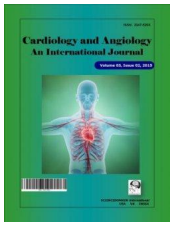

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Maternal Risk Factors Predisposing to Congenital Heart Disease: A study in South India

Jayavelan Ramkumar[1*], Benjamin M. Sagayaraj[2] and Nidhi Sharma[3]

[1]Department of Cardiothoracic Vascular Surgery, Sri Ramachandra Medical College, Sri Ramachandra University, Chennai, India.
[2]Department of Pediatrics, Saveetha Medical College, Saveetha University, Chennai-602105, India.
[3]Department of Obstetrics and Gynaecology, Saveetha Medical College, Saveetha University, Chennai-602105, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author JR designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors BMS and NS managed the analyses of the study. Author NS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Congenital Heart Diseases (CHD) are defined as malformations of the heart and great vessels that develop in utero which may manifest at birth or later in childhood. They can be caused by numerous genetic and environmental factors. Genetic factors are nonmodifiable. However, identification of modifiable environmental risk factors is important to develop population based prevention strategies to reduce the incidence of CHD.
Objectives: The primary objective of the study was to find an association of the maternal lifestyles with CHD in new-borns. The secondary outcome of the study was to identify maternal factors that can be modified for the primary prevention of CHD.
Materials and Methods: This prospective study involved cardiovascular system examination of newborns after delivery in term gestations in 1394 singleton pregnancies. The maternal risk factors

**Corresponding author: E-mail: drbonuramkumar@yahoo.co.in, drbonuramkumar@gmail.com;*

considered were age, prepregnancy Body Mass Index (BMI), consanguineous marriage, caffeine intake, diabetes, stress and intake of periconceptional Folic acid tablets.

Results: In this study, 22 (1.58%) out of 1394 pregnancies resulted in Congenital Heart Defects. Teenage pregnancy (p value= 0.0002), consanguineous marriage (p value=0.0004), overt diabetes mellitus (p value=0.0001), caffeine intake (p value=0.0031), prepregnancy BMI>24(p value=0.0001), maternal stress (p value<0.0001, history of previous congenital malformations (p value=0.004) and non intake of folic acid tablets in the first trimester (p value=0.0023 were found to be the most likely risk factor associated with CHD.

Conclusion: Community education programmes should be initiated in the high-risk population to prevent teenage pregnancies and consanguineous marriages. Maternal counseling for periconceptional control of blood glucose, adequate weight maintenance, intake of folic acid tablets, avoidance of stress and caffeine is needed to prevent CHD.

Keywords: Congenital heart defects; maternal risk; folic acid; BMI; maternal age; diabetes; stress.

1. BACKGROUND

Congenital heart disease (CHD) is a group of defects that arise during the intra uterine development of heart and great vessels. According to a recent survey, the incidence of CHD in developing countries is 0.8-1 % [1]. The incidence rate in India is 8/1000 live births and nearly 180,000 children are born with CHD each year in India. Of these, nearly 60,000 to 90,000 suffer from critical CHD requiring early intervention. Approximately 10% cases of infant mortality in India are caused by CHDs [1]. Structural defects can be classified as left to right shunts, valvular or obstructive defects and defects with a dominant right to left shunt. The most common defects are left to right shunts. These include atrial septal defects, ventricular septal defects and persistent patent ductus arteriosus. Valvular and nonobstructive defects include coarctation of aorta, aortic and pulmonary stenosis, mitral stenosis and Ebstein's anomaly. Dominant right to left shunt defects are tetralogy of Fallot, tricuspid atresia, pulmonary atresia, transposition of great vessels, double exit right ventricle, truncus arteriosus, hypoplastic left heart syndrome and anomalous inflow of pulmonary veins. Another way to classify these defects is syndromic defects and non-syndromic defects. These malformations develop during the development of the cardiovascular system and are present at birth even if they are discovered much later, and thus, are referred to as birth defects [2,3]. The anomalies may be single or multiple. The cardiovascular anomalies frequently are the result of defective morphogenesis that occurs during the embryological development. The malformations may be limited to the cardiovascular system (nonsyndromic) or occur in association with anomalies of other systems as part of defined syndromes (syndromic). They may develop as a result of random alterations in morphogenesis or as a result of several environmental factors [4]. The genetic factors of cardiovascular anomalies are non-modifiable though a number of environmental risk factors can be identified and treated.

This study was conducted to reduce the burden of CHD by identifying the maternal factors in south Indian population.

2. MATERIALS AND METHODS

The prospective study was conducted in the outpatient department of Obstetrics and Gynecology at Saveetha Medical College and Hospital, Chennai. Study was carried out by consecutive enumerative sampling between 1 April 2014 and 31 December 2017 after getting written informed consent from participants in local language.

Sample size was calculated $N = Z^2 \times p (1-p)/d^2$=1.96 X 1.96 X 0.8 X 99.2/0.05X 0.05= 1219.47 [5]. The sample size was adjusted for the attrition rate of 15%. The final sample size (1219.47+182.85) was 1403. The pregnant women were recruited in first trimester for study.

Multiple Pregnancies were excluded as the risk for congenital heart defects to eliminate selection bias. In multiple pregnancies, the likely cause of CHD is not maternal but abnormal placentation [6]. The CHD in twin pregnancy may be attributed to ischemic organ damage caused by placental vascular anastomoses leading to feto-fetal transfusion.

All pregnant women were asked to fill a questionnaire about age, consanguineous

marriage, number of cups of coffee/tea per day, previous history of any congenital malformations and intake of folic acid in the first trimester. Prepregnancy weight and height was also recorded. History of recent divorce, separation, and job loss, loss of any close relative or friend was used to identify bereavement issues pertaining to stress. A first trimester scan was done to measure Crown Rump Length (CRL) to date the pregnancy in all cases.

In the newborn, gestational age as calculated by Naegle's formula was confirmed according to the Ballard's modification of Dubowitz et al [7]. The detailed account of postpartum events like Apgar score and resuscitation were recorded. The pulse oximeter used was GT 700 (with sensors for infants). A saturation of value of < 95% or a difference in measurement of >3% in 48 hours of birth in the hospital, the presence of murmurs, apnea, duration of oxygen therapy and ventilator support were noted. Neonatal echocardiogram was done using P7-3e Phased array neonatal cardiac probe by Mindray (North America) to confirm the diagnosis by trained pediatric cardiologist in the Department of Neonatology [Table 1]. The cardiac vascular imaging involved performing cross-sectional echocardiography, and Doppler and color flow imaging in various views. Data was entered in Microsoft excel sheet in password protected computer. The diagnosis was reconfirmed in the Department of Cardiothoracic surgery by IE-33 Philips Echocardiography Equipment, Bothell, WA, USA. Statistical analysis was done by first comparing the data with χ^2test. Odd's ratio and p-value were calculated by MEDCALC (Belgium). Confidence level was kept at 95% Interval. The Institutional Ethical Committee of Saveetha Medical College and Hospital approved this study.

Table 1. Types of congenital heart defects diagnosed (n=22)

S. no	Congenital heart disease	No of cases
1	VSD	9
2	ASD secundum	4
3	Complex cyanotic heart disease	2
4	Regurgitant tricuspid valve	2
5	Tetralogy of Fallot	1
6	TAPVC	2
7	Common Atria/ Levocardia/ TAPVC/ASD/TR	1
8	Ebstein's Anomaly	1

VSD=Ventricular septal defect, ASD= Atrial septal defect, TAPVC=Total anomalous pulmonary venous connection, TR= Tricuspid regurgitation

3. RESULTS

Data was analyzed for 1394 pregnancies. Nine pregnant women were lost for follow up. During the study period, 22 (1.58%) pregnancies resulted in CHD out of total 1394 pregnancies. Out of 22 CHD newborns, 21 survived beyond four weeks of life. A newborn with Ebstein's anomaly died on the 5th day of life. In 4 neonates (18.18%) no maternal risk of CHD could be identified. Table 1 shows the various cardiac defects diagnosed in newborns. Three CHD newborns were associated with other congenital malformations (syndromic) and 19 CHD newborns had isolated cardiac defects (nonsyndromic) not associated with any other congenital malformation.

Table 2 is a compilation of maternal risk factors associated with CHD. A consanguineous marriage was associated with significant risk for CHD (Odd's ratio 4.77,p value=0.0004) as shown in [Table 2]. Maternal age less than 19 years as compared to >19 years confers a significant risk for CHD (Odd's Ratio 11.87,p value= 0.0002). Maternal stress was noticed to have a high risk of CHD (Odd's ratio 15.82, p value<0.0001). History of previous congenital malformations was found in 16 pregnancies, which was associated with two cases of CHD (Odd's ratio 9.7, p value=0.004). Prepregnancy BMI> 24 was a significant risk factor for CHD (Odds ratio 6.87,p value=0.0001). Maternal caffeine intake of >4 cups a day was associated with significant risk of CHD (Odd's ratio 10.45, p value<0.0031). Fourteen women gave history of no intake of folic acid in first trimester and 2 of these women had congenital heart disease (Odd's Ratio 11.33, p value=0.0023).

It was found that maternal overt diabetes in 39 cases had an Odd's ratio association of 11.57 with CHD (p value =0.0033). Gestational diabetes did not confer an additional risk of CHD (Odd's ratio 1.01, p value=0.9953).

4. DISCUSSION

Developments in neonatal and pediatric cardiovascular surgery and anesthesia have improved the prognosis of CHD. Current challenges in the primary prevention of CHD include accurate identification of modifiable maternal risk factors. The frequency of CHD found in this study is 1.59%, the reported incidence varies from 0.8-1 % [8]. This increased incidence of CHD in this study as compared to

reported incidence could be explained, as our centre is a tertiary referral hospital receiving cases from peripheral villages surrounding Chennai.

Fig. 1(a) and Fig. 1(b) are the graphical representation of prevalence of maternal risk factors in normal and CHD newborns. Maternal age less than 19 years is associated with compromised placental nutrient transfer as the metabolic needs of a growing teenager competes with the requirements of an intrauterine fetus [9]. Maternal age more than 35 years may also increase the risk of CHD by increasing the risk of chromosomal anomalies and syndromic CHD [10]. The mechanism by which caffeine could produce CHD is by increasing the levels of homocysteine and promoting insulin resistance [11,12,13]. The mechanisms of association between prepregnancy BMI and CHD are not clear, but probably related to protein energy bioavailability and changes in maternal hemodynamic status [14-18].

In this study, consanguineous marriage was a significant factor that contributed to CHD. This may be explained fetal genetic and chromosomal aberration, which are common in first and second-degree consanguineous marriages [19,20]. Vascular disruption and oxidative stress associated with increased blood sugar levels may lead to increased risk of CHD in diabetes mellitus [21]. GDM, on the contrary, is associated with hyperglycemia and worsening glucose control as the gestation progresses, and may not be a significant contributor during the developmental period. Folic acid and other concurrent nutrient deficiencies are an important contributing factor [22].

Table 2. Maternal Risk factors and risk of offspring with congenital heart defects

S. no	Maternal characteristics	Odds ratio	95% CI	Z statistic	Significance level (p value)
1	Age<19 years	11.87	3.23-43.73	3.21	0.0002
2	BMI>24	6.87	2.61-18.09	3.90	0.0001
3	Consanguineous marriage	4.77	2.01-11.36	3.54	0.0004
4	Maternal caffeine intake	10.45	2.21-49.39	2.96	0.0031
5	Maternal diabetes	11.57	4.04-33.19	4.56	<0.0001
6	GDM	1.01	0.13-7.60	0.006	0.9953
7	Maternal stress exposure	15.82	4.89-15.20	4.61	<0.0001
8	Anomaly in previous pregnancy	9.7	2.07-45.52	2.80	0.004
9	No intake of foliate	11.33	2.38-53.97	3.05	0.0023

GDM=Gestational Diabetes Mellitus, BMI=Body Mass Index

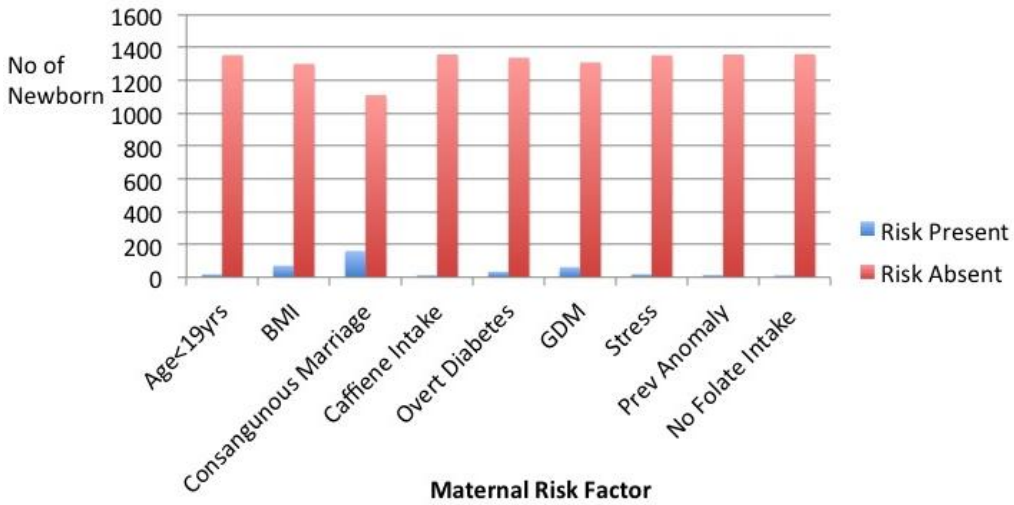

Fig. 1 (a). Distribution of maternal risk factors in neonates without congenital heart disease

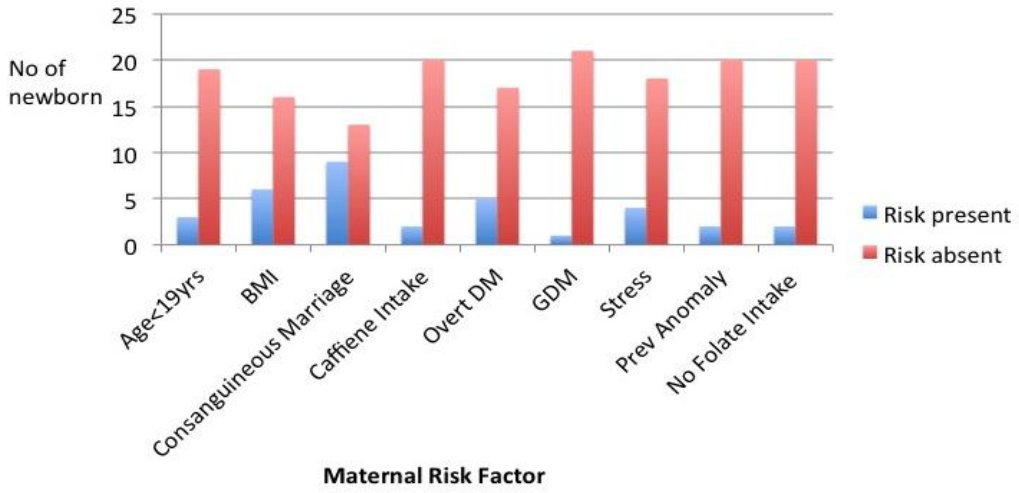

Fig. 1(b). Distribution of maternal risk factors in 22 neonates with congenital heart disease

In our study women with stress are more likely to have CHD. Stress by increasing the corticosteroid and catecholamine production may interfere with organogenesis [23,24,25].

Maternal age, prepregnancy BMI, uncontrolled diabetes, caffeine intake, consanguineous marriages, stress and folic acid deficiency are reliable significant risk factors contributing to CHD in south Indian population. Similar studies done in North Indian population also report an incidence of 0.87% [26]. The prevalence rate in other studies varies between 1.3/1000 to 13.8/1000. Some studies assess the prevalence of CHD in school statistics and this may include the rheumatic heart diseases and miss out critical life-threatening early CHDs of infancy [27-32].

5. CONCLUSION

The results of this study suggest that in reducing the incidence of CHD, public health strategy needs to focus on avoidance of teenage pregnancy and consanguineous marriages. Pregnancy associated with stress should be monitored more closely. Prepregnancy maternal BMI, coffee intake and folic acid deficiency have to be corrected. Maternal overt diabetes and hyperglycemia during pregnancy needs to be screened and managed timely to reduce the incidence of CHD.

CONSENT

As per international standard or university standard, participants written consent has been collected and preserved by the author(s)

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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