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Original Research Article

Sex selection drug and congenital malformations in North India

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ABSTRACT

Background: An increasing incidence of congenital malformations (CMF) has been reported in North India in cases use of traditional drug by Mothers to have male child. Aim was to ascertain the association of Sex selection drug (SSD) and congenital malformations.
Methods: This hospital-based age-sex matched pair case control study was done at Advanced Pediatric Centre, Obstretics and Gynaecology department (ANC clinic, Maternity ward, labor room etc.) and Special Clinics, PGIMER, Chandigarh, India in 2019. The mothers were interviewed to collect information about risk factors.
Results: Two hundred three CMF (under five children and gestational CMF) cases and same number of controls were studied. Significant association of CMF was observed with the use of sex selection drugs by mothers (OR= 4.35).
Conclusions: The use of sex selection drugs is an avoidable risk factor of CMF and is of high public health importance. People need to be educated about this.

Keywords: Antenatal care, Child health, Congenital malformations, Reproductive health, Sex selection

INTRODUCTION

In this era of epidemiological transition communicable diseases are on the decline and a relative increase has been noted in the incidence and prevalence of non-communicable, chronic and genetic diseases. One such group of disorders is congenital malformations (CMF).[1] Every year an estimated 8 million children - 6 percent of total births worldwide-are born with a serious birth defect of genetic or partially genetic origin. Additionally, hundreds of thousands more are born with serious birth defects of post-conception origin due to maternal exposure to environmental agents. At least 3.3 million children less than 5 years of age die annually because of serious birth defects and the majority of those who survive are mentally and physically disabled for life.[2] The reported prevalence of congenital malformations in different studies shows a marked variability depending upon the nature of the study, inclusion of the minor defects and still birth and the period of follow up.[3] Cardiovascular malformations have been reported to be the commonest type of CMF (37%), followed by musculoskeletal (30%), gastrointestinal (23%), Central nervous system (13%) and genitourinary (6.6%).[4]

Congenital malformations have been documented to be responsible for about 15% of the perinatal mortality in India.[5,6] With advancements in perinatal and neonatal care, other causes of perinatal mortality have been controlled and as in the west, the time is not far when the leading cause of perinatal mortality would be malformations.[7] Congenital malformations (CMF) compromise the quality of life as these affect all spheres of our activities e.g. physical performance, competence and capability in case of major limb anomalies, central nervous system and cardiac anomalies. CMF also decrease the self image of the affected person. In some cases, it makes a person dependent on others for whole life e.g. absence of limbs. CMF may make one dependent on drugs for lifelong e.g. congenital thyroid disorders.[8] In

this context, to ensure the optimum level of health of the surviving children, it is vital that due emphasis is given to tackle the problem of congenital malformations. As a corollary, it is essential to understand their etiological factors so that relevant prevention strategies can be planned. Against this background present study was planned with the following objective.

The aim of study was to ascertain the determinants of congenital malformations seen in PGIMER, Chandigarh, North India.

METHODS

The methodology followed was a matched pair case control study conducted in the Advanced Pediatrics Centre (APC) and labor room/maternity ward/antenatal clinic/medical termination of pregnancy (MTP) centre of Department of Obstetrics and Gynecology, Post Graduate Institute of Medical Education and Research, Chandigarh. The data was collected during May- July 2019. All cases of congenital malformation reporting at these places were registered for the study. Consecutive subjects whom the investigator was able to contact were interviewed. Consent was duly taken from the respondents. Case definition of WHO was used for CMF i.e. structural defects at birth and any CMF detected through ultrasound during pregnancy.[9,10] ICD-10 classification (Code Q00 - Q99) was used to categorize the cases.

For each case selected an age and sex matched control was selected from the other children attending clinics who did not have any obvious congenital malformation. In case of prenatal detection of CMF through ultrasound, another woman of ± 1 week of gestational age of the case was taken as control. For neonates (0-1 month) a time tolerance of ± 1 day and for children aged above one month up to one year plus or minus 15 days tolerance was allowed while selecting the controls. e.g. for a 6 month old male case, the control was taken from boys aged 5.5 month- 6.5 month. For children above one year a time tolerance of one month was allowed when deciding about selection of controls. Mother/parents of the cases and controls were interviewed for ascertaining the determinants of CMF with the help of the study tool. Congenital malformations detected prenatally or in children less than 5 year were included in the study. Multiple pregnancy cases with mixed, anomalous and normal outcome and children above 5 year were excluded.

Matched pair analysis was used for this study. Mantle-Haenszel odd's ratio, 95% confidence intervals (CIs) and P value for the strength of association were calculated. Univariate analysis using Mc Nemar Chi square test with or without Yates' continuity correction was done wherever the total number of discordant pairs was at least 20. Chi-square was calculated from the discordant pairs i.e. pairs with different status of exposure in cases and controls. Multicollinearity was considered which was absent. Then logistic regression analysis was performed. Initially, univariate logistic regression was performed to examine association of various factors with CMF (congenital malformation). The category with no exposure was regarded as reference. For other variables without the 'no exposure' category, the group with 'least exposure' was regarded as the baseline. Respective observations with missing data were excluded, in order to maintain consistency in the univariate and multivariate analyses.

Variables identified as significant risk factors in the univariate analysis were included in logistic regression analysis. The confounding effect of age and sex were controlled by matching. Forward stepwise logistic regression using maximum likelihood ratio test was then used to test if the model would change significantly by inclusion of other factors. The level of statistical significance for univariate analysis and for the logistic model was set at 0.05. The p values for entry and removal during step wise selection were 0.05 and 0.1, respectively.

Other variables, which were of borderline significance in the univariate analysis but were known important risk factors from the literature, were also included. Each significant and important variable was first examined to determine whether it was a confounder. This was done by examining with each of the exposures and comparing the crude and adjusted ORs. If association and a difference between crude and adjusted OR was observed, then the independent variables were considered as confounders. The confounders were tested with a forward modeling strategy, with likelihood ratio tests (LRTs) performed to assess the goodness of fit achieved by adding each variable into the model. The order in which the variables should add into the model was indicated by the results of the crude univariate analysis. However, it has been suggested that parameter estimates obtained from a logistic regression model may be unreliable unless 10-20 events (observations) per variable are available.[11] In the current study, a total of 14 parameters were estimated in the maximum logistic regression model under consideration. A best-fit model was developed in which the variables were mutually adjusted. Epi info 6 version, SPSS17 version and STATA 9.0 statistical package was used for analysis.

Further to evaluate the predictive accuracy of logistic regression model, the software Med Calc version 12.1.3.0 was used. The fifteen variables found significant in univariate logistic regression were taken together for logistic regression with classification table and ROC curve based upon cross classification results using stepwise method.

RESULTS

Two hundred three cases and same number of controls, who were of singleton birth and age less than five year,

were taken for study. No still birth case was recorded during the period of study. In 92% (375) children the informant was the mother. Father was the informant in 18 (4.4%) children and other close relatives in 13 (3.2%) children. The main source of cases was APC OPD and that of controls was the healthy baby clinic or immunization centre. The age of the patients ranged between "4 months" intrauterine to "57 months" after birth. Maximum numbers of cases were aged between 1month to one year i.e. 85 (42%). Males outnumbered the females in the ratio of 2.6:1 (Table 1). Cardiovasular malformations (Q20-28) were commonest followed by gastrointestinal (Q38-45), genitourinary (Q50-64) and central nervous system (Q00-07) (Table 2). Matched pair analysis for risk factors is shown in the tables 3, 4 and 5.

Table 1: Age and sex distribution among cases and controls (n=190).

Age of child	Cases		Controls	
	M	F	M	F
</= 1 month	37	7	37	7
>1 month- 1 year	60	25	60	25
>1 year- 5 year	40	21	40	21
Total	137	53	137	53

Table 2: System wise frequency of CMF (n=203).

Systems affected by malformations	No. of cases	Percentages (%)	ICD 10 codes
Circulatory system	55	27.1	Q20.0 - Q28.9
Gastro intestinal system	47	23.1	Q38.0 - Q45.9
Central nervous system	26	12.8	Q00.0 - Q07.9
Urinary system	20	9.8	Q60.0 - Q64.9
Musculo skeletal system	15	7.4	Q65.0 – Q79.9
Syndromes*	11	5.4	Q80.0 – Q89.9
Genital organs	9	4.4	Q50.0 – Q56.9
More than one system involved but not specified as syndromes	8	3.9	More than one codes for each of eight cases.
Chromosomal Anomalies not elsewhere classified	7	3.4	Q90.0 – Q90.9
Cleft lip, cleft palate	3	1.5	Q35.0 – Q37.9
Respiratory system	1	0.5	Q30.0 – Q34.9
Eye, ear, face, neck	1	0.5	Q10.0 – Q18.9

*11 Syndromes are: Q87.8-Laurence moon bidel Syndrome;Q87.8-Zellweger Syndrome; Q87.0-Oro facio digital syndrome;Q87.8- Wiskot Aldrich Syndrome; Q 87.2- Klippl-Trenauaunay Weber Syndrome; Q86.8- Congenital Rubella Syndrome; Q 87.0- Moebius Syndrome; Q87.0- Robin syndrome; Q 87.0- Cryptophthalmus syndrome; Q85.8- Sturge Weber Syndrome; Q87.8-Ive mark's Syndrome

Table 3: Risk factors having highly significant association with CMF.

Risk factors	Cases with exposure (n=203)	Control with exposure (n=203)	Exposure status of case and controls				Odds ratio B/C	Chi-square $(B-C)^2$ B+C	P value (d.f.=1)	95% CI
			A	B	C	D				
Family H/O CMF	16	6	1	15	5	182	3	5	0.025	1.09-8.25
Father alcohol	84	42	21	63	21	98	3	21	<0.001	1.83– 4.9
Father smoke	48	16	7	41	9	146	4.55	20.48	<0.001	2.21-9.3
Father tobacco	29	13	4	25	9	165	2.7	7.5	0.006	1.29-5.95
Non intake of folate	57	31	11	46	20	126	2.3	10.24	0.0013	1.36-3.88
Contraceptive use	31	12	2	29	10	162	2.9	9.25	0.0023	1.44-6.23
H/O abortion	163	141	115	48	26	14	1.84	6.54	0.01	1.14-2.97
H/O any drug	64	27	10	54	17	122	3.17	19.28	<0.001	1.84-5.47
H/o traditional drug	83	26	9	74	17	103	4.35	34.46	<0.001	2.56-7.37

A= Concordant pairs with both cases and controls exposed; B= Discordant pairs with case exposed and controls unexposed; C= Discordant pairs with cases not exposed and controls exposed; D= Concordant pairs with both cases and controls not exposed

Univariate logistic regression analysis of all the risk factors of CMF studied in the present study among matched subjects showed family history of CMF, alcohol, smoking and tobacco habituation in father, non intake of folate by mother during the pregnancy, contraceptive use, history of abortion, history of any drug, history of traditional drug usage, stay near high tension tower, stay near mobile tower, age of mother at marriage <18 yr, age of mother at first pregnancy < 20 yr and age at conception of present child< 20 yr as significant factors.

Use of traditional drugs, father habituated of alcohol, no folate intake by mother, age of mother at marriage <18yr, history of abortion were found to be the significant risk factors by the forward stepwise approach in regression modelling (Table 5).

Table 4: Logistic regression model including variables chosen from those found significant in univariate analysis.

Risk factors	Odds ratio	Std. err.	z	P> z	95% confidence intervals
Traditional drug	3.14	1.01	3.54	0.000	1.66 - 5.9
H/o any drug	1.30	0.46	0.74	0.457	0.65 - 2.60
Father alcohol	1.84	0.61	1.83	0.067	0.96 - 3.53
Contraceptive	1.91	0.91	1.35	0.176	0.74 - 4.88
No folate	2.62	0.93	2.69	0.007	1.30 - 5.28
Stay near high					
Tension tower	1.74	0.68	1.43	0.154	0.81 - 3.77
Father tobacco	1.16	0.66	0.27	0.786	0.38 - 3.57
Mat Age at mrg<18yr	1.75	0.65	1.52	0.129	0.84 - 3.63
Mat Age at concep<20yr	4.45	4.64	1.43	0.152	0.57 - 34.38
H/o abortion	1.71	0.55	1.67	0.095	0.90 - 3.23
Stay near mobile tower	1.04	0.33	0.12	0.905	0.55 - 1.95
Family h/o CMF	3.25	2.55	1.50	0.133	0.69 - 15.18
Fever in pregnancy	3.14	1.75	2.05	0.041	1.05 - 9.37

Table 5: Logistic model using forward stepwise methods.

Risk factors	Odds ratio	Std. err	Z	P > Z	95 % confidence intervals
Traditional drug use	3.38	0.98	4.18	0.000	1.91 - 6.003
Alcohol use by father	2.25	0.73	3.27	0.001	1.45 - 4.48
No folate intake	2.74	0.91	3.04	0.002	1.43 - 5.27
Age of mother at marriage<18yr	2.30	0.75	2.58	0.010	1.22 - 4.36
History of abortion	1.89	0.57	2.14	0.033	1.05 - 3.41

Table 6: Model based upon cross classification table and ROC curve analysis based upon this.

Method	**Stepwise**		
Enter variable if P<	0.05		
Remove variable if P>	0.1		
Overall model fit			
Null model -2 log likelihood	550.356		
Full model -2 log likelihood	464.562		
Chi-square	85.794		
Significance level	P < 0.0001		
Coefficients and standard errors			
Variable	**Coefficient**	**Std. error**	**P**
Traditional drug	1.40302	0.27337	<0.0001
H/oany drug	0.72080	0.28879	0.0126
Father alcohol	0.81991	0.24885	0.0010
Non intake folic acid	-1.03424	0.30142	0.0006
h/oabortion	0.58219	0.27777	0.0361
Agmother at conception	1.98878	0.81426	0.0146
Constant	-0.4084		
Odds ratios and 95% confidence intervals			
Variable	**Odds ratio**	**95% CI**	
Traditional drug	4.0674	2.3802 to 6.9506	
H/oany drug	2.0561	1.1674 to 3.6213	
Father alcohol	2.2703	1.3940 to 3.6975	
Non intake folic acid	0.3555	0.1969 to 0.6418	

Continued.

Method		Stepwise	
h/oabortion		1.7900	1.0385 to 3.0852
Agmother at conception		7.3066	1.4812 to 36.0438
Cross classification table (cut-off value p=0.5)			
Actual group	**Predicted group**		**Percent correct,** %
	0	1	
Y = 0	156	43	78.39
Y = 1	77	121	61.11
Percent of cases correctly classified			69.77
ROC curve analysis			
Area under the ROC curve (AUC)			0.747
Standard Error			0.0247
95% Confidence interval			0.702 to 0.789

Use of traditional drugs, history of use of any drug, father habituated of alcohol, no folate intake by mother, history of abortion and age of mother at conception of the present child <20yr were found to be important predictors of CMF in the predictive model; with 69.77% cases correctly classified and the area under the ROC curve was (c-statistic or concordance index) 0.702 to 0.78 (Figure 1 and 2). Thus the final model (Table 6) correctly predicts 69.7 to 78% of the cases.

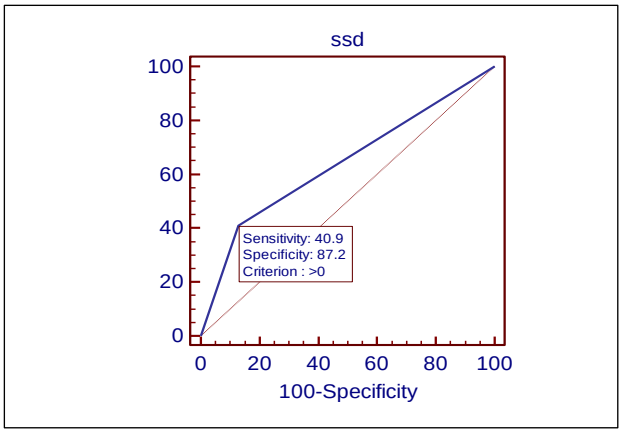

Figure 1: ROC curve with Sex selection drug (SSD).

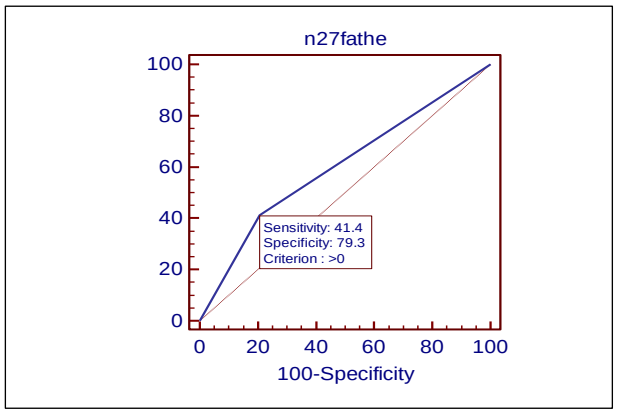

Figure 2: ROC curve with Father alcohol habituation.

DISCUSSION

Birth defects are found in 2-3% of all newborns, this rate doubles in the first year and reaches 10% by the age of five years, as more defects become evident and can be diagnosed. Almost 20% of deaths in newborns are caused by birth defects.[12]

The present study could identify many potential etiological factors for CMF. In concordance with earlier observations, our study also showed association of CMF with heredofamilial factors and consanguineous marriages.[13-15] There was a significant association of CMF with family history of CMF in our study (adjusted OR=3).

Previous history of abortion was found to be associated significantly (adjusted OR=1.84) with CMF. Agarwal et al study and Chaturvedi and Banerjee study also found history of previous abortion to be most significantly associated with CMF.[16,17] Ronya et al found that higher incidence of CMF was associated with previous history of CMF.[18]

History of threatened abortion in the present pregnancy was observed in 20 cases and 10 controls. Henry and Varma also showed a high positive relation between threatened abortion and major life-threatening congenital malformations.[19]

Etiology of CMF is also linked to factors related to fathers. Higher odds of CMF in families where fathers were smoker (OR=4.55) as observed in this study might be due to passive exposure of mother to smoke. In David et al study also, father's cigarette smoking was more common among children with cleft lip ± cleft palate, hydrocephalus, ventricular septal defect, and urethral stenosis.[15] Plausible mechanisms for a paternal influence on birth defects may be through genotoxic effect of smoking on the sperm. If the ovum is fertilized with a genetically altered sperm, the resulting conceptus might develop abnormally and result in a miscarriage or a live birth with malformation.[15] In our study also, like David et

al, we found that habituation of father to alcohol (adjusted OR=3) and tobacco (adjusted OR=2.7) was linked to CMF positively.[15] Increased economic burden and family tension due to such addictions may also result in stressful environment in family for the pregnant women. Stress itself may act as a causal factor for CMF as also shown in many studies.[20,21]

In a large prospective study reported on EMF exposure in 1063 pregnant women around the San Francisco area, after participants wore a magnetic field detector, the researchers found that rates of pregnancy loss grew significantly with increasing levels of maximum magnetic field exposure in routine day-to-day life.[22]

A study from Shimla (North India) showed higher percentage of malformations in low maternal age group.[23] Agarwal study found the highest incidence of CMF in children born to mothers in the age group 40-44 yrs, whilst the lowest incidence was in the age group of 20-24 yrs.[16] In our study, when maternal age at conception <20 yr was taken in univariate logistic regression analysis it was found to be significantly associated with CMF (OR =5.49). This might be due to predisposition of such women for early pregnancy complications resulting from lack of proper development/maturity of reproductive tract.

Our study showed cardiovascular CMF as the commonest (55; 27.1%) followed by gastro intestinal (47; 23.1%), genitourinary (29; 14.2%), and central nervous system CMF (26; 12.8%). Kumar et al also showed malformations involving cardiovascular system as the commonest 37%, followed by musculoskeletal 30%, gastrointestinal 23%, central nervous system 13% and genitourinary system 6.6%.[5] In Agarwal et al study defects of central nervous system were the most common, accounting for almost one third (31.7%) of all birth defects and musculoskeletal defects were equally frequent.[16] Roychoudhury et al also reported that 23.7% malformed babies were affected with neural tube defects, 16.8% had cleft palate and 14% showed talipes.[24] Ronya et al showed the higher incidence of gastrointestinal and genitourinary (20.4% each) followed by central nervous system (17.3%) CMF.[18]

History of contraceptives usage was significantly (adjusted OR=2.9) associated with CMF. But only 9 cases and two controls gave positive history of contraceptive pill intake during or just before pregnancy. Others had used barrier method mostly where the association might be due to usage of spermicidal agents. In our study history of any drug usage during pregnancy was also found to be significantly associated with CMF (adjusted OR=3.17).[25] These drugs included pain killers, paracetamol, drugs for morning sickness and antibiotics.

In the present study, males outnumbered the females for CMF cases in the ratio of 2.6:1. Agarwal et al study on 9405 consecutive single births, male to female ratio was 1.2: 1 and in Kumar et al study on children between 0-6 yrs, the ratio was 1.3:1 in malformed babies.[16,4] The higher representation of males in our study may be related with skewed sex ratio in Haryana and Punjab due to a high incidence of sex selective abortions in this region.[26] The widely prevalent son preference also manifested in this study as the linkage of traditional sex selection drug (SSD) usage during pregnancy to have male child (especially taken during first trimester in most cases) with CMF (OR= 4.3). In Bandyopadhyay and Singh study also more than 90% respondents were aware of SSDs and 45.5% (40) had used SSD to have male baby.[26] Chaung et al study also showed usage of traditional drug as risk factor of CMF (OR 8.62).[27] Anecdotal reports are also available about an apparent increase in cases of CMF in North India due to use of Sex Selection Drugs (as reported by doctors from private nursing homes).[26]

There has some limitations for this study. Many studies on CMF have shown linkage of CMF with environmental factors. But in hospital-based studies it is difficult to establish the linkage as the surveyor may not have access to water samples to know the nitrate content in the drinking water, assess lead or methyl mercury exposure from environment, food samples, utensil samples etc. For information on effect of these environmental factors and pollution on CMF, large scale community-based studies are recommended. Recall bias on exposure is also a limitation of case control study. Though, we tried to reduce this by including children aged less than five years only.

CONCLUSION

To conclude, the use of traditional drugs (sex selection drugs), nonintake of folate and maternal fever during pregnancy were found to be the major risk factors associated significantly with CMF in our study. We also found significant association of CMF with habits of father like taking alcohol (OR 3), smoking history in father (OR 4.5), father taking tobacco (OR 2.7). Besides these factors age of mother at marriage <18 yr and history of abortion were the important predictors of CMF.

If CMF are not prevented, they decrease both subjective and objective quality of life. Given the present scenario of single child norm and the focus of Government on healthy mother and child, it becomes significantly important for the general public to know the harmful effects of the preventable factors of CMF. As still male preference cribs the mind set of public in country like India this case control study increase the awareness about the effect of traditional drugs on foetus.

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