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"Congenital Heart Defects and Environmental Factors: A Snapshot of CHD Cohort from a Tertiary Cardiac Care Centre in India"

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Abstract

Background: Congenial Heart Defects are amongst the leading causes of childhood mortality with varied presentation. CHDs have complex etiology of with interplay of several genetic and environmental factors. This article discusses various factors in the data compiled in Biobank at Sri Sathya Sai Sanjeevani Research Foundation (SSSSRF), Palwal, Haryana, India which have been reported in literature as the potential contributors to CHD.

Methods: This is a retrospective study, on the data collected in the period of June 2018-June 2022 at SSSSRF, Palwal. The data was collected prospectively from parents using validated institutional questionnaires.

Results: The study has presented analysis of the data from 2970 CHD cases. Commonest acyanotic CHD form was Ventricular Septal Defect (38.48%) was and the commonest cyanotic form was Tetrology of Fallot (25.82%). Majority of the cases were from Uttar Pradesh (50.47%) indicating the significant disease burden in the state. Gender distribution in our study was Male: Females = 1.77:1. There was no CHD specific trend of blood group. Intake of folic acid and iron-calcium supplements during conception was significantly associated with birth weight of neonate ($p < 0.05$). Maternal bad obstetric history may increase the risk of CHD in newborn ($P<0.05$).

Conclusion: The presented study from India discusses some of the key environmental factors implicated in etiology of CHD with the backgdrop of factual subjective patient information. This study is beacon and first step for future research study models oriented towards finding causal association of various modifiable and non-modifiable risk factors with CHD.

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Keywords: Congenital Heart Defect; Environmental factors; CHD Etiology; Tertiary cardiac care centre; Folic acid.

Introduction

According to March Of Dimes (MOD) global report, in India 6-7 babies are affected with congenital birth defects per 100 live births corresponding to 1.7 million birth defect cases annually [1]. Preterm births are the highest contributors to about world's quarter of neonatal deaths occurring in India. Amongst all causes leading to death in early years of life, congenital anomalies are the fifth largest [2]. A recent meta-analysis puts forth pooled prevalence of 18.45 per 1000 live births in India highlighting the significance of this burden on healthcare system [2]. Though, Congenital Heart Defects (CHDs) are amongst the most common anomalies present since birth and correspond to around 28% of birth defects with highest prevalence in Asia with 9.3 affected per 1000 live births [3,4]; the estimated low prevalence might be attributed to lack of specialized diagnostic tools along with the physical examination done at birth [2]. CHDs range from simple septal defects and shunt lesions like Atrial Septal Defects (ASDs) to complex critical forms like single ventricle morphologies [4].

CHDs being structural malformations present at birth, the etiology of the disease has prenatal and even periconceptional associations and there is interaction of several genetic/familial factors and environmental/nongenetic factors contributing to complex etiology of CHD [5]. Maternal prenatal exposures [5] and paternal occupational and environmental exposures [6] alter the fate of development of heart in the fetus. Some of these external factors are modifiable to some extent like maternal nutrition, obesity, exposure to pollution etc. whereas the others are nonmodifiable including maternal health conditions, genetics or exposure to certain medications [5]. The genetic or environmental causes could be found implicated only in 20-30% of CHD cases with environmental associations identified in only 2% of CHDs. This suggests that for a majority of the affected population the etiology is yet illusive [7].

Over past few decades, with advances in diagnostic techniques and corrective treatment modalities, there is rise in number of detected CHD affected patients surviving till adulthood. With disparity in the availability of treatment centres for CHD in India, lack of awareness, improper distribution of resources, financial constraints, nonavailability of skilled specialists, deficiency of quality healthcare and several other factors limit the timely diagnosis and treatment of CHD [8]. Towards this, to address this grave health issue, Sri Sathya Sai Sanjeevani Paediatric Cardiac Care centres have been established in India with three functional centres at Naya Raipur, Kharghar, Navi Mumbai and Palwal, Haryana.

In the last 10 years, the hospitals have performed over 27,000 child heart surgeries - totally free of cost. Sri Sathya Sai Sanjeevani Research Foundation (SSSSRF), works with these hospitals with the vision of primary prevention of CHD. SSSSRF holds 'Sai Sanjeevani Biobank for Congenital Heart Disease (SSBCHD)'with potential national importance. Retrospective analysis of the patient information collected in Research Electronic Data Capture (REDCap) application can provide noteworthy insights in future research to explore underlying etiological factors in CHD.

Materials and Methods

Ethics Committee approval was provided by Institutional Ethics Committee (IEC), SSSSRF, Palwal, Haryana, India (Provisional certificate with reg no. EC/NEW/ INST/2022/2673 from NECRBHR, DHR, Govt of India). This study is retrospective analysis of the data (of in-patients) collected in Biobank during the period- June 2018 to June 2022. Data collection was done using questionnaire format developed at SSSSRF with guidance from clinicians and other experts. Statistical analysis was done using Microsoft excel.

Categorization of CHD

CHD evaluation in pre-operative period was done by physical examination and Echocardiography (ECHO) and cardiac catheterization in selected cases. This data was extracted from ECHO reports and other clinical records. CHDs were assigned International Statistical Classification of Diseases and Related Health Problems (ICD10) codes for ease of disease classification. All pre-operative diagnoses were confirmed intraoperatively by surgical findings or during cath procedure. The treatment procedure and when to intervene was decided by the clinicians based on the need for urgency of treatment, CHD type, physical fitness of the patient and availability of slots.

Results

Demographic details and disease classification

Refer figure 1 for characteristics of study populations (available figures presented)

Table 1 shows demographic details and clinical features of the data. In the biobank, sample collection happened for a total of 2970 patients out of which 94.5% samples were from the surgical patients. 5.15% samples were collected from patients who underwent catheterization interventions. Samples were also collected from 8 patients who were advised palliative care. Mainly blood samples were collected from available patient trios. The large variability in this number is attributed to the institutional policies of case selections for surgeries and interventions and phase wise expansion of biobank facility. The cases showed more males (64%) than females (36%) with male:female ratio (1.77:1). Out of total patients, 59.53% (=1768) were diagnosed in the first year of life followed by 21.48% cases getting diagnosed in the age 1-5 years. But only 18.21% patients were treated before their first birthday **(Table 1)**. In only 0.7% patients, CHDs were diagnosed during pregnancy ultrasounds. Though dysmorphisms were recorded in a few cases, the characterization of underlying syndrome could not be completed in absence of genetic testing.

Amongst our CHD patients, blood group B+ was found most common, amongst 34.59% followed by O+ 30.55%. Rh+ blood group was found in 94.94% case whereas only 5.06% patients had Rh- blood group.

In our data, 94.84% cases were sporadic occurrences of CHD whereas 5.15% reported family history of CHD. Amongst familial cases, 18 patients had siblings affected with CHD.

Parental factors and birth outcomes in CHD

We evaluated various parental environmental factors like delivery location, intake of supplements during pregnancy, maternal obstetric history, parental education and parental addiction status in our study. We also studied the distribution of birth weight and birth term of the index patient. We compared our data with available national data (8). The analyses are presented in subsequent figures.

Maximum, i.e., 64.72% mothers were in the age group of 20-30 years whereas maximum, i.e., 49.02 % fathers were in the age group 30-40 years **(Figure 2.1-B)**. Illiteracy rate in mothers (19.42%) was more than fathers (11.14%). The parental education status is summarized in **Figure 2.1-A**. Proportion of consanguineous marriages was less (4.33%) in our data.

13.01% of mothers and 12.16% fathers reported previous underlying disease during periconceptional period. Mothers' diseases ranged from asthma, low blood pressure, major infections like TB, complex neurological conditions, kidney stones, gall stones, diabetes, occasional malignancies and hypothyroidism, which was the commonest. Only 3 subjects and spouses reported HCV infections. Fathers' illnesses varied from acquired heart conditions, diabetes, gall stones, kidney stones, neurological complications, asthma, high blood pressure and infections. The data being self reported, classification could not be discretely done in absence of medical reports.

In our data, 76.77% mothers reportedhospital deliveries whereas 20.88% women reported home births **(Figure 2.2B)**. Most common (76.87%) were Normal Vaginal Deliveries (NVD) whereas 23.12% reported caesarean section during delivery of index patient.Previous bad obstetric history was reported by significant 31.95% of mothers;17.33% women reported >1 miscarriages, ≥1 abortions in 6.9% mothers, ≥1 stillbirths in 2.14% and ≥1 death of previous siblings before 5 years of age,in8.42% mothers were reported **(Figure 2.2-A)**. This data is significantly different from NFHS-5 report (p=0.05).

The questionnaire inquired for intake of recommended antenatal supplements consumed by mothers during conception of index patient.61.08% women did not take folic acid whereas 49.98% women never took iron-calcium supplements during pregnancy (Figure 2.2C). Our data shows significant association of intake of folic acid and iron- calcium during pregnancy with birth weight of the patient, when analysed using Chi-square statistics ($p < 0.05$). Irregular or no intake of dietary supplements during critical period of conception, adversely affects the birth outcome. We also checked for the impact of mother's age at time of delivery of the patient. Using Fisher's Exact Test for count data with simulated p-value (based on 1e+05 replicates) our data shows association between birth weight and mother's age at the time of delivery ($p < 0.05$). We also analyzed the month of birth for all patients and observed that maximum number of CHD patients had their birthday in the month of January (12.56%) followed by July (9.09%). Lowest number of patients had their birthday in May (6.36%).

Out of total parents 46.70% men reported addiction in some form where was in mothers the proportion was as low as 0.9%. Major addiction form was chewable tobacco (32.59%) followed by tobacco smoking in 16.8% of men. The data thus show lesser percentage of men addicted to tobacco as compared to national data [8]. Alcohol addiction was in 13.8% of men. Apart from this, the parental education status showed higher illiteracy in women (19.42%) as compared to men (11.14%). There was fairly higher education status till graduation in both mothers (19.22%) and fathers (22.99%).

Table 1: Demographic and clinical characteristics of CHD patients at Sanjeevani Hospital.

Parameters	No. of CHD Cases (%)
Age group (years)	
Total	**2970**
0-1	541 (18.21%)
1-5	1211 (40.77%)
5-12	861 (28.98%)
12-18	243 (8.1%)
18-30	98 (3.29%)
>30	15 (0.5%)
Gender	
Male	1903 (64%)
Female	1067 (36%)
CHD Subtypes	
Cyanotic	1010 (34%)
Acyanotic	1960 (65.9%)
CHD classification	
ASD	373 (12.55%)
VSD	1143 (38.48%)
TOF	767 (25.82%)
VSD+PS	98 (3.29%)
DCRV	113 (3.8%)
TGA	34 (1.14%)
SINGLE VENTRICLE	54 (1.8%)
AVSD	57 (1.9%)
TAPVC/PAPVC	145 (4.8%)
OTHERS	186 (6.26%)
Location	
Uttar Pradesh	1499 (50.47%)
Bihar	309 (10.4%)
Delhi	122 (4.1%)
Punjab	84 (2.8%)
Rajasthan	179 (6.02%)
Uttarakhand	87 (2.9%)
Haryana	450 (15.15%)
Others	240 (8.08%)
Intervention type	
Surgery	2809 (94.5%)
Cath	153 (5.15%)
Palliative	8 (0.026%)

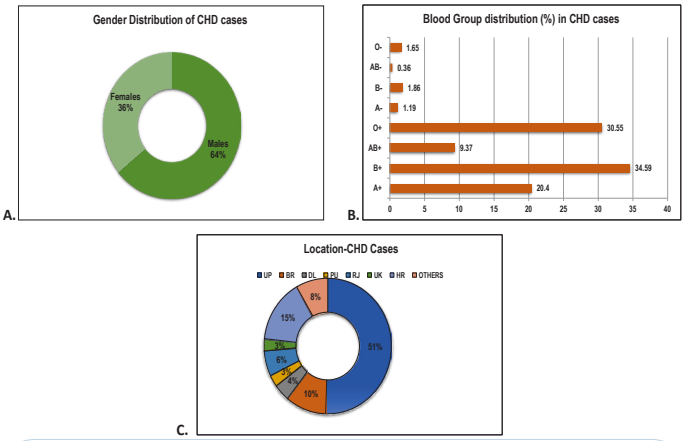

Figure 1: Demographic characteristics and blood group distribution in CHD patients.

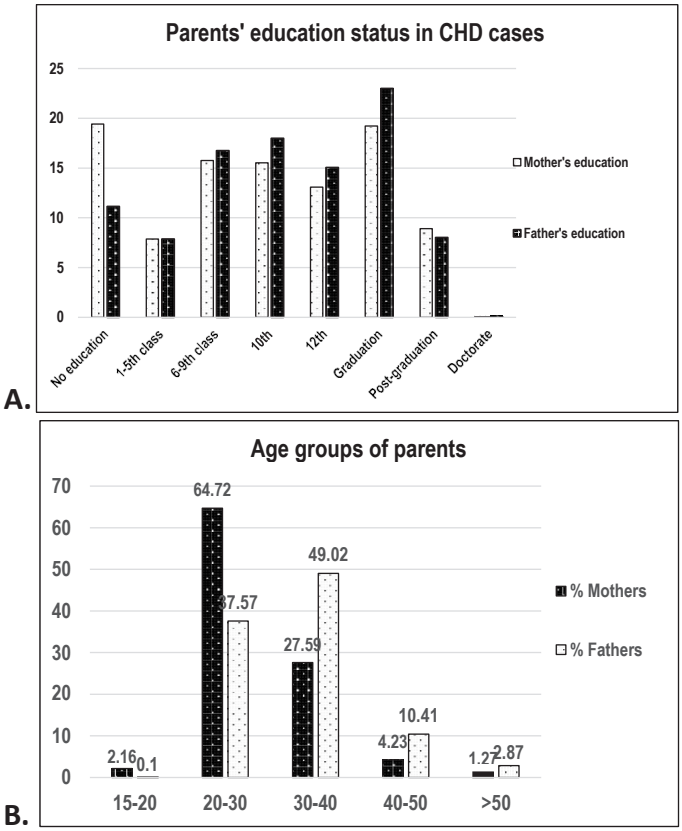

Figure 2.1: Parental factors in CHD.

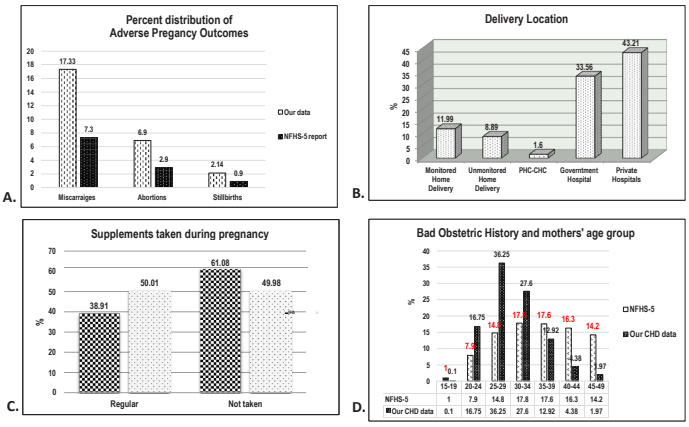

Figure 2.2: Parental factors in CHD.

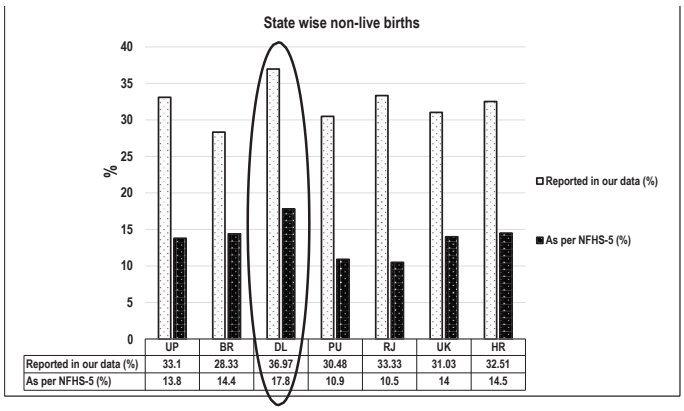

Figure 3: State-wise non-live births in CHD cohort.

Discussion

Existing as a collective diagnosis of structural abnormalities in heart and great vessels, CHDs present diverse anatomic subtypes [9]. There is reportedly 34% collective contribution of de novo mutations, CNVs, chromosomal modifications, aneuploidies and transmitted traits; whereas the estimated environmental contribution is 10%. Yet 56% factorsare unknown in CHD etiology even today [10]. Since heart is the first organ to develop in growing embryo and cardiac development is complete in the initial 8 weeks of gestation, the parental environmental factors during periconceptional period, i.e. 3 months before pregnancy through 3rd month of conception; are the most crucial ones [9,11]. Alterations with cardiac development can be due to reduced supply of vital nutrients during critical embryonic windows or due to presence of excess toxic molecules [12]. Maternal malnutrition, exposure to certain drugs during pregnancy, pollution, tobacco, infections, major systemic diseases, etc. have been reported by previous researchers as the potential contributors to pathogenesis of CHD [13,11,10].

In India, there is high proportion of unplanned pregnancies and neglected antenatal care compromising on the essential preventive strategies against birth defects [14]. The critical period of organ development, i.e., first trimester is not addressed well due to inability to detect pregnancy in time in absence of antenatal care, financial limitations, social constraints faced by women and firm traditional disbeliefs about healthcare system. Hence, several external factors apart from intrinsic aspects operating during embryonic development need careful attention in order to investigate the etiology of congenital anomalies. Significantly higher proportion of sporadic cases (94.84%) in our data, justifies the focus of this paper about exploration of environmental factors towards potential causal association with CHD.

Our study is on the patient population from a tertiary paediatric cardiac care centre from North India. Hence we majorly have the data from patients of North Indian ethnicity. The analysis shows maximum cases (50.47%) from UP followed by Bihar (BR) (10.4%) **(Figure 1)** The state also has highest infant and under-five mortality rate in India followed by BR (8). This has also been reported by [3] stating, high birth rate in Northern and Eastern part of India as compared to other states and higher CHD burden in UP, BR, Jharkhand (JH) and Madhya Pradesh (MP). Antenatal and post natal care services are crucial in improving the overall birth outcomes along with reducing the maternal and child mortality [15]. Uttar Pradesh is India's fourth largest and most populated state in India contributing to 16% of national population with 78% rural population [15]. Infant mortality rate is second highest in Uttar Pradesh in India followed by MP (16). Though number of subcentres, PHCs and

CHCs, are highest in UP, there are less than 1% subdivisional hospitals and district hospitals in UP (RHS 2020-21). Limited reach to ANC workers, marginalization, inadequate awareness, low mass- media exposure are some of the factors which cause underutilization of ANC services in UP [15]. According to NHFS-5, in the state of just above 3/5th (63%) women are reported to have antenatal care in first trimester which is the most critical period, with urban women undergoing more antenatal visits than the rural ones. The report shows that ultrasound is done for 74% of women during pregnancy. The report also states a serious finding that half of UP women are anemic with 24% having mild to moderate anemia and 2% having severe anemia. All these factors are important considerations around birth and influence the birth outcome significantly. These factors might be important contributors to observed high proportion of CHD cases from UP as compared to other North Indian states.

In literature the Human ABO blood group system has varied phenotypes depending on the glyconjugate antigens present on red blood cells (RBCs) [17]. In India, allelic frequency of blood group O (34.56%) is greater than blood group B (34.10%) as reported in a recent systematic review [18]. On the contrary our data shows higher frequency of blood group B (36.45%) in our study population of CHD afflicted childrenas compared to O (32.2%).But a previous study shows prevalence of blood group B in North India with the trend as B>O>A>AB which falls in line with our observation [18]. First ever study to explore association of ABO blood groups and risk of CHD in a well-defined cohort was presented in recently [19]. Genes important in cardiovascular development namely NOTCH1 & EHMT1 are located on chromosome 9q34 near ABO locus. In the study it is stated that, genetic inheritance can answer the association between ABO blood groups and CHD [19]. One limitation to note here is that, critical CHD cases do not survive till 1st year of life and may be missed in the study of blood groups. In the previous studies, Rh positive and Rh negative population showed a mixed trend and hence a wide variation range was reported [20]. In all different regions Rh negative population in the east, central, west, north and south regions of the country was in the range of 3.72-7.02% while Rh positive was in the range of 92.97-96.23%. In our study, Rh negative is 5.06% and Rh positive is 94.91% which are close to that reported for north Indian population 5.19% and 94.8% for Rh negative and Rh positive, respectively [20]. Our study hence apparently hints at no association between blood group and CHD and no gender specific trend of blood group.

Consanguineous marriages or marriages between blood relations are fairly found linked with CHD in offspring [21-23]. In our study, 4% cases reported consanguineous marriages. In India 11% marriages are consanguineous majorly in Southern states except Kerala (NFHS-5). Percentage of consanguineous marriages is ≤10% in northern states including UP, BR, Rajasthan (RJ), Delhi (DL), Haryana (HR) and Uttarakhand (UK). Our observation of 4.33% consanguineous marriages in study population is thus comparable with the national data.

Bad maternal obstetric history including recurrent pregnancy loss due to spontaneous abortions are reported to be associated with increased risk of CHD in next child [24]. In India, due to lack of awareness and education, there is no enough gap between two consecutive pregnancies compromising the woman's health grossly and thereby affecting the health of the newborn. We captured data related to this in our data set and in our data there is significantly higher proportion of bad obstetric history (31.95%) before index pregnancy than the normal Indian population where the 11% pregnancies conclude with non-live birth outcome (P<0.05). Women majorly reported multiple adverse outcomes in conception history including consecutive /non-consecutive miscarriages, still births and/or abortions. Similar to national data [8], where miscarriage is the most common type of non-live birth (7% of all pregnancies), our data shows highest proportion of spontaneous abortions in bad obstetric history 17.33%).Previous literature supports possibility ofthe association of maternal history spontaneous abortions and CHD in newborn stating increased risk of CHD in newborns for such mothers [24,25]. Also, in our CHD cohort we found maternal hypothyroidism as the underlying disease condition, linked with increased risk of bad obstetric history using Z-test statistics ($p< 0.05$).

Additionally, 26.61% women reported nonaccidental death of older siblings of proband after birth due ailments not limited to symptoms of CHD. With these findings, this factor of obstetric history with major focus on spontaneous termination of pregnancy, can be explored further in association with CHD to enrich the counselling features for future pregnancy planning. The statewise distribution (in major states as per study cohort) of reported bad obstetric history (non live births) is summarized in **Figure 3**. It can be seen in the **Figure 3** that both our data and NFHS-5 report show higher proportion of non- live births from Delhi, both in our study cohort and normal population.

Preventable maternal and infant deaths can be averted by institutional deliveries or delivery assisted by skilled health attendant [26]. 81.5% women in India receive ANC from a skilled health care provider including doctor, nurse, midwife, auxiliary nurse midwife, and lady health visitor [8]. According to NHFS-5, institutional delivery percentage is raised to 88.6% in India, whereas our data shows 78.37% i.e., significantly less, institutional deliveries ($p < 0.05$). Our results are comparable with the recently published report which states that 22% deliveries in India happen in home (P=0.073) [27]. Timely detection, diagnosis and treatment of adverse birth outcomes including CHD can be facilitated only in institutional deliveries especially in asymptomatic cases at birth. Detection of CHD as early as in neonatal stage (0-1 month after birth), can significantly reduce childhood mortality and post intervention morbidity. Contrary to our this statement, the recent research reports that large scale positive impact of a road construction programmeon efficient mobilization of pregnant ladies from remote villages to healthcare centreshad apparently no improvement in rates of neonatal mortality or postpartumcomplications. The study emphasized urge for improved policies encouraging institutional deliveries complemented with superior quality of healthcare available at these institutions [28].

In our data, 26.58% of deliveries in private hospitals & 21.21% of births in government hospitals were diagnosed with CHD in first month of life. Proportion of early detection of CHD in neonates reduced to 19.14% in deliveries in primary health centres (PHC-CHCs) with further reduction in unmonitored (11.49%) and monitored (6.81%) home births.

Folate deficiency culminates into elevated risk of anemia, pregnancy complications and foetal anomalies [29]. Women in underprivileged populations are naturally at greater risk of folate and other micronutrient deficiencies. No or irregular intake of key dietary supplements during pregnancy, with the backdrop of these underlying deficiencies, further worsens the scenario. As per the guidelines of Ministry of Health and Family Welfare in India, 100mg of elemental iron and 500 mcg of folic acid daily for 100 days during pregnancy is the recommended

dietary dose during pregnancy. But the national data shows low compliance as though the Iron-Folic Acid (IFA) supplementation was made available to 89.4% of urban and 86.95 of the rural pregnancy mothers; only 54% and 40.2% ladies respectively had actually consumed the supplements regularly for more than 100 days [8]. Even though the program is being executed for over 3 decades multiple factors including, marginalized life quality, lack of awareness, social constraints etc. limit the use of supplements during pregnancy. In our study, only 38.91% of case mothers reported to have consumed folic acid supplements regularly for 100 days or more. Iron and Calcium supplementation was taken for more than 100 days or more by 50.01% mothers. The supplement composition in the form of IFA tablets or elemental iron was unclear attributable to recall bias. The birth weight of index patients was found significantly associated with the intake of folic acid and iron supplementation during pregnancy using chi-square statistics ($p< 0.05$), stating low birth weight (≤ 2.5 KG) [30,31] as adverse birth outcome in case of non-consumption of these dietary supplements. A recent study reported that profile of maternal predictive biomarkers of offspring DNA methylation depends on seasonal variations and the levels of these biomarkers change in rainy and dry seasons [32]. Based on this notion, in our analysis we found maximum number of patients born in January (12.56%) followed by July (9.09%) and lowest number in May (6.36%). All these are the months of extreme seasonal variations especially in North India. Hence the observed trend can further be analyzed in depth based on further studies with larger sample size.

We also analyzed the association between maternal age at delivery and birth weight in CHD cohort to find that increase in mother's age increased the risk of low birth weight of the child ($p<0.05$). The association of increased risk of CHD and/or with other developmental errors in child with increase in maternal ageis always anticipated, but a recent study reports very little association with insignificant increase in risk of CHD in mothers aged ≥35 years [33].

This study in CHD cohort thus analyses several modifiable and nonmodifiable risk factors implicated in complex etiology of CHD. Though there are few significant leads, this study has certain limitations,one of which is the basis of study on subject recall. The apparent reflection of no association of parental addiction status with CHD in our study compared to national data may be attributed to the same. Another limitation is the absence of non-CHD or healthy control population to validate the associations. Presented analysis in CHD cohort is only to explore the several environmental factors to be implicated in CHD and reported in literature; and arrive at the significant ones which will be foundation for future research strategies.

Conclusion

Burden of CHD is very high in India with very little research to understand the etiology of the problem. Ours is the first study from India in this line to investigate the role of several risk factors contributing to pathogenesis of CHD. The study puts forth certain leads as:

1. Majority of CHD cases are sporadic with very less proportion showing family history. This fact highlights the importance of environmental factors shaping the birth outcome.
2. There is more preponderance of CHD in offsprings of mothers having bad obstetric history.
3. Irregular or no intake of prescribed dietary supplements (eg. iron, folic acid, calcium) during pregnancymay increase the risk of CHD in offspring and is potentially associated with low birth weight of newborn.

Future systematic studies with population baselines to determine prevalence of CHD are required. Prospective study designs with objective measures for estimating the key environmental factors implicated in etiology of CHD, will provide substantial evidences for causal associations. These studies can potentially contribute to formulation of the national registry for CHD which is need of the hour to understand the actual disease load, to reduce mortality & morbidity and also to benefit research initiatives with the vision to help policy makers to evolve strategies oriented towards primary prevention of CHD in India.

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