Drug Saf (2015) 38:789–797
DOI 10.1007/s40264-015-0309-5

ORIGINAL RESEARCH ARTICLE

Indigenous Medicine Use for Sex Selection During Pregnancy and Risk of Congenital Malformations: A Population-Based Case-Control Study in Haryana, India

Sutapa Bandyopadhyay Neogi[1] · Preeti H. Negandhi[1] · Navraj Sandhu[2] · Ravi Kant Gupta[3] · Abhijit Ganguli[4] · Sanjay Zodpey[1] · Amarjeet Singh[5] · Arun Singh[6] · Rakesh Gupta[3]

Published online: 20 June 2015

Abstract

Introduction Congenital malformations (CMFs) are a major public health problem in India. Consanguineous marriages, infections during pregnancy, folic acid deficiency during the periconceptional period, exposure to pesticides and a history of intake of drugs during pregnancy have been hypothesized as risk factors. Drugs include oral contraceptive pills, progesterone analogues, medications for ailments and indigenous drugs to bear male offspring. It is important to analyze the risk factors in order to implement preventive measures. The prime objective of this study was to study the risk factors of visible structural CMFs, with a focus on indigenous medicines for sex selection.

Methods A population-based, case-control study was undertaken in Haryana state. Cases included children (0–18 months) with any apparent structural deformity as reported by various Government sources. A consecutive birth from the same area as the case was labelled and included as the control. The sample size calculated was 175 in each group. Mothers of every case and control were interviewed at their respective homes using a structured tool. Descriptive analysis, bivariate analysis, followed by logistic regression was conducted to establish the association between risk factors and CMFs.

Results The sociodemographic profiles of the cases and controls were similar. Among the various risk factors studied, more than two living children (unadjusted odds ratio [OR] 1.6, 95 % CI 1.04–2.4) and intake of sex-selection drugs (unadjusted OR 2.8, 95 % CI 1.6–5.1) were significant risk factors on bivariate and regression analyses. The risk of having a child with CMFs was threefold more among mothers with a history of intake of indigenous medicines for sex selection (adjusted OR 3; 95 % CI 1.7–5.6).

Conclusions The intake of indigenous drugs during pregnancy increased the risk of CMFs almost threefold. This has social as well as economic implications, and hence needs further investigation.

Key Points

The practice of consuming indigenous medicines during the first trimester of pregnancy to beget a male offspring is commonly observed in north Indian states.

The intake of such medicines increases the risk of visible congenital malformations among newborns.

Electronic supplementary material The online version of this article (doi:10.1007/s40264-015-0309-5) contains supplementary material, which is available to authorized users.

✉ Sutapa Bandyopadhyay Neogi
sutapa.bneogi@iiphd.org

[1] Indian Institute of Public Health–Delhi (IIPH–D), Public Health Foundation of India (PHFI), Plot number 47, Sector 44, Gurgaon 122002, Haryana, India

[2] Government of Haryana, Panchkula, Haryana, India

[3] National Health Mission, Panchkula, Haryana, India

[4] Thapar University, Patiala, India

[5] Department of Community Medicine, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[6] Rashtriya Bal Suraksha Karyakram, Government of India, New Delhi, India

1 Introduction

Congenital malformations (CMFs) or birth defects are the seventh cause of death in children <5 years of age, seventh cause of year of life lost (YLL), twelfth cause of year of life lived with disability (YLD) and the seventh cause of disability-adjusted life-years (DALYs) lost [1, 2]. CMFs affect an estimated 1 in 33 infants, and result in approximately 3.2 million birth defect-related disabilities every year [1, 2]. They causes 6 % of global infant deaths, of which 92 % occur in low- and middle-income countries [3, 4].

The birth prevalence of major CMFs is approximately 2 % in developed countries, which, when translated to India, would result in an estimated 500,000 children born with major anomalies [5]. Reports from India have a documented prevalence ranging from 0.3 % to 3.6 % [6–19]. CMFs account for 8–15 % of perinatal deaths and 13–16 % of neonatal deaths [6]. In fact, the rates of certain CMFs in India, such as neural tube defects, are the highest in the world [16–18]. Although state-wise prevalence of CMFs is not readily available, recent sporadic reports, as well as anecdotal findings, indicate a rising burden of birth defects in the northern part of India [20, 21].

Apart from consanguineous marriages, infections during pregnancy, folic acid deficiency during the periconceptional period, exposure to pesticides and high uranium levels in the environment, and a history of intake of drugs during pregnancy, such as oral contraceptive pills, progesterone analogues and antiepileptic drugs, have been hypothesized as risk factors [20, 22–29]. Anecdotal reports exist on the intake of some indigenous medicines during early pregnancy in parts of North India, perceived to help a woman beget a male offspring [23–26]. These medicines are usually available from local healers, in various forms (powders, tablets) and are indigenously prepared. Such medicines, which are often also termed sex-selection drugs (SSDs), cannot alter the sex of a fetus since chromosomal sex is determined at the time of fertilization and cannot be changed thereafter. However, exposure of such medicines during pregnancy can have a deleterious effect on the growth and development of the actively growing fetus which is strongly linked to the timing of exposure during pregnancy. The association between the intake of such medicines and CMFs warrants scientific investigation.

Studies on CMFs have always been a matter of controversy owing to their multifactorial etiologies and failure to pinpoint one factor or establish the interaction between two or more factors. However, knowledge regarding risk factors can aid in informing some preventive interventions to combat the growing burden. As other causes such as birth asphyxia, prematurity and sepsis affecting newborns get addressed, proportionate mortality due to CMFs is bound to increase in the coming years. Therefore, we undertook this research to study the risk factors for CMFs, with a special focus on the intake of indigenous drugs for sex selection during pregnancy.

2 Methods

Our study was a population-based, case-control (1:1) study covering all 21 districts of Haryana state in North India. Approximately 65 % of the population in Haryana is rural. The health profile of the state is comparable to the national average, while the sex ratio is highly skewed (879 females per 1000 males against a national average of 940) [30].

Started in 2013, Rashtriya Bal Suraksha Karyakram (RBSK) is a new initiative in India aimed at screening children from 0 to 18 years for the four Ds—defects at birth, diseases, deficiencies and developmental delays, including disabilities. Screening of newborns (which includes both retrospective and prospective cases), both at public health facilities and at home, is an important component of the strategy. Screening of preschool and school-age children to 18 years of age is carried out at Aganwadi centres (daycare centres) and schools, respectively [31]. Children diagnosed with any of the prespecified illnesses receive follow-up referral support and treatment, including surgical interventions at tertiary level, free-of-cost under this programme.

Different methods are used to detect CMFs in Haryana. In addition to RBSK, three additional sources under National Rural Health Mission (NRHM) were utilized [31, 32]. The Anemia Tracking Module is a web-based portal through which data regarding antenatal women coming to the health facilities can be obtained retrospectively and the gaps in service delivery can be sought. Other portals such as Mobile Health Teams run by Accredited Social Health Activists (ASHA) and data from Special Newborn Care Units (SNCUs) which were shared with the Government were also used as sources of data on children with CMFs across the state. Study subjects were children less than 18 months of age drawn from the list compiled as part of the ongoing programmes.

The list consisted of cases already diagnosed and treated by state health teams. The list shared with the research team had data on more than 1000 children less than 2 years of age with some form of malformations, from all districts of Haryana. Of these, children less than 18 months of age with visible structural malformations were identified for the study considering the feasibility of data collection.

2.1 Sampling and Sample Size

Cases that met our eligibility criteria were selected purposively from the lists that we received from the state over

a period of 5 months (February to June 2014) (Fig. 1). The sample size was calculated based on the following assumptions: power = 80 %, level of significance = 0.05; prevalence of intake of drugs during pregnancy to have a male child was taken as 20 %, as reported from a previous study [29]. The odds ratio (OR) was assumed to be 2 instead of 3 since that study was conducted in a tertiary care facility where the severity of cases was high, whereas our study was a population-based study. Therefore, the sample size was 346 (173 cases and 173 controls), which was rounded off to 175 cases and 175 controls.

2.2 Cases and Controls

Cases were children born with any apparent structural malformation—open neural tube defects, cleft lip/palate, club foot, hypospadius, epispadius, imperforate anus, hydrocephalus, omphalocele, adactyly, and fused knee by birth. These included live births, singleton and multiple pregnancies. Standard case definitions used in RBSK were used to report structural CMFs in our study [31].

Diagnosis was verified by a team of trained researchers based on medical records and visual inspection of the defect or the scar (if the defect was surgically repaired) before data collection. Controls were consecutive births without any apparent structural malformation in the past 18 months based on reporting by ASHAs in the same village or urban areas as the case.

Children undergoing treatment for any emergency condition or whose mothers were not willing to participate were excluded from the study. The research team collected the data by personally visiting the families.

2.3 Risk Factors

Risk factors in the study included lack of folic acid supplementation during the periconceptional period; conception induced by medications or treatment; exposure to radiation (x-rays), infections and intake of drugs during the first trimester of pregnancy; consanguineous marriage; increased maternal and paternal age; use of pesticides to store grains; and the presence of a mobile tower (exposure to radiation) or industry (exposure to toxic wastes and gases from textile and plastic industry) near the house (within an approximately 1 km radius). Information was elicited on indigenous medicines consumed in the first trimester to beget a male child. All these were elicited by taking history from the mother primarily. In some cases, other family members, such as husband and mothers-in-law, also participated in the interviews. Medical records, wherever available, were used to triangulate the responses. In-depth interviews were conducted in select cases and controls where there was a suspicion of maternal infections during pregnancy or intake of any drug during pregnancy.

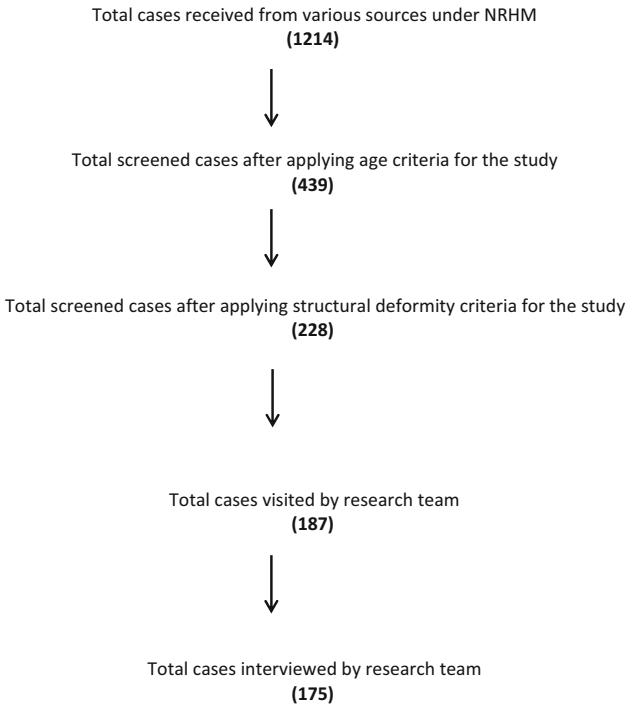

Fig. 1 Process of screening of cases for inclusion in the study—flow of events. *NRHM* National Rural Health Mission

2.4 Data Collection and Management

A semi-structured questionnaire was developed in English, later translated into the local language and pretested (see the electronic supplementary material). The questionnaire included sociodemographic variables, exposures and possible risk factors. Research staff were trained in data collection before initiating the process. Customized data-entry formats were designed in CSPro version 5.0 (developed and maintained by the US Census Bureau http://www.census.gov/population/international/software/cspro/) by the database administrator. Built-in checks for consistency, range and missing data were designed. Data management included creation of data description tables, validation of the database, data cleaning, processing and analysis. Approximately 10 % of the data entered were cross-checked by verifying the data from the hard copies kept with the investigators. Patient confidentiality was maintained by restricting access of data to the research team only.

2.5 Statistical Analysis

All data were exported to SPSS version 19.0 (IBM Corporation, Armonk, NY, USA) for quantitative analysis.

Descriptive analysis was performed for the sociodemographic factors. Cases and controls were compared for sociodemographic variables and other risk factors using the unpaired t test for continuous variables and the Chi-square test for categorical variables. Association between the risk factors and CMFs was also ascertained through bivariate analysis. A logistic regression model was developed using the backward stepwise method of inclusion/exclusion of variables in the model to measure the effect of the risk factor on the probability of having CMFs. The level for inclusion of the adjusted variables was specified as $p < 0.05$. The factors found to be significant in bivariate analysis were included in the regression model.

3 Results

The cases included had at least one visible structural deformity. Neural tube defect (33 %) and cleft lip/palate (30 %) were the most commonly found cases (Table 1).

3.1 Sociodemographic Variables

The average age of cases and controls was approximately 5.5 months, and the cases and controls were similar as far as sociodemographic variables were concerned ($p > 0.05$) (Table 2). Most of the mothers in both cases and controls had completed education up to primary-school level (37.1 and 36 %, respectively). In both categories, most of the fathers were manual labourers, and more than 95 % of mothers were homemakers. The majority of households in both categories had an average annual income of less than 1 lakh (100,000) Indian rupees (INR) in a year.

Table 1 Distribution of cases as per their structural congenital malformations

Structural congenital malformation	Frequency[a] ($n = 175$)	Percentage
Neural tube defect	58	33.1
Cleft lip and palate	52	29.7
Imperforated anus	19	10.9
Adactyly	1	0.6
Club foot	33	18.8
Tracheoesophageal fistula	5	2.9
Fused knee joint	1	0.6
Hydrocephalus	6	3.4
Omphalocele	3	1.7

[a] Three cases had more than one congenital malformation

3.2 Risk Factors

The age of the fathers of the study participants ranged from 18 to 58 years, with approximately 93 % of fathers being less than 35 years of age; more than 95 % of the mothers were less than 35 years of age. History of consanguineous marriage was very low (<2 %) in the study population.

Most of the cases presented with a history of fever with or without rash between the seventh and ninth month of pregnancy (eight cases 42.1 %) followed by the fourth to sixth month (six cases 31.6 %), which is a less dangerous period compared with the first trimester (five cases 26.3 %). Among controls, nine mothers with a positive history of fever were equally distributed across the three trimesters (33.3 % each). The strength of association between the presence of fever with or without rash during the first trimester of pregnancy and CMFs was found to be 0.6 (95 % CI 0.14–2.5) (Table 3). The mothers were also asked about any history of TORCH infections (Toxoplasmosis, Rubella, Cytomegalovirus and Herpes Simplex virus) or diabetes that they might have had during their pregnancies. None gave a documented positive history of TORCH infections or diabetes. No association could be elicited with the use of pesticides, exposure to radiation or the presence of a mobile tower in the vicinity. Folic acid supplementation is an important preventive measure for CMFs, especially neural tube defects. Unfortunately, in the study population, folic acid supplementation during the periconceptional period was not reported. The reported intake of folic acid was in combination with iron supplementation usually consumed after the first trimester. This was not included in the analysis due to the fact that it would not have any preventive effect.

CMFs were found to be significantly associated with the number of living children. Families with more than two living children were 1.6-fold (95 % CI 1.04–2.4) more likely to have a child with a birth defect compared with families with two or less than two children.

More than 25 % of mothers (45) of cases reported a positive history of intake of indigenous medicines during pregnancy compared with 11 % of controls [19]. A strong association was found between intake of such medicines and CMFs (OR 2.8; 95 % CI 1.6–5.1). History was considered to be positive when either the mother or any close relative admitted to having taken such drugs during pregnancy for the child included in the study. Mothers whose children had a birth defect were 2.8-fold more likely to give a positive history compared with mothers of healthy children.

Considering the link between the number of living children and intake of such indigenous medicines, a subgroup analysis was undertaken. Association between history of intake of such medicines and birth defects was

Table 2 Sociodemographic profile of cases and controls

Sociodemographic variables	Cases	Controls	*p* value[a]
Age of child, months [mean (SD)]	5.8 (5.0)	5.6 (4.3)	0.67
Sex of child			
Male	101 (57.7)	100 (57.1)	0.91
Female	74 (42.3)	75 (42.9)	
Age of mother, years [mean (SD)]	24.2 (3.4)	24.8 (4.0)	0.13
Age of father, years [mean (SD)]	27.3 (4.2)	28.4 (5.4)	**0.04**
Education status of mothers			
Illiterate	26 (14.9)	20 (11.4)	0.59
Literate	13 (7.4)	21 (12.0)	
Primary school	65 (37.1)	63 (36.0)	
High school	30 (17.1)	32 (18.3)	
Senior secondary	27 (15.4)	20 (11.4)	
Graduation	7 (4.0)	9 (5.1)	
Post-graduate and above	7 (4.0)	9 (5.1)	
Education status of father			
Illiterate	8 (4.6)	7 (4)	0.06
Literate	12 (6.9)	21 (12.0)	
Primary school	68 (38.9)	44 (25.1)	
High school	33 (18.9)	32 (18.3)	
Senior secondary	32 (18.3)	50 (28.6)	
Graduation	18 (10.3)	16 (9.1)	
Post-graduate and above	4 (2.3)	5 (2.9)	
Occupation of father			
Agriculture	20 (11.4)	23 (13.1)	0.35
Homemaker	0	1 (0.6)	
Office Job	8 (4.6)	8 (4.6)	
Industry	0	1 (0.6)	
Manual labour	83 (47.4)	65 (37.1)	
Other	64 (36.6)	77 (44.0)	
Occupation of mother			
Agriculture	1 (0.6)	1 (0.6)	0.59
Homemaker	168 (96.0)	169 (96.6)	
Office job	1 (0.6)	3 (1.7)	
Industry	0	0	
Manual labour	1 (0.6)	1 (0.6)	
Other	4 (2.3)	1 (0.6)	
Annual income of household (in INR)[b]			
<1 lakh	131 (74.9)	140 (80)	0.46
1–3 lakh	38 (21.7)	27 (15.4)	
3.1–5 lakh	5 (2.9)	6 (3.4)	
>5 lakh	1 (0.6)	2 (1.1)	

Data are expressed as *n* (%) unless otherwise specified

Bold value indicates $p < 0.05$

INR Indian rupees, *SD* standard deviation

[a] A *p* value <0.05 was considered a statistically significant difference or association, based on Chi-square estimates for proportions and *t* test for means

[b] 1 lakh is equivalent to 100,000

Table 3 Risk factors for congenital malformations (bivariate analysis)

Explanatory variables (risk factors)	Cases [*n* (%)]	Controls [*n* (%)]	Odds ratio (95 % CI)	*p* value[a]
Age of mother				
≤30 years	170 (97.1)	163 (93.1)		
>30 years	5 (2.9)	12 (6.9)	2.5 (0.9–7.2)	0.082
Age of father				
≤30 years	147 (84.0)	128 (73.1)		
>30 years	28 (16.0)	47 (26.9)	1.9 (1.1–3.2)	**0.013**
Fuel used for cooking[b]				
LPG	71 (40.6)	76 (43.4)	1.1 (0.7–1.7)	0.59
Kerosene	1 (0.6)	2 (1.1)	2.0 (0.2–22.4)	0.56
Biomass (wood, cow dung)	148 (84.6)	146 (83.4)	0.9 (0.5–1.6)	0.77
Ventilation of kitchen				
Good	25 (14.3)	40 (22.9)	1.7 (0.8–3.3)	0.16
Poor	22 (12.6)	14 (8.0)		
Outdoor cooking	128 (73.1)	121 (69.1)		
Presence of industry near the house	18 (10.3)	15 (8.6)	1.2 (0.6–2.5)	0.58
Presence of mobile tower near house	92 (52.6)	96 (54.9)	1.1 (0.7–1.7)	0.66
History of pesticides use to store grain	36 (20.6)	35 (20.0)	1.03 (0.6–1.7)	0.89
History of consanguineous marriage	2 (1.1)	3 (1.7)	1.5 (0.2–9.1)	0.65
Number of living children				
More than two	42 (24.0)	26 (15.9)	1.6 (1.04–2.4)	**0.04**
Two or less	133 (76.0)	138 (84.1)		
Family history of congenital malformation	7 (4.0)	6 (3.4)	1.5 (0.2–9.1)	0.65
History of infections during pregnancy	8 (4.6)	2 (1.1)	4.1 (0.87–19.8)	0.054
History of fever with/without rash during pregnancy in the first trimester	5 (2.9)	3 (1.7)	1.7 (0.4–9.1)	0.48
History of intake of drugs during the first trimester	13 (7.4)	5 (2.9)	2.9 (0.7–11.9)	0.13
History of intake of indigenous drugs for a male child in the first trimester (sex selection drugs)			2.8 (1.6–5.1)	**<0.001**
Yes	45 (25.7)	19 (10.9)		
No	130 (74.3)	156 (89.1)		
History of intake of indigenous drugs for a male child if the first child was a female ($n = 182$)[c]			3.4 (1.7–6.9)	**<0.001**
Yes	34 (39.1)	15 (15.8)		
No	53 (60.9)	80 (84.2)		

Bold values indicate $p < 0.05$

[a] A p value <0.05 was considered a statistically significant difference or association, based on Chi-square estimates

[b] More than one type of fuel was used in a household

[c] Subgroup analysis

explored in families where the first child was a girl; the strength of association increased to 3.4 (95 % CI 1.7–6.9). This indicates that a strong preference for a male child compels families to resort to such medication after a girl is born (Table 3). None of the mothers reported to have consumed any indigenous medicine for a fair child.

A model for multivariable analysis was developed to ascertain the effects of paternal age, intake of indigenous medicines and more than two living children on the likelihood of development of CMFs. The logistic regression model was statistically significant (Chi-square = 17.32; $p < 0.001$). The model explained 6.6 % (Nagelkerke R^2) of the variance in the CMFs and correctly classified 51.6 % of cases. Results showed that the odds of having a child with CMFs among mothers who took such medicines during their pregnancy were threefold higher than those mothers who reported not having taken any such drug during their pregnancy. This association was shown to be significant

Table 4 Multivariable analysis for risk factors of congenital malformations (final step of the logistic regression model)[a]

Risk factor	Odds ratio	95 % CI	*p* value
History of intake of indigenous drugs for a male child	3.0	1.7–5.6	<0.001
Number of living children (more than 2)	2.0	1.1–3.4	0.021

[a] A p value <0.05 was considered a statistically significant association

(95 % CI 1.7–5.6). Mothers with more than two living children were twofold (95 % CI 1.1–3.4) more likely to give birth to a baby with CMFs, after having adjusted for other factors (Table 4). Since CMFs are a rare event, it may be interpreted that the risk of giving birth to a child with CMFs was threefold more likely if there was a history of intake of such medicines. Other sociodemographic factors, such as maternal age, education of mother and annual family income, which might influence the outcome were also included in the regression model. No statistically significant association was observed; however, the effect of residual confounding factors cannot be ruled out.

4 Discussion

CMF is a multifactorial condition whose risk factors are amenable to prevention. We undertook population-based research to study the risk factors for CMFs, with a special focus on intake of indigenous drugs during pregnancy. The study revealed that a strong association existed between intake of indigenous medicines for sex selection during the first trimester of pregnancy (adjusted OR 3) and more than two living children with the likelihood of having CMFs.

The fact that women resort to such medications during pregnancy is now well-documented from studies in North India [24–26]. Although evidence on such an association seems to be limited, the findings corroborate well with those obtained in a hospital-based, case-control study in North India focusing on life-threatening CMFs [29]. The lip usually closes by 5–6 weeks after conception, and the palate by 10 weeks. Fusion of neural tubes takes place between 3 and 4 weeks after conception. An imperforate anus occurs during the fifth to seventh week of fetal development, and tracheoesophageal fistula occurs between 4 and 8 weeks after conception [33]. Biological plausibility is established since these medicines are consumed during 3–8 weeks after conception. However, temporality for individual CMFs could not be established since data for the exact time of intake of the medicine was difficult to elicit. Therefore, data on the timing of intake was collected in months, not weeks.

In our study, CMFs were associated more with women who had two living children or at least one female child. This basically stems from a strongly-felt need to restrict the family size and also have at least one son. Several anecdotal reports indicated the presence of a probable association in the past [23–26].

Previous studies have shown that such indigenous medicines contain some herbal ingredients—*Shivalingi (Bryonia Laciniosa)* and *Majuphal (Gtuercus infectoria*). These are reported to be consumed during the first trimester and procured mainly from faith healers. Preliminary analysis indicated that some of these drugs contained steroids (phytoestrogens and testosterone) [24].

Data on 14,551 live births from a prospective pregnancy cohort in Taiwan found evidence for a possible link between the use of specific herbal medicines in the first trimester and increased risk of malformations of the nervous system (adjusted OR 8.6; 95 % CI 2.5–29.3), musculoskeletal system (adjusted OR 1.6; 95 % CI 1.1–2.4), and the eye (adjusted OR 7.3; 95 % CI 1.5–36.2) [34]. These findings have been corroborated in another study in which abortions and skeletal abnormalities were observed when commonly used herbal medications during pregnancy were administered to pregnant mice [35]; however, no effect on fetal growth was reported [36].

Recent studies have highlighted that 32 % of women in Taiwan use traditional Chinese medicines compared with 22 % among males ($p < 0.001$) [37]. The use of herbal medications during pregnancy was reported to be higher in Asian countries compared to Western world (8.1 vs. 5.8 %) [38]. Use of such products seems to be correlated with geographic region, even after adjusting for race and ethnicity, as reported from a study on non-malformed children in the US. The prime indications for its use were nausea, vomiting or respiratory infections [38]. Herbal medications were also reported to be used to enhance the beauty of the skin of infants and to prevent abortion [39]. Use of herbs during the first trimester has been associated with increased perinatal mortality in Malaysia [40], and has also been found to be associated with early-onset bronchial asthma [39] and neonatal jaundice [41], as well as CMFs. In our study, no-one reported having taken medication for a fair child.

A previous study from India highlighted that 0.5 % of mothers took indigenous medicines in the hope of having a male child. This proportion increased to 10 % if the first child was a girl, and to 40 % if they had two daughters [25].

A history of fever with or without rash was elicited from the mothers only on the basis of history in the absence of documented evidence. Evidence shows that the true burden of diseases such as congenital rubella syndrome (CRS) in

India is not available [27]. However, it is estimated that 1–15 % of all infants suspected of having intrauterine rubella infections were found to have laboratory evidence of CRS, and 10–50 % of children with CMFs have laboratory evidence of CRS. An epidemiological study from Vellore showed an increase in CRS from 4 to 11 % between 2000 and 2008 [28]. In our study, we could not have ruled out TORCH infections since the presence of antibodies could have meant infections either during or before pregnancy.

Paternal age showed a strong association in unadjusted analysis but not when adjusted for other factors. Association between some of the risk factors, such as consanguinity, exposure to radiation, pesticides, fuel used in cooking, and industry, cannot be commented on since the study was not powered enough to study these factors. The reasons could be variability in the responses, which made it difficult to define the association objectively. The association of CMFs with gestational diabetes could not be studied since screening for diabetes is not performed routinely, especially in the rural set-up. Moreover, most of the cases were from rural areas, away from the industrial belt. Studies from India suggest that exposure to pesticides could be a risk factor for cardiac toxicity [42, 43]. In our study we elicited this information by asking if the families used pesticides to store grains (reported from 20 % of cases and controls) and indirectly correlated this with their occupation (agriculture). It is important to note here that since the controls were selected from the same rural or urban area as the case, these factors would have been adjusted for because of inherent matching. The lists (from various sources) shared by the state Health Department included more cases from rural areas. Based on the urban rural distribution of cases, it is difficult to state whether cases are actually more prevalent in rural areas compared with urban areas. However, the possibility of a selection bias or having better screening and elective termination of pregnancy in urban areas cannot be ruled out. Bias could also have been introduced because of the exclusion of stillbirths resulting from CMFs. Moreover, we considered a group of visible CMFs as a single outcome. These are a group of heterogenous collections of disorders, with each malformation having its own set of risk factors. Risk factors for individual malformation could not be studied due to inadequate power.

Despite its limitations, the study lends support to the association between indigenous medicines and CMFs. Age- and area-matched cases and controls, as well as logistic regression analyses, accounted for the confounders. Only children below the age of 18 months were included in the study so as to minimize recall bias. A history of intake of any drugs during pregnancy was verified from medical records wherever available. Intake of medicines for sex selection is usually a well-planned affair, and is therefore less liable to be forgotten. Given the sensitive nature of the topic, it was difficult to elicit a positive history, and therefore underreporting could be a possibility. This may have resulted in a non-differential misclassification of the exposure. It would essentially mean that the actual strength of association might be more than what was inferred from the study.

The intake of medicines for sex selection is more of a social problem arising out of a strong desire to have a son. Haryana has the lowest sex ratio in the country (879 females per 1000 males) [30]. A lot of measures (legal and regulatory) are being undertaken by the Government to curb the problem. This needs to be investigated further given the enormity of the problem as well as ethical issues.

5 Conclusions

There is a significant association between intake of indigenous medicines for sex selection and CMFs. Stronger evidence establishing the effect is required through animal studies and studies on gene–environment interaction. CMFs pose huge economic implications on families as well as the health system. Prevention of such defects is the key. The findings of this study ought to inform policies and programmes of the state of such malpractices. More than the supply side, it is the demand side that plays a greater role in the process. Education of the community on the potential risk of intake of such medicines must ensue.

Acknowledgments The research team acknowledges the contribution of Dr. Amit Phogat, Dr. Rupinder Sahota and Dr. Deepika Gupta from the National Health Mission, Haryana, India, for the support they extended during the completion of the study. The team also appreciates the work of its research associates, Mr. Shamlal Sikri and Dr. Sapna Chopra from the Indian Institute of Public Health–Delhi, for their contribution towards data collection, and of Mr. Manoj Soni, Data Management and Support Unit, Indian Institute of Public Health–Delhi, for helping the team with database development and data management. The authors are grateful to Professor Pat Doyle, Department of Epidemiology, London School of Hygiene and Tropical Medicine, for her contribution in improving the manuscript.

Compliance with Ethical Standards

Funding The National Health Mission, Government of Haryana, India, provided financial assistance to conduct the study described in this article.

Conflicts of interest Sutapa Bandyopadhyay Neogi, Preeti H. Negandhi, Navraj Sandhu, Ravi Kant Gupta, Abhijit Ganguli, Sanjay Zodpey, Amarjeet Singh, Arun Singh and Rakesh Gupta have no conflicts of interest that are directly relevant to the content of this study.

Ethical approval Permission was sought from the state and district authorities before initiating the study. Approval was obtained from Institutional Ethics Committees of the Indian Institute of Public Health–Delhi, Public Health Foundation of India.

Patient consent The project team provided potentially eligible parents with detailed information about the study, in the local language. Written consent was provided by every mother who voluntarily agreed to participate in the study. Confidentiality of the information collected was maintained at every level.

References

1. World Health Organization. Congenital anomalies. Geneva: World Health Organization; 2014.
2. Rosano A, Botto LD, Botting B, Mastroiacovo P. Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. J Epidemiol Community Health. 2000;54:660–6.
3. Higashi H, Barendregt JJ, Vos T. The burden of congenital anomalies amenable to surgeries in low-income and middle-income countries: a modelled analysis. Lancet. 2013;381:S62.
4. Christianson A, Howson CP, Modell B. March of dimes global report on birth defects. March of Dimes Birth Defects Foundation; 2006. http://www.marchofdimes.org/materials/global-report-on-birth-defects-the-hidden-toll-of-dying-and-disabled-children-full-report.pdf. Accessed 9 June 2015.
5. Jha P. Reliable mortality data: a powerful tool for public health. Natl Med J India. 2001;14:129–31.
6. Shamnas M, Arya P, Thottumkal VA, Deepak MG. Congenital anomalies: a major public health issue in India. Int J Pharm Chem Biol Sci. 2013;3(3):577–85.
7. Taksande A, Vilhekar K, Chaturvedi P, Jain M. Congenital malformations at birth in Central India: a rural medical college hospital based data. Indian J Hum Genet. 2010;16(3):159–63.
8. Agarwal SS, Singh U, Singh PS, Singh SS, Das V, Sharma A, et al. Prevalence and spectrum of congenital malformations in a prospective study at a teaching hospital. Indian J Med Res. 1991;94:413–9.
9. Singh M. Hospital-based data on perinatal and neonatal mortality in India. Indian Pediatr. 1986;23(8):579–84.
10. Sarkar S, Patra C, Dasgupta MK, Nayek K, Karmakar PR. Prevalence of congenital anomalies in neonates and associated risk factors in a tertiary care hospital in eastern India. J Clin Neonatol. 2013;2(3):131–4.
11. Sridhar K. A community-based survey of visible congenital anomalies in rural Tamil Nadu. Indian J Plast Surg. 2009;42(Suppl):S184–91.
12. Kumar V, Singh AJ, Marwaha RK. An epidemiological study of congenital malformations in rural children. Indian Pediatr. 1994;31(8):909–14.
13. Shah K, Pens C. Study of incidence of congenital anomalies in new borns. Gujarat Med J. 2013;68(2):97–9.
14. Bhat BV, Babu L. Congenital malformations at birth: a prospective study from south India. Indian J Pediatr. 1998;65(6):873–81.
15. Grover N. Congenital malformations in Shimla. Indian J Pediatr. 2000;67(4):249–51.
16. Mahadevan B, Bhat BV. Neural tube defects in Pondicherry. Indian J Pediatr. 2005;72(7):557–9.
17. Cherian A, Seena S, Bullock RK, Antony AC. Incidence of neural tube defects in the least-developed area of India: a population-based study. Lancet. 2005;366(9489):930–1.
18. Godbole K, Deshmukh U, Yajnik C. Nutrigenetic determinants of neural tube defects in India. Indian Pediatr. 2009;46(6):467–75.
19. Sharma R. Birth defects in India: hidden truth, need for urgent attention. Indian J Hum Genet. 2013;19(2):125–9.
20. Punjab: uranium deforms kids in Faridkot. Punjab Newsline Network. 2009. http://cndpindia.org/2009/04/punjab-uranium-deforms-kids-in-faridkot/. Accessed 9 June 2015.
21. Yadav P. Farmers suffer toxic-induced dent. Times of India. 2007. http://timesofindia.indiatimes.com/city. Accessed 9 June 2015.
22. Putra ki chah mein mor pankh kha rahin mahilayen. Dainik Bhaskar. 2007; 7(col7–8).
23. Neogi S. Congenital malformations: unexplored causes. Indian Paediatr. 2007;44:941.
24. Bandyopadhyay S, Singh AJ. Sex selection through traditional drugs in rural north India. Indian J Community Med. 2007;32:32–4.
25. Manchanda S, Saikia B, Gupta N, Chowdhary S, Puliyel J. Sex ratio at birth in India, its relation to birth order, sex of previous children and use of indigenous medicine. PLoS One. 2011;6(6):e20097.
26. Bhagat N, Laskar AR, Sharma N. Women's perception about sex selection in an urban slum in Delhi. J Reprod Infant Psychol. 2012;. doi:10.1080/02646838.2011.635297.
27. Dewan P, Gupta P. Burden of congenital rubella syndrome (CRS) in India: a systematic review. Indian Pediatr. 2012;49(5):377–99.
28. Chandy S, Abraham AM, Jana AK, Agarwal I, Kekre A, Korula G, et al. Congenital rubella syndrome and rubella in Vellore, South India. Epidemiol Infect. 2010;139(6):962–6.
29. Panda C, Singh A. Risk factors of congenital malformations reporting at PGIMER, Chandigarh: a case-control study [MPH thesis]. Chandigarh: School of Public Health, Post Graduate Institute of Medical Education and Research. 2009.
30. Census Info India. http://censusindia.gov.in/2011-common/censusdataonline.html. Accessed 9 June 2015.
31. Rastriya Bal Suraksha Karyakram (RBSK)—child health screening and early intervention services under NHM. Available at: http://nrhm.gov.in/nrhm-components/rmnch-a/child…/guidelines.html. Accessed 13 Mar 2015.
32. National Health Mission, Haryana. Available at: http://www.nrhmharyana.gov.in/. Accessed 1 May 2015.
33. Chung W. Teratogens and their effects. Available at: http://www.columbia.edu/itc/hs/medical/humandev/2004/Chpt23-Teratogens.pdf. Accessed 13 Mar 2015.
34. Chuang CH, Doyle P, Wang JD, Chang PJ, Lai JN, Chen PC. Herbal medicines used during the first trimester and major congenital malformations: an analysis of data from a pregnancy cohort study. Drug Saf. 2006;29(6):537–48.
35. Wang CC, Li L, Tang LY, Leung PC. Safety evaluation of commonly used Chinese herbal medicines during pregnancy in mice. Hum Reprod. 2012;27:2448–56.
36. Chuang CH, Lai JN, Wang JD, Chang PJ, Chen PC. Use of Coptidis Rhizoma and foetal growth: a follow-up study of 9,895 pregnancies. Pharmacoepidemiol Drug Saf. 2006;15(3):185–92.
37. Shih CC, Liao CC, Su YC, Tsai CC, Lin JG. Gender differences in traditional Chinese medicine use among adults in Taiwan. PLoS One. 2012;7(4):e32540.
38. Louik C, Gardiner P, Kelley K, Mitchell AA. Use of herbal treatments in pregnancy. Am J Obstet Gynecol. 2010;202:439.e1–10.
39. Chen YC, Tsai CH, Lee Y. Gestational medication use, birth conditions, early postnatal exposures for childhood asthma. Clin Dev Immunol. 2012;2012:913426.
40. Rahman AA, Ahmad Z, Naing L, Sulaiman SA, Hamid AM, Duad WNW. The use of herbal medicines during pregnancy and perinatal mortality in Tumpat district, Kelantan, Malaysia. Southeast Asian J Trop Med Public Health. 2007;38:1150–7.
41. Chan TY. The prevalence use and harmful potential of some Chinese herbal medicines in children and children. Vet Hum Toxicol. 1994;36(3):238–40.
42. Gupta SK, Jani JP, Saiyed HN, Kashyap SK. Health hazards in pesticide formulators exposed to a combination of pesticides. Indian J Med Res. 1984;79:666–72.
43. Saiyed HN, Sadhu HG, Bhatnagar VK, Dewan A, Venkaiah K, Kashyap SK. Cardiac toxicity following short-term exposure to methomyl in spraymen and rabbits. Hum Exp Toxicol. 1992;11(2):93–7.