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Prenatal, Neonatal and Pediatric Health Care and Reproductive Medicine in Relation to Hemoglobinopathies in Three Stratified Communities of Central India

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Abstract

Background: *Hemoglobinopathies cause a high degree of maternal morbidity and maternal and fetal mortality, and reproductive wastage in vulnerable communities/populations of India. Both prospective and retrospective studies in this context are lacking in central India.*

Objectives: *Prospective and retrospective studies of referral index cases of hemoglobin disorders may provide most valuable data for analysis with respect to introspection and prospective re-evaluation in vulnerable communities.*

Methods: *In a cross-sectional prospective study of suspected cases of hemoglobin disorders routinely referred to us from NSCB Medical College and Hospital, Jabalpur for electrophoresis and other hematological investigations, a total of 213 couples with their offspring were studied from March 2010 to June 2011. Couples were stratified according to their caste/tribe and also depending upon the detection of β-thalassemia or other hemoglobin disorders in either of the family members. Reproductive history, i.e. number of abortions, still births, neonatal death, death under 1 year, death below 10 years of age, etc. of each couple was recorded retrospectively for each category of couples. Of the couples with hemoglobinopathies, 27 belonged to scheduled tribes (ST), 48 scheduled castes (SC) and 32 were Other Backward Castes (OBC). Of the 213 couples studied, 106 (mixed group belonging to above OBC, SC and ST) found free of hemoglobinopathies (β-thalassemia or hemoglobin disorders) were labelled as normal-controls and others (107) had different hemoglobinopathies.*

Results and Discussion: *The number of conceptions including the affected surviving offspring per couple with hemoglobinopathies was higher in both OBC (2.750) and SC (2.521). Broadly, it was observed that the number of stillbirths was higher in couples with hemoglobinopathies in ST (186) as compared to other caste categories, whereas, the number of abortions was similarly higher in couples with hemoglobinopathies in SC (141) per 1000 live-births. The number of deaths of offspring below 10 years age per 1000 live-births was also higher in couples with hemoglobinopathies in SC (111) and OBC (98).*

Conclusions: *Carrier and affected offspring of hemoglobin disorders further increases, maternal morbidity and fetal mortality, which is a major health burden on the vulnerable communities. Roles of preventive genetic counselling, prenatal, neonatal and pediatric health care are over emphasized in the affected communities.*

Keywords: *Prenatal, Neonatal and Pediatric health, Reproductive medicine, Hemoglobinopathies, Maternal morbidity, Fetal wastage, Prospective genetic counseling.*

Introduction

Hemoglobinopathies are one of the major genetic and public health challenges in the state of Madhya Pradesh in central India [1-6]. Anemia in pregnancy is emerging as one of the most important causes of maternal complications, maternal and fetal morbidity and mortality in almost all the developing countries of the world including in India [7-18]. Inadequate availability of oxygen to fetus also leads to abortion, miscarriage or stillbirth [19, 20]. Patients suffering from sickle cell disease disability are generally anemic and are susceptible to infections that cause aggravation and severity of manifestations leading to early death [19, 20]. Affected infants with sickle cell disease may present with dactylitis, fever and overwhelming sepsis, chronic hemolytic anemia, jaundice, episodic vaso-occlusive crises, hyposplenism, periodic splenic sequestration (which can be life threatening in a small child) and bone marrow sepsis [21-25]. Inherited disorders of hemoglobin cause high degree of hemolytic anemia, clinical jaundice, frequent infections, painful crises, splenomegaly, etc. and are responsible for the high infant morbidity, mortality and fetal wastage in India [21-25]. The genetic victims include: infants, growing children, adolescent girls, pregnant women and a large number of ignorant people [26-28].

The primary purpose of screening for hemoglobino pathies is the identification of infants with sickle cell disease or beta-thalassemia for whom early intervention has shown markedly reduced morbidity and mortality [13, 14]. 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. In view of credit for the highest infant mortality rate (IMR) in the state of Madhya Pradesh (62 per thousand live-births in 2011) in comparison to other states and the average of 47 for India; and the high prevalence of hemoglobinopathies in the state of Madhya Pradesh [4, 5, 11-14, 16-18, 28], it was presumed that hemoglobinopathies especially the sickle cell disorders might be one of the significantly contributing factors for neonatal/infant mortality in carrier couples in Madhya Pradesh, India.

Material and Methods

This was a cross-sectional prospective study. A total of 213 suspected couples including their offspring with at least 1 suspected/confirmed case of anemia/hemoglobinopathies routinely referred by the experts in Out-Patient Department of Gynaecology and Obstetrics for investigations/confirmation of diagnosis, attending Netaji Subhash Chandra Bose Medical College & Hospital, Jabalpur, Madhya Pradesh in Central India were included in the study. The ethical clearance was obtained from the Human Ethical Committee of ICMR - National Institute for Research in Tribal Health, Jabalpur.

Confirmed cases of hemoglobinopathies including sickle cell disorders formed our study group and the negatives, free of hematological disorders/anemia, after rigorous scrutiny, were taken as control group. The cases, suffering from other genetic abnormalities were excluded from the study. Those cases with iron deficiency anemia, other hematological disorders, malaria, accidental or induced abortion, were also excluded from the study. All the non-genetic confounding factors more or less were similar for both groups (being matched case controls), and taken from the same population source. Detailed reproductive history of each couple was recorded retrospectively like total number of conceptions, abortions, miscarriages or still-births, live-births, surviving children, infant or neonatal deaths, etc.

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. Of the couples with hemoglobin disorders, 27 belonged to scheduled tribes (ST), 48 scheduled castes (SC) and 32 were Other Backward Castes (OBC). Of the 213 couples studied, 106 (mixed group belonging to OBC, SC and ST) found free of hemoglobinopathies (beta-thalassemia or hemoglobin disorders) were labelled as normal-controls and others (107) had hemoglobinopathies.

Intravenous 2-3ml blood was taken under aseptical conditions from each individual after taking informed/ written consent for screening of hemoglobinopathies. Hematological parameters were studied using an automated Blood Cell Counter (Model-$MS_5$9, Melet Schloesing Laboratories, Cergy-Pontoise Cedex, France). Laboratory investigations were carried out following the standard procedures after cross checking for quality control from time to time. The sickling test was performed using 2% freshly prepared sodium metabisulphite solution as reducing agent for the presence or absence of sickle cell hemoglobin [29]. The routine hemoglobin lysate electrophoresis was carried out on cellulose acetate membrane (CAM) in Tris-EDTA-Borate buffer at pH 8.9 and quantification of A_2 fraction of adult hemoglobin was done by elution method [29, 30]. The value more than 3.5% of A_2 fraction of adult hemoglobin was taken as cut off point for determining the β-thalassemia trait. Those individuals having the very high hemoglobin A_2 value, i.e. more than 10% were suspected to have Hb A_2 plus Hb E; and the test was confirmed by the investigations of other family members. Estimation of fetal hemoglobin was done according to technique described by Weatherall [30].

The diagnosis of sickle cell-β-thalassemia was based on the findings of hemoglobin (Hb) A, F, S and A_2 on electrophoresis under alkaline pH, elevated HbA_2 levels (>3.5%). All the doubtful cases were further subjected to hemoglobin variant analysis for detecting any discrepancy (made for Bio-Rad Diagnostics, Hercules California, USA).

Data results were given to parents for treatment and further clinical management by the concerned referring doctor. All the carriers/affected persons were imparted genetic or marriage counselling by the competent expertise for further course of action and for follow up as and when need arises.

Results

The reproductive history of couples with and without hemoglobinopathies in absolute numbers is shown in Table 1. It is apparent from the Table that the number of total conceptions and still-births are higher in couples with hemoglobinopathies than in the normal control group. Further, the childhood (deaths below 10 years of age) mortality is considerably higher in couples with hemoglobinopathies than the normal controls (Table 1).

Table1. *Reproductive history of couples with different hemoglobinopathies and the normal controls (figures in absolute numbers)*

Diagnosis	No. of Couples	Concetions	Abortions	Still-births	Neonatal Deaths•	<1 year Deaths ■	<10 year Deaths
HbAA X HbAA Normal-controls	**106**	**185**	**19**	**6**	**10**	**11**	**12**
HbAA X HbAS	27	57	6	4	3	3	3
HbAA X HbSS	4	10	0	3	1	1	1
HbAS X HbAS	26	84	9	0	5	6	15
HbAS X HbSS	6	9	0	0	2	3	4
HbAS X HbAE	1	3	1	0	0	0	0
HbSE X β-Thal.T	1	4	0	0	0	0	0
HbAE X β-Thal.T	1	7	0	0	0	0	0
HbAS X β-Thal.T	7	21	1	0	0	0	1
HbAA X S- β-Thal	2	2	0	0	0	0	0
HbAS X S- β-Thal	5	11	0	1	1	1	1
β-Thal.T X S- β-Thal	2	3	0	0	0	0	0
HbAA X β-Thal.T	15	22	0	3	1	1	1
β-Thal.T X β-Thal.T	10	22	1	0	0	0	1
Hemoglobinopathies (Pooled)	**107**	**255**	**18**	**11**	**13**	**15**	**27**

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

Table 2 shows the absolute number of normal control couples and carrier as well as affected surviving offspring (children) in couples with different hemoglobinopathies. These figures further indicate that the carrier as well as affected couples not only produce abnormal offspring but also enhance the morbidity and genetic and health care burden, in the families/communities. This leads to a perpetual trend of overproduction of abnormal offspring in families/communities generation after generations.

Table2. *Surviving offspring of couples with and without hemoglobinopathies*

Diagnosis	No. of Couples	Conceptions	Total Survivals	Hb AA M	Hb AA F	Hb AS M	Hb AS F	Hb SS M	Hb SS F	S- β Thal M	S- β Thal F	β -Thal T M	β -Thal T F	β- Thal Major M	β- Thal Major F	Hb SE M	Hb SE F	Hb E-Thal M	Hb E-Thal F	Hb AE M	Hb AE F
HbAA X HbAA Normal-controls	**106**	**185**	**146**	**67**	**79**																
HbAA X HbAS	27	57	44	21	10	9	4														
HbAA X HbSS	4	10	6	2	0	2	2														
HbAS X HbAS	26	84	60	13	10	7	8	12	11												
HbAS X HbSS	6	9	5			2	2	0	1												
HbAS X HbAE	1	3	2	0	1											1	0				
HbSE X β-Thal.T	1	4	3			0	2													0	1
HbAE X β-Thal.T	7	21	19	1	1	0	3			5	1	3	5								
HbAS X β-Thal.T	5	11	9	0	0	1	1	1	1	2	1	0	2								
HbAA X S- β-Thal	2	2	2	0	1							0	1								
HbAS X S- β-Thal	15	22	19	8	6							0	4								
β-Thal.T X S- β-Thal	10	22	20	3	9							3	2	1	2						
HbAA X β-Thal.T	2	3	3			2	0			1	0										
β-Thal.T X β-Thal.T	1	7	7	1	4							1	0					0	1		
Hemoglobinopathies (Pooled)	**107**	**255**	**199**	**49**	**42**	**23**	**22**	**13**	**13**	**8**	**2**	**7**	**14**	**1**	**2**	**1**	**0**	**0**	**1**	**0**	**1**

It has been noted from Table 3 that there is an increased number of conceptions per couple among Other Backward Castes (2.750), followed by Scheduled Castes (2.521); and the least by Scheduled Tribes (2.074) as compared to normal Controls (1.745). However, the number of abortions per couple was the highest among the Scheduled Castes (0.292), compared to other communities and the controls. The number of still-births per couple was recorded to be the highest among the Scheduled Tribes (0.296) in comparison to other communities and the controls (Table 3). The number of live-births per couple was the highest among the Other Backward Castes (2.562), followed by Scheduled Castes (2.062 and the least among the Scheduled Tribes (1.592) in comparison to normal controls (1.509). Neonatal (birth to 28 days) deaths (0.187), infant (under 1 year) deaths (0.187), and childhood (<10 years of age) deaths (0.250) were higher in the Other Backward Castes (0.187) as compared to other communities and the controls (Table 3).

Table3. *Reproductive history of couples with and without hemoglobinopathies in stratified communities of Madhya Pradesh in India.*

Stratified Communities	No. of couples	Conceptions	Live-births	Abortions	Still-births	Neonatal Deaths•	< 1 year Deaths ■	<10 years Deaths
Normal controls**	106	185	160	19	6	10	11	12
Per Couple	-	1.745	1.509	0.179	0.057	0.094	0.104	0.113
Per 1000 Live-births	-	1156	1000	119	37	62	69	75
Scheduled Tribes	27	56	43	5	8	0	0	3
Per Couple	-	2.074	1.592	0.185	0.296	0.000	0.000	0.111
Per 1000 Live-births	-	1302	1000	116	186	0	0	70
Scheduled Castes	48	121	99	14	8	4	4	11
Per Couple	-	2.521	2.062	0.292	0.167	0.083	0.083	0.229
Per 1000 Live-births	-	1222	1000	141	81	40	40	111
Other Backward Castes	32	88	82	4	2	6	6	8
Per Couple	-	2.750	2.562	0.125	0.062	0.187	0.187	0.250
Per 1000 Live-births	-	1073	1000	49	24	73	73	98

•Birth to 28 days. ■ Birth to 365 days or within 1 year **Mixed communities

Discussion

The findings of the present study are interesting and revealing many practical aspects of the couples inflicted with recessively-inherited-hemolytic disorders (hemoglobinopathies) such as sickle cell disease in Central India. This study strongly supports the contention that hereditary factors in the carrier couples, apart from concomitant non-genetic confounding factors, are responsible for the high reproductive loss in the form of abortions, still-births, neonatal and infant mortality, and mortality (<10 years of age) in India. It is apparent from Table 1 that the number of total conceptions, still-births and the childhood mortality (below 10 years of age) are higher in couples with hemoglobinopathies than in the normal controls. This is an outcome of nonviable homozygosity of the recessively-inherited-genetic disorders (hemoglobinopathies) such as sickle cell disease due to the practice of consanguinity and inbreeding that is inadvertently taking place in the vulnerable communities of the region that enhances morbidity and neonatal/infant mortality. This is the 1st study carried out taking into consideration these causative aspects of high mortality in the state of Madhya Pradesh, India. These results are consistent with the almost similar findings reported from Odisha state [8] in eastern coast of India.

Looking at the overall scenario of reproductive loss and surviving offspring in different carrier couples of hemoglobinopathies, the number of normal children born to carrier couples was lower (91/255; 35.7%) than the inflicted children (164/255; 64.3%), indicating the progressive increase of inflicted offspring in these families (Table 2). This trend shows the lower fitness of the carrier couples or affected families, and, consequently, of the vulnerable communities/populations.

It has been noted from Table 3 that there is an increased number of conceptions per couple among Other Backward Castes (2.750), followed by Scheduled Castes (2.521); and the least by Scheduled Tribes (2.074) as compared to normal controls (1.745). However, the number of abortions per couple was the highest among the Scheduled Castes (0.292), compared to other communities and controls. The number of still-births per couple was also recorded to be the highest among the Scheduled Tribes (0.296) in comparison to other communities and the controls (Table 3). The number of live-births per couple was the highest among the Other Backward Castes (2.562), followed by Scheduled Castes (2.062); and the least among the Scheduled Tribes (1.592) in comparison to normal controls (1.509). Neonatal (after birth less than 28 days) deaths (0.187), infant deaths (under 1 year) (0.187), and childhood (<10 years of age) deaths (0.250) were higher in the OBC (0.187) as compared to other communities and the controls (Table 3).

It has been observed that enhancement of the institutional delivery accompanied by quality public healthcare services provide added advantage to reproductive outcome, whereas, the widespread undernourishment and anemia among pregnant women lead to under-weight children. Moreover, lack of public health facilities to cope with specialized newborn care, coupled with infliction of hemoglobinopathies bring adverse reproductive outcome [16-18]. It was envisaged to bring awareness among these couples through genetic/marriage counseling about the deleterious genetic disorders (related to hemoglobinopathies) and their causal effects on health. Their eradication is necessary because they are not curable but preventable through carrier detection, prenatal diagnosis and, education and genetic counselling [31]. This has ample implications in those families, communities and tropical countries where sickle cell disease is widely prevalent and is a major cause of high morbidity and mortality.

Prospective Genetic Counselling

Clinical Diagnosis

Out of 213 couples referred and investigated by us for different hemoglobinopathies, 106 couples did not have any problem related to hematology or hemoglobin disorders, whereas, 107 couples who were either the carriers or homozygous for sickle cell disease/β-thalassemia/hemoglobin E or compound cases of sickle cell/β-thalassemia, sickle cell/hemoglobin E or hemoglobin E/β-thalassemia. Before screening of the family members, it was ensured the availability all concerned members for drawing blood on specific date and time in the laboratory. Hemoglobinopathies, being inherited genetic disorders, the screening of all first degree family members was done to identify the carrier as well as full-blown (homozygous or compound) cases. Each couple was requested individually on specific date and time to attend the genetic counselling session along with their child/children to discuss the laboratory investigations report prior to handing over to them.

Genetic Counseling

Genetic counseling is the process by which the patients or relatives at risk of an inherited disorder (hemoglobinopathies) were advised of the consequences and nature of the disease, the probability of developing or transmitting it, and the options open to them in management and family planning [32]. Genetic counseling can facilitate the decision making process by providing the patient/family with education about the genetic condition as well as the medical management options available to individuals at risk of developing the condition. All these aspects were discussed or explained through colored charts (specially prepared for the purpose), visuals and practical demonstrations of the carriers and affected patients. A list of resource persons and hospitals/laboratories in the country where DNA analysis facilities for identifications of different mutations of hemoglobinopathies and prenatal diagnostic services are available in India, were also provided to the concerned/interested couples.

The goals of genetic counseling are to increase understanding of genetic diseases, discuss disease management options, and explain the risks and benefits of testing. Genetic counselors are present at high risk or specialty prenatal clinics that offer prenatal diagnosis, pediatric care centers, and adult genetic centers before conception. Counseling sessions focus on giving vital, unbiased information and non-directive assistance in the patient's decision-making process [32, 34]. The summary phase and a follow-up phase are as important as the initiation phase of consultation.

In order to bring the reduction/prevention and control of these hemoglobin disorders (sickle cell anemia) in affected families, all the referred and affected families were given genetic/marriage counseling to prevent the birth of an abnormal child in their families [32-35] for the betterment of their future generations.

Conclusions

The number of conceptions per couple with hemoglobinopathies was higher in both Other Backward Castes (2.750) and Scheduled Castes (2.521), and also the affected surviving offsprings. Broadly, it was observed that the number of stillbirths per 1000 live-births in couples with hemoglobinopathies was higher in Scheduled Tribes (186) as compared to other caste categories, and the number of abortions in couples was higher in Scheduled Castes (141) per 1000 live-births. The number of deaths of offspring below 10 years age per 1000 live-births was also higher in couples with hemoglobinopathies in Scheduled Castes (111) and Other Backward Castes (98).

The increased production of inflicted trait and diseased surviving offspring (64.3%) than the normal children (35.7%), leads to increased morbidity and mortality; and perhaps may be contributing towards increased neonatal/infant mortality in Madhya Pradesh. This is the 1st study that has revealed hereditary causes, apart from other concomitant non-genetic factors, responsible for the high neonatal/infant mortality (reproductive loss) in the vulnerable population. Further, the progeny of sickle cell disease couples contributes disproportionately to enhance the neonatal/infant mortality in Madhya Pradesh. This requires extra care and additional input to tackle them. Role of preventive genetic strategy and, paediatrics and neonatal care is over emphasized in the affected communities. Genetic/marriage counseling is highly desirable in affected couples/families to ameliorate the sufferings.

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