathies are higher as compared to normal couples (Tables 1- 4). These results are consistently similar to our previous findings [5, 6-12]. Moreover, the number of deaths of offspring below 1 year of age (infant mortality) and below 10 years of age (childhood or pediatric mortality) in such couples is also higher than in normal couples. These findings show that couples of sickle-cell trait, -thalassemia, and sickle cell/ -thalassemia, etc. contribute disproportionately to the progeny with the high neonatal/infant mortality. Similar findings are also expected from the adjacent state of Chhattisgarh, earlier being the part of undivided state of Madhya Pradesh.

Further, in the state of Madhya Pradesh, it is intriguingly valid that the number of conceptions (fertility) per poor abnormal couple (having combined hemoglobinopathies) is said to be higher than in the normal controls (Tables 1-4). This implies that the abnormal poverty-stricken couples produce more children than the normal couples to overcome the non-survival of some of their children. These results are consistent with our previous findings reported from the state of Orissa [5, 6, 19, 32, 33].

Fetal wastage from abortions, stillbirths, and neonatal deaths is increased in mothers with homozygous sickle-cell disease [18]. Spontaneous abortions occurred in 19.2% of pregnancies of sickle-cell disease mothers [32, 33]. An increased rate of stillbirths (11.5%) in pregnant women with sickle cell disease [18] and 5% was observed in pregnant women in Baltimore [18]. Overall

perinatal mortality (stillbirths and neonatal deaths) was 8.1%, four-fifths attributable to stillbirths and one-fifth to neonatal deaths [20, 32, 33]. In the present study, a comparatively lower number of abortions, stillbirths, neonatal mortality, and infant mortality per 100 livebirths have been observed to be 6.8%, 6.3%, 6.8%, and 7.9%, respectively, in couples with carrier status of hemoglobinopathies (combined) in the state of Madhya Pradesh. These findings show comparatively improvement of medical health care facilities in India with the passage of time.

Lastly, it is emphasized that there is an urgent need to take up intervention and prevention program at least in affected couples at grass root level in the state of Madhya Pradesh to mitigate the sufferings of poverty stricken underprivileged, innocent, and vulnerable people. Prenatal diagnostic facilities/newborn screening programs need to be developed in the localities of vulnerable communities. Consanguineous marriages need to be discouraged to prevent inbreeding among the vulnerable communities in Madhya Pradesh state. Appropriate genetic/marriage counselings need to be imparted to the carrier and affected families to prevent the homozygosity of hemoglobin disorders in the vulnerable communities in central India.

Acknowledgements

Author expresses gratitude to Dr. V. M. Katoch, Secretary, Department of Health Research, Government of India, and Director General, Indian Council of Medical Research, New Delhi for the permission and providing the necessary research facilities. Technical help of Mr. P. Patel, Laboratory Technician is thankfully acknowledged. Thanks are due to all the couples and the staff of Netaji Subhash Chandra Bose Medical College & Hospital, Jabalpur, Madhya Pradesh for their kind cooperation during the study.

References

1. Balgir RS (1995) The clinical and hematological profile of sickle cell disease cases in India. Indian Practr 48: 423- 432.
2. Balgir RS (2006) Clinical genetics and hematological profile of sickle cell cases in twenty families of Orissa. Indian J Hemat Blood Transfus 22: 45-52.
3. Balgir RS (2007) Epidemiology, population health genetics and phenotypic diversity of sickle cell disease in India. Internet J Biol Anthropol 1: 1-26.
4. Balgir RS, Dash BP, Das RK (1997) Fetal outcome and childhood mortality in offspring of mothers with sickle cell trait and disease. Indian J Pediatr 64: 79-84.
5. Balgir RS (2007) Infant mortality and reproductive wastage associated with different genotypes of hemoglobinopathies in Orissa, India. Ann Hum Biol 34: 16- 25.
6. Balgir RS (2013) Reproductive wastage in carrier couples of hemoglobinopathies: Experiences from a retrospective study in Madhya Pradesh, India. Intl J Child Health Hum Develop 6(2): 235-242.
7. Balgir RS (2014) Reproductive outcome in carrier couples of β–thalassemia disorders in a tertiary hospital in central India. Thalassemia Reports 4: 10-15.
8. Balgir RS (2014) Population and public health implications of child health and reproductive outcomes among carrier couples of sickle cell disorders in Madhya Pradesh, India. Intl J MCH AIDS 2(2): 229-235.
9. Balgir RS (2015) Prevalence of hemolytic anemia and hemoglobinopathies among the pregnant women attending a tertiary hospital in central India. Thalassemia Reports 5(4644): 16-20.
10. Balgir RS (2018) Hematological profile of hemoglobinopathies in maternal health and reproductive outcome in pregnant mothers at a tertiary hospital in central India. J Hematol Mult Myeloma3(1):1012.
11. Balgir RS (2019) Hematological-genetics, reproductive health and family welfare in Madhya Pradesh, India. Clin Res Hematol 2(2): 1-6.
12. Balgir RS (2019) Maternal genetics, health and hematological profile of pregnant women in Madhya Pradesh, India. Arch Hematol Blood Dis 2(2): 14-20.
13. Balgir RS (2020) Prenatal, Neonatal and Pediatric Health Care and Reproductive Medicine in relation to Hemoglobinopathies in Three Stratified Communities of Central India. Arch Hematol Blood Dis 3(1):44-52.
14. Balgir RS (2013) Contribution of marital distance to community inbreeding, Homozygosis, and reproductive wastage for inherited genetic disorders in Madhya Pradesh, India. Mediterr J Hematol Infect Dis 5(1): 5.
15. Balgir RS (2010) Detrimental intrinsic factors contain population explosion for sustainable development in 18 indigenous communities of Orissa, India. In: Pati RN & Jain Atul Kumar (Editors) Biodiversity and Sustainable Development. (40th Chapter). Sarup Book Publishers Private Limited, New Delhi pp. 507-516.
16. Balgir RS (1992) Reproductive profile of mothers in relation to hemoglobin E genotypes. Indian J Pediatr 59: 449-454.
17. Kalaivani K (2009) Prevalence and consequences of anemia in pregnancy. Indian J Med Res 130: 627-633.
18. Prema K, Neela Kumari S, Ramalakshmi BA (1981) Anemia and adverse obstetric outcome. Nutr Rep Intl 23: 637-643.
19. Balgir RS (2010) Birth control necessary to limit family size in tribal couples with aberrant heterosis of G6PD deficiency and sickle cell disorders in India: An urgency of creating awareness and imparting genetic counseling. J Assocn Phys India 58: 357-362.
20. Serjeant GR, Serjeant BE (2001) Sickle cell disease. (3rd edn.) Oxford University Press; New York, USA.
21. Surbek D, Vial Y, Girard T, Breymann C, Bencaiova GA, Baud D, et al. (2020) Patient blood management (PBM) in pregnancy and childbirth: literature review and expert opinion. Arch Gynecol Obstet 301: 627-641.
22. Ickx BE (2010) Fluid and blood transfusion management in obstetrics. Eur J Anaesthesiol 27(12): 1031-1035.
23. Bernstein IM, Ziegler W, Badger GJ (2001) Plasma volume expansion in early pregnancy. Obstet Gynecol 97 (5 Pt 1): 669-672.
24. Hytten F (1985) Blood volume changes in normal pregnancy. Clin Haematol14 (3): 601-612.
25. Harstad TW, Mason RA, Cox SM (1992) Serum erythropoietin quantitation in pregnancy using an enzyme-linked immunoassay. Am J Perinatol 9(4): 233-235.
26. De Leeuw NK, Lowenstein L, Tucker EC, Dayal S (1968) Correlation of red cell loss at delivery with changes in red cell mass. Am J Obstet Gynecol 100(8): 1092-1101.
27. Cavill I (1995) Iron and erythropoiesis in normal subjects and pregnancy. J Perinat Med 23 (1-2): 47-50.
28. Koller O (1982) The clinical significance of hemodilution during pregnancy. Obstet Gynecol Surv, 37 (11): 649-652.

29. Clapp JF, Little KD, Widness JA (2003) Effect of maternal exercise and fetoplacental growth rate on serum erythropoietin concentrations. Am J Obstet Gynecol 188(4) :1021-1025.

30. Flo K, Wilsgaard T, Vartun A, Acharya G (2010) A longitudinal study of the Relationship between maternal cardiac output measured by impedance cardiography and uterine artery blood flow in the second half of the pregnancy.BJOG 117(7): 837-844.

31. Bothwell TH (2000) Iron requirements in pregnancy and strategies to meet them. Am J Clin Nutr 72 (1 suppl): 257s-264s.

32. Milner PF, Jones BR, Dobler J (1980) Outcome of pregnancy in sickle cell anemia and sickle cell-hemoglobin C disease. Am J Obstet Gynecol 138: 239-245.

33. Charache S, Scott J, Niebyl J, Bonds D (1980) Management of sickle cell disease in pregnant patients. Obstet Gynecol 5: 407-410.

DOI: 10.32474/JCCM.2020.02.000134