

Maternal Gestational Fever and Congenital Malformations

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ABSTRACT The relationship between congenital malformations and hyperthermia due to maternal fever in humans was investigated in the present study. The frequency of congenital malformations was significantly higher (especially of the cardiovascular system, central nervous system and musculoskeletal system) in the offspring of the mothers who had a history of gestational fever as compared to the control population. The malformations observed included atrial septal defect, ventriculo septal defect, patent ductus arterioses hydrocephaly, meningomyelocele, microcephaly, anencephaly, shortened femur and humerus, hypospadias, micropenis and cryptorchidism. This finding emerges amid a resurgence of concern over the hazards of maternal hyperthermia and strongly supports the hypothesis that maternal gestational hyperthermia is an extremely potent teratogen.

INTRODUCTION

Environmental factors may be wholly or partly responsible for some recognizable human malformations. These factors may be inherent in the maternal environment or may be an extragenous agent, which may act as a teratogen. Hyperthermia, as an agent for producing congenital defects has been demonstrated in a wide range of experimental animals. Surprisingly, it has attracted less attention as a possible teratogen in humans. However, the evidence for human teratogenicity from gestational fever is now accumulating.

Hyperthermia refers to an abnormal elevation of the body temperature. There is concern when

the body temperature reaches 38.9° C (102° F) or higher during pregnancy. Many studies support the hypothesis of teratogenicity of hyperthermia (Skreb et al. 1963; Edwards, 1969; Leck, 1978; Shiota et al. 1980; Layde et al. 1980; Milunsky et al. 1992; Martinez et al. 2001). However, some investigators were skeptical about the results of this kind of study (Leck 1978) and pointed out to the possibilities of recall bias if cases upto the age 10 were considered. Such methodological pitfalls that might lead to biased results are minimized considerably in this study, by considering only the newborns. Advantages of considering only the newborns were stressed upon by Shiota (1982).

MATERIALS AND METHODS

A total of 8551 newborns born in the neonatal unit of Goa medical college, a major tertiary hospital in Goa between 1999 to 2001 were screened for congenital malformations. A total of 166 malformed newborns were noted. The mothers of the babies were interrogated and information about the prenatal exposure of the mother to various factors, including gestational fever was collected. Wherever applicable the information was verified with antenatal hospital records. Same number of mothers of normal babies were considered as the control group. The association of maternal fever with congenital malformations was then analyzed by comparing it with the control. The significance was tested adopting the chi-square test.

RESULTS

The frequency of occurrence of the congenital malformations in the offsprings of those mothers who had a history of gestational fever was significantly higher (73.53%) than those of the control (47.32%) [$\chi^2 = 11.9$, $p < 0.001$]. The malformations observed in the newborns were grouped systemwise [Fig. 1]. The most frequently affected systems were the cardiovascular system (CVS), central nervous system (CNS) and musculoskeletal system (MSS) which constituted

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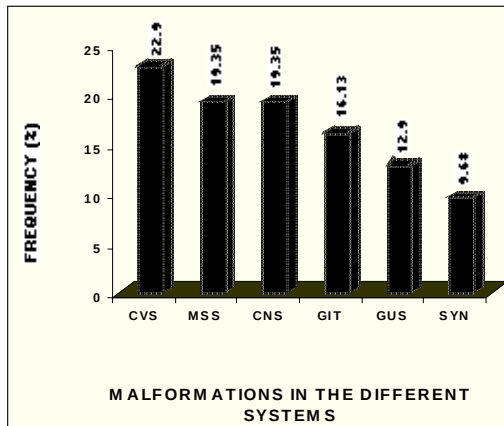


Fig 1. The frequency of malformations in the different systems associated with gestational fever

22.9%, 19.35% and 19.35% respectively. CVS malformations found to be associated with gestational fever included atrial septal defect, ventricular septal defect and patent ductus arteriosus. CNS malformations included hydrocephaly, meningomyelocele, microcephaly and anencephaly. MSS malformations included absence of depressor angular oris muscle, congenital tal-

ipes equinovarus and other limb abnormalities such as polydactyly, shortened femur and humerus. Urogenital malformations were noted mostly in the male babies and included hypospadias, micropenis and cryptorchidism (Table 1).

DISCUSSION

The result of the present study shows that there is an association between congenital malformations and fever during pregnancy. The association was statistically significant [$\chi^2 = 11.9$, $p < 0.001$] and was seen to affect mostly the CVS, CNS and the MSS. In most of these cases the fever was not an account of the viruses which are known to be teratogenic, hence we attribute the effect on the fetus to the hyperthermia on account of the fever. Hyperthermia accompanying fever may be acting as a teratogen and resulting in the manifestation of these abnormalities in the newborns. Hyperthermia may be either causing death of the cells or altering the tissue growth or interfering with the cellular differentiation. The ability of the hyperthermia to induce malformations in only some and its failure to induce in all the mothers who had gestational fever may be because only some have ge-

Table 1: Types and frequencies of various congenital malformations associated with Maternal gestational fever

System	Malformations	No. of cases	Frequenncy (%)
Cardiovascular system (CVS)	-Ventricular septal defect	3	22.90
	-Patent ductus arteriosus	3	
	-Auriculo septal defect	1	
	Total	7	
Musculo skeletal system	-Absence ofdepressor angular oris	1	19.35
	-Limb deformities	4	
	-Congenital talipes equinovarus	1	
	Total	6	
Central nervous system(CNS)	-Hydrocephalus	3	19.35
	-Anencephaly	1	
	-Microcephaly	1	
	-Meingomyelocele	1	
	Total	6	
Gastrointestinal tract (GIT)	-Cleft lip and cleft palate	2	16.13
	-Micrognathia	2	
	-Trafcheo-oesophageal fistula	1	
	Total	5	
Genitourinary system (GUS)	-Micropenis	3	12.90
	-Cryptchorism	1	
	Total	4	
Syndromes	-Down's syndrome	2	9.68
	-Turner's syndrome	1	
	Total	3	

netic predisposition which is determined by the genotype of the conceptus. Association of hyperthermia with CNS malformations in human population was reported by many investigators (Edwards 1972; Miller 1978; Shiota 1982; Peterka et al. 1994; Edwards et al., 1995). These findings were supported by the animal studies of Skreb et al. (1963), Edwards (1968) and Shiota et al. (1989). Our results agree with these earlier observations.

We also noted an association between hyperthermia and CVS malformations, indicating that hyperthermia might influence the development of the cardiac tissue also. These observations are consistent with the findings of Fraser and Shelton (1978) and Tikkanen et al. (1991).

Gestational fever was also seen to influence the development of the limbs. Hyperthermia may be altering the tissue growth resulting in the shortening of the femur and the humerus and bowing of the femur. Remarkably similar observations were reported earlier by Martinez et al. (2001). Other malformations seen were hypospadias, micropenis and cryptorchidism. Similar reports were reported earlier (Fraser and Shelton 1978).

The present study therefore supports numerous other studies and suggests that hyperthermia is an extremely potent teratogen affecting the development of the CVS, CNS and MSS, thus resulting in cardiac malformations, malformations of the brain and spinal cord and limb

abnormalities.

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