Iraqi JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: iraqijms@colmed-alnahrain.edu.iq
http://www.colmed-nahrain.edu.iq

Environmental Risk Factors for Congenital Cardiovascular Defects among Infants and Children in Basra, Southern Iraq

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Abstract

Background In Basra, Southern Iraq, an increased prevalence of congenital cardiovascular defects was reported. Although genetic and environmental factors predispose to these defects, little information is available concerning the non-inherited modifiable factors that may cause these defects.

Objectives To determine the environmental risk factors for congenital cardiovascular defects in infants and children.

Methods A total of 109 patients with congenital cardiovascular defects and 252 infants and children without congenital cardiovascular defects were studied. Their age ranged from 1 day-14 years. History included residence, family history of congenital heart diseases, maternal factors, employment, maternal exposure to drugs and radiation during pregnancy, and maternal illnesses and potential paternal risk factors.

Results A significant association between maternal age (less than 20 years or more than 34 years) (odd ratio, OR 4.65), influenza (OR 4.25), maternal phenobarbital intake (OR 1.54) was demonstrated with congenital cardiovascular defects. On the other hand, lower birth order (OR 0.412), absence of maternal exposure to air pollution like carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter (OR 0.852), and maternal stressful events (OR 0.822) were associated with a reduced risk for congenital cardiovascular defects.

Conclusions Birth order, maternal age, maternal exposure to air pollutions, maternal stressful events, influenza and phenobarbital therapy are independent risk factors for congenital cardiovascular defects.

Keywords Congenital cardiovascular defect, children, Basra

List of abbreviation: CCVDs = congenital cardiovascular defects, ACEI = angiotensin-converting enzyme inhibitors, NSAID = non-steroidal anti-inflammatory drugs, ECG = electrocardiography.

Introduction

Congenital cardiovascular defects (CCVDs) represent some of the more prevalent malformations among live births and remain the leading cause of death from congenital malformations [1,2]. Disease prevention has been limited by a lack of information about modifiable risk factors for abnormalities in cardiac development [1].

Heart defects at birth may occur as an isolated malformation, but may also be associated with other anomalies or occur as part of a syndrome [3].

Nearly a two-fold increase in the reported rate of heart defects since the early 1970s was described [4]. In Basra, which is located in the extreme south of Iraq and an estimated population of 2,531,997, a hospital-based study has found that the relative risk of CCVDs for the years 1991-1994, 1995-98, 1999-2000 in comparison to 1990, was 2.4, 5.8, and 8.3, respectively. In 1999-2000 the reported prevalence of the CCVDs in Basra was 14/10, 000 [5,6].

The cause of most CCVDs is unknown [2,3]. Most cases of CCVDs are thought to be multifactorial

and result from a combination of genetic predisposition and environmental stimulus [2,7]. A small fraction of cases, perhaps 15%, can be traced to a known cause, even when including environmental teratogens with genetic and chromosomal conditions [4].

Some types of CCVDs can be related to an abnormality of an infant's chromosomes (5-6%), single gene defects (3-5%), or environmental factors (2-4%) [2,4]. As CCVDs may result in significant lifelong morbidity, and are an important cause of mortality attributed to birth defects, the development of effective prevention interventions is very important forward step. This study was carried out to study the potential environmental risk factors associated with CCVDs.

Methods

This study is a case-control study; infants and children with CCVDs who have been admitted to pediatric wards or referred to Echocardiography Clinic at Basra Maternity and Children Hospital, over the period from the 15th of February 2008 till the end of June 2008, were recruited (excluding those with chromosomal abnormalities like Down syndrome and multiple congenital anomalies). A total of 109 patients aged 1 day -14 years were included in the study.

A total of 252 age and sex matched infants and children without CCVDs consulting the outpatient department of the same hospital for minor illnesses were considered as control group.

Information taken included age, sex, birth order, family history of CCVDs, and diagnosis, which depended on clinical data, chest x-ray findings, electrocardiography (ECG), and Echocardiogram.

Maternal factors included: age, abnormal pregnancy outcome (previous miscarriage, still birth, preterm birth), employment (either unemployed, or employed). If employed; the type of employment is considered as without risk or with risk of occupational exposure to organic solvents like dyes, lacquers, paints, mineral oil products, maternal employment in agricultural industry, and maternal exposure to herbicides, rodenticides, pesticides, and insecticides [8-10].

The residence was also reported; Basra Center, Northern Area which includes (Al-Garma, Al-Qurna, Al-Hartha, Al-Madina), Western Area (Al-Zubair District), Southern Area (Fao, Abu-Al-Khaseeb), Eastern Area (Shatt Al-Arab and Shalamjah) [11].

Maternal illnesses and drugs used during the first trimester; including angiotensin-converting enzyme inhibitors (ACEI), aspirin, ibuprofen, diclofenate, phenytoin, phenobarbital, valproic acid, carbamazepine, metronidazole, cotrimoxazole, clomiphene (before pregnancy), vitamin A, corticosteroids, folic acid, and multivitamins containing folic acid (women were considered if they take folate and multivitamin supplements regularly from 3 months before conception through the third month of pregnancy, while women who started to take drug after they become pregnant were considered as not taking the drug) [3].

Maternal exposure to radiation (exposure in occupational settings or as part of medical or dental evaluations). Maternal water consumption, habits (smoking, coffee, and tea) and stressful events like close relative death, divorce or separation, and job loss were also assessed.

Paternal factors included: age, occupation (occupation at risk include jewelry making, welding, lead soldering, ionizing radiation, and paint stripping) [12] and habits (smoking and alcohol drinking).

Environmental factors included maternal exposure to air pollutants (distance 8.6 km-14.2 km which is the distance from air pollution source to the maternal residence) like carbon monoxide, nitrogen dioxide, ozone, sulfur dioxide, and particulate matter (such as dust, ash, and smoke) during first trimester of pregnancy [13,14]. These pollutants released by incomplete combustion of fuels such as coal, gas, and oil. In Basra these factories located in Um-Qasir, Al-Zubair, Khur Al-Zubair, Abu Al-Khaseeb, AL-Hartha, and AL-Najibia.

An informed consent was obtained from one of the parents, usually the mother before

recruitment in the study. The study approved by the Ethical Committee of Basra Medical College.
Statistical analysis was done using SPSS program (version 11), data were expressed and comparisons of proportions was performed using chi square and / or Exact Fisher`s test when appropriate. Logistic regression analysis was also done for the analysis of different potential risk factors. *P* value of <0.05 was considered as statistically significant.

Results

Ventricular septal defect (VSD) was the most common type of CCVDs detected in 35 (32.1%), followed by Tetralogy of Fallot in 12 (11%), VSD and pulmonary stenosis in 11 (10.1%), patent ductus arteriosus in 7(6.4%), atrial septal defect in 6(5.5%), hypertrophic cardiomyopathy in 6(5.5%) followed by transposition of great arteries in 5(4.6%). Other types of CCVDs were less common and accounted for (24.8%) in this study.
A significantly higher number of patients with CCVDs have a sibling, mother or father with CCVD, ($P < 0.01$). In addition, it was found that the frequency of CCVDs increases significantly with increasing birth order of the child ($P < 0.001$) as shown in Table 1.

Table 1. Distribution of cases according to age and sex, birth order and family history of congenital cardiovascular defects

Parameter		Patient Group N = 109		Control Group N = 252		*P* Value
		No.	%	No.	%	
Age (years)	<1	60	55	161	63.9	> 0.05
	1-4	29	26.6	70	27.8	
	5-9	15	13.8	17	6.7	
	10-14	5	4.6	4	1.6	
Sex	Male	56	51.4	146	57.9	> 0.05
	Female	53	48.6	106	42.1	
Family history of CCVDs in first degree relatives	None	101	92.7	249	98.8	< 0.01
	Any*	8	7.3	3	1.2	
Birth order	1st	7	6.4	50	19.8	< 0.001
	2nd	9	8.3	70	27.8	
	3rd	10	9.2	44	17.5	
	4th	10	9.2	43	17	
	5th	13	11.9	16	6.3	
	6th	15	13.7	11	4.4	
	7th	17	15.6	9	3.6	
	8th	18	16.5	6	2.4	
	≥9th	10	9.2	3	1.2	

*Any; CCVD in siblings, mother or father

Table 2 demonstrate significantly higher number of mothers of children with CCVDs were either younger than 20 years of age (30.3%) or older than 34 years (41.3%) compared to mothers of control group (6% and 13.5%) respectively, ($P < 0.001$). In addition, a significantly higher number of mothers of children with CCVDs have a history of reproductive problems (35.8%) than mothers of the control group (21.4%) ($P < 0.05$), and 23.9% of mothers of children with CCVDs have a history of stressful events during the

periconceptional period, compared with mothers of control group (6.4%), ($P < 0.001$).
The study also has revealed that a significantly higher number of mothers of children with CCVDs did not take folic acid 102 (93.6%) and multivitamins 105 (96.3%) during peri-conceptional period; whereas, mothers in the control group reported a significantly higher frequency of intake of folic acid 72 (28.6%) and multivitamins 64 (25.4%), ($P < 0.001$).
Pre-gestational diabetes, gestational diabetes, fever, influenza, and epilepsy were reported in a significantly higher number of mothers of children with CCVDs None of mothers in both groups reported history suggestive of rubella.

Table 2. Selected maternal characteristics among patients andcontrol group

Variable		Patient Group N = 109		Control Group N = 252		*P* Value
		No.	%	No.	%	
Age (years)	<20	33	30.3	15	6.0	< 0.001
	20-34	31	28.4	203	80.5	
	≥35	45	41.3	34	13.5	
History of abnormal Pregnancy outcomes	No	70	64.2	198	78.6	< 0.05
	Miscarriage	33	30.3	48	19.0	
	Stillbirth	2	1.8	3	1.2	
	Preterm birth	4	3.7	3	1.2	
Maternal stress event	No	83	76.1	236	93.6	< 0.001
	Close relative death	19	17.4	15	6.0	
	Job loss	7	6.5	1	0.4	

The study revealed that a significantly higher number of mothers in the control group (81.3%) were not taking drugs during pregnancy ($P < 0.001$), while mothers of children with CCVDs showed a highly significant association between ibuprofen ($P < 0.01$), clomiphene ($P < 0.001$), phenobarbital ($P < 0.01$), and cotrimoxazole intake ($P < 0.05$) and CCVDs. None of mothers in both groups gave a history of intake of angiotensin-converting enzyme inhibitors, phenytoin, carbamazepine, valproic acid, and vitamin A (Table 3).
Most of mothers of both groups were not consuming coffee (93.5% and 95.5%), and there was no significant difference among them concerning tea consumption. None of mothers in both groups were smokers. A significantly higher number of mothers in the control group (66.3%) were living in Basra center, while a significantly higher number of mothers of children with CCVDs were living in North, West and South of Basra, compared with mothers of the control group, ($P < 0.001$). A statistically significant association between the sources of air pollution in Basra (oil refineries, natural gas company, cement factory, petrochemical factory, electrical power station, and fertilizer factory) and CCVDs in children ($P < 0.001$) .
Regarding maternal employment; (14.9%) from all mothers of children with CCVDs and control group were employed in occupations without risk of exposure. None of mothers in both groups gave a history of exposure to radiation during pregnancy (Table 4).
Concerning paternal risk factors; young paternal age < 25 years and advanced paternal age ≥40 years were significantly higher among children with CCVDs, ($P < 0.01$) and a significantly higher number of fathers in the control group have no occupational risk (93.3%), compared with fathers of children with CCVDs (87.2%) ($P < 0.05$) as noticed in Table-5. None of fathers in both groups gave a history of alcohol drinking.

Table 3. Potential Maternal risk factors during pregnancy

Variable			Patient Group N = 109		Control group N = 252		OR	95% CI	P value
			No.	%	No.	%			
Maternal illness	No		58	53.2	218	86.6			< 0.001
	Fever		20	18.3	16	6.3	3.313.	1.64-6.68	< 0.001
	Influenza		21	19.3	16	6.3	52	1.75-7.05	< 0.001
	Epilepsy*		2	1.8	0	0.0	3.35	2.86-3.93	< 0.05
	GD		6	5.5	2	0.8	7.28	1.44-36.6	< 0.01
	Pre-GD*	Type 1	1	0.9	0	0.0			< 0.05
		Type 2	1	0.9	0	0.0			
Maternal drug ingestion during pregnancy	No		55	50.4	205	81.3			< 0.001
	Clomiphene		24	22	18	7.1	3.68	1.74-3.72	< 0.001
	Phenobarbital		5	4.6	1	0.4	0.154	1.37-1.72	< 0.01
	Cotrimoxazole		6	5.5	3	1.2	4.83	1.18-19.70	< 0.05
	Metronidazole		5	4.6	13	5.2	0.88	0.30-2.54	> 0.05
	Corticosteroids		3	2.8	6	2.4	1.16	0.28-4.72	> 0.05
	Aspirin	1st TM	2	1.8	2	0.8			> 0.05
		2nd TM	1	0.9	1	0.4			
	Diclofenac sodium	1st TM	1	0.9	1	0.4			> 0.05
		2nd TM	1	0.9	1	0.4			
	Ibuprofen	1st TM	1	5.5	1	0.4			< 0.01

GD = gestational diabetes, TM = trimester, * P-value of pre-gestational diabetes and epilepsy were calculated by Fisher's Exact Test.

Table 4. Potential environmental risk factors during pregnancy

Risk factors		Patient Group N = 109		Control Group N = 252		*P* Value
		No.	%	No.	%	
Residence	Basra center	50	45.9	167	66.3	< 0.001
	North of Basra	23	21.1	31	12.3	
	South of Basra	11	10.1	13	5.2	
	West of Basra	23	21.1	27	10.7	
	East of Basra	2	1.8	14	5.6	
Maternal exposure to air pollutants	No	71	65.1	229	90.9	< 0.001
	Oil refineries	3	2.8	2	0.8	
	Natural gas company	5	4.6	4	1.6	
	Cement factory	5	4.6	2	0.8	
	Petrochemical factory	5	4.6	3	1.2	
	Electrical power station	11	10.1	8	3.2	
	Fertilizer factory	9	8.3	4	1.6	
Employment	Yes	8	7.4	19	7.5	> 0.05
	No	101	92.6	233	92.5	
Maternal water consumption	Home tap water	10	9.2	18	7.2	> 0.05
	Bottled water	99	90.8	234	92.8	

Table 5. Paternal risk factors

Risk factors			Patient Group N = 109		Control Group N = 252		*P* Value
			No.	%	No.	%	
Age (years)	<25		24	22.0	31	12.3	< 0.01
	25-29		12	11.0	58	23.0	
	30-34		20	18.3	66	26.2	
	35-39		15	13.7	49	19.4	
	40-44		17	15.6	23	9.1	
	≥ 45		21	19.2	25	9.9	
Paternal habits	No		53	48.6	129	51.2	> 0.05
	Smoking	< 20/day	10	9.2	6	2.4	
		20-40	36	33.0	105	41.6	
		> 40	10	9.2	12	4.8	
Occupation	With risk		14	12.8	17	6.7	< 0.05
	Without risk		95	87.2	235	93.3	

The whole variables included in the study were subjected to logistic regression analysis to know the variables that are associated with CCVDs. It was observed that the higher birth order, young or advanced maternal age, maternal influenza, and maternal phenobarbital intake were found to be independent significant risk factors for CCVDs. On the other hand, lower birth order, absence of maternal exposure to air pollution, and maternal stressful events confer a protection against the development of CCVDs (Table 6).

Table 6. Independent variables associated with CCVDs

Variables	B*	SE*	OR	95% CI	*P* value
Birth order	0.888	0 .111	0 .412	0.331-0.511	< 0.001
Maternal age	1.53	0 .374	4.65	2.23-9.68	< 0.001
Influenza	1.44	0.538	4.25	1.48-12.22	< 0.01
Phenobarbital	0.432	0 .056	1.54	1.37-1.72	< 0.01
Absence of Maternal exposure to air pollution	0.160	0 .036	0 .852	0.79-0.91	< 0.001
Absence of Maternal stressful events	0.196	0 .052	0.822	0.74-0.91	< 0.001

B*: regression coefficient, SE*: standard error

Discussion

This case-control study describes the potential environmental risk factors for CCVDs in Basra. The current study reported significantly higher frequency of CCVDs in first degree relatives of patients compared to control group (7.3% and 1.2% respectively). A significant association among first degree relatives of patients with CCVDs was also reported by Bassili *et al* in Egypt [(15)], Stoll *et al* in France [(16)], and Correa *et al* in Baltimore [(17)]. Increased incidence of CCVDs in the same family suggests genetic influences [(4)], or because the family is exposed to the same environmental factors.

Higher birth order was significantly associated with higher risk of CCVDs; this is in agreement with that reported by Taksande *et al* in India [(18)] and Materna-Kiryluk *et al* in Poland [(19)]. This finding provides indirect evidence of environmental influence in the causation of CCVDs, which are known to be inherited in a multifactorial manner [(19)].

A significant association between CCVDs and young maternal age < 20 years and advanced maternal > 34 years was reported, similar results were found by Ferencz *et al* in Baltimore [20], Reefhuis *et al* in Atlanta [21]. Advanced age is associated with chromosomal anomalies, which could be the underlying cause for these associations.

History of abnormal pregnancy outcomes were significantly associated with increased risk of CCVDs, similar results were reported also by Ferencz *et al* in Baltimore [20], Cedergren *et al* in Sweden [7], and Pradat in Sweden [22]. Whether a history of reproductive problems represents a proxy for teratogenic exposures or for an inherent increased susceptibility for CCVDs is unclear [1].

Maternal stressful events including close relative death, and job loss were reported in a significantly higher percent of mothers of children with CCVDs, similar result was reported by Carmichael *et al* in California [23]. The exact mechanism is not known but it was presumed that increased catecholamine production due to stress, leads to decreased uterine blood flow and increased fetal hypoxia that could result in different types of birth defects [24].

Maternal periconceptional intake of multi-vitamin and folic acid was significantly associated with reduced risk for CCVDs in their offspring's, a similar results were reported by Beynum *et al* in Netherlands [3], Botto *et al* in USA [25], and Scanlon *et al* in Atlanta [26]. In contrast, a hospital-based case control study by Werler *et al* in Boston didn't report such association [27]. The maternal methylene-tetrahydro folate reductase 677TT genotype is associated with two folds increased risk of CCVDs in offspring, especially for a conotruncal heart defects if mothers did not use folate supplements [3].

Among maternal illnesses during pregnancy, there was a significant association with maternal diabetes. This is in agreement with other studies in different countries [7,20,28]. Both human and animal studies have demonstrated that diabetic embryopathy is associated with hyperglycemia during organogenesis. The precise pathogenic mechanisms remain unclear. Abnormal glucose levels disrupt expression of a regulatory gene in the embryo. Oxidative stress with generation of free radicals is another possible mechanism [4].

Maternal fever and influenza are also important risk factors for CCVDs, similar result was reported by ACS *et al* in Hungary [29], and Botto *et al* in Atlanta [30]. Both fever and infection have documented biological effects on specific developmental pathways. Altered apoptosis is a possible mechanism for this association [4].

Maternal epilepsy was significantly associated with CCVDs in this study; similar result was reported by Pradat in Sweden [22]. It has been difficult to determine whether maternal seizures are independently associated with an increased risk of heart defects [22,31].

Among medication intake during early pregnancy, this study showed a statistically significant association of CCVDs with maternal intake of Ibuprofen, a similar result was reported by Wilson *et al* in Baltimore [32]. In contrast, a study reported by Nielson *et al* in Denmark [33] has concluded that there is no evidence that any NSAID is teratogenic. The use of NSAID during pregnancy poses a potential threat to the myocardium. Persistent pulmonary hypertension and premature closure of the ductus arteriosus were reported in infants whose mothers took NSAID toward the end of pregnancy [8].

Maternal use of clomiphene was found to be significantly associated with an increased risk of CCVDs; similar results were reported by Bassili *et al* in Egypt [15], and Ferencz *et al* in Baltimore [20]. In contrast, a study by Niebyl *et al* in USA showed no association between maternal use of clomiphene with cardiac defects [9].

Folic acid antagonists (cotrimoxazole) intake during early pregnancy were also significantly associated with CCVDs, a similar result was found by Diaz *et al* in USA [31] and Czeizel *et al* in Hungary [34]. Folic acid antagonists act through different mechanisms including dihydrofolate reductase inhibitors, impairing absorption of folate, increasing the degradation of folate, or

affect various other enzymes in folate metabolism [31].

For antiepileptic drug, a significant association of CCVDs with phenobarbital intake during early pregnancy was found, a similar result was reported by Cedergren *et al* in Sweden [7], and Diaz *et al* in USA [31]. These findings are consistent with the view that phenobarbital may exert a teratogenic effect through mechanisms other than the depletion of folic acid, and a direct toxic effect has been proposed [31].

Drinking tea and coffee by mothers during pregnancy were not significantly associated with CCVDs in their offspring's; similar result was reported by Olsen *et al* in Denmark [35].

Maternal exposure to ambient air pollutions during early pregnancy is among the important environmental triggers of CCVDs, similar result was reported by Gilboa *et al* in Texas [13] and Ritz *et al* in California [14], who confirmed that increased ambient air levels of pollutants (carbon monoxide, ozone, sulfur dioxide, nitrogen dioxide, and particulate matter) are associated with increased risk of CCVDs. It was observed that mutations in fetal DNA may follow exposure to air toxics during pregnancy [13]. This could explain the significantly higher percent of children with CCVDs living in the north, west, and south of Basra where factories like petrochemical factory, Natural Gas Company, oil refineries, electrical power station, cement factory, and fertilizer factory are located.

There was a significant association between young paternal age <25years and advanced paternal age ≥45years with CCVDs in their offspring, similar results were obtained by Bassili *et al* in Egypt [15], and Yang et al in USA [36] possibly through dominant mutations. However, Cedregren *et al* in Sweden did not find certain paternal age effect [7].

The current study did not reveal a significant association between paternal smoking and CCVDs in their offspring's. While a study reported by Cresci *et al* in Italy [37] and Kuciene et *al* in Kaunas [38] had found an increased risk of CCVDs with paternal smoking. In addition, a significant association was identified between paternal occupational exposure and CCVDs in their offspring's, similar result was reported by Snijder *et al* in Netherlands [12].

From this study, it can be concluded that birth order, maternal age, maternal exposure to air pollutions; maternal stressful events, influenza, and phenobarbital therapy are independent risk factors for congenital cardiovascular defects.

Acknowledgment

We like to thank Dr. Asaad Yahya, Department of Animal Production, College of Agriculture for his indispensable help in the statistical effort of this work.

Author Contribution

Meaad Hasan designed the study and co-writes the manuscript, Ghada M Abboud collected and analyzed the data and write the paper

Conflict of Interest

Authors disclose no conflicts of Interest

Funding

The research was supported by the Iraqi Commission of Medical Specialization.

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Received 3rd Apr. 2013: Accepted 27th Jan. 2014