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Consanguinity, Maternal Age, and Maternal Diabetes as Potential Risk Factors for Congenital Heart Diseases: A Nested Case Control Study from Saudi Arabia

Mohamed M Shoukri[1]*, Mansour AlJufan[2], Shazia Subhani[3], Mansoor Baig[4], Futwan Al-Mohanna[1] and Zohair Al-Halees[2]

[1]*Department of Cell Biology, King Faisal Specialist Hospital and Research Center, Riyadh, 11211 Kingdom of Saudi Arabia*
[2]*Heart Center, King Faisal Specialist Hospital and Research Center, Riyadh, 11211 Kingdom of Saudi Arabia*
[3]*Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, 11211 Kingdom of Saudi Arabia*
[4]*Department of Biostatistics, King Faisal Specialist Hospital and Research Center, Riyadh, 11211 Kingdom of Saudi Arabia*

***Corresponding author:** Mohamed M Shoukri, Department of Cell Biology and the National Biotechnology Center, King Faisal Specialist Hospital and Research Center, P.O. Box 3354, Riyadh 11211, Saudi Arabia, Tel: 966509491454; **E-mail:** shoukri@kfshrc.edu.sa

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Abstract

Background: Several risk factors have been implicated as possible causes of congenital heart diseases (CHD), some are genetic and others are environmental. Previous studies have suggested presence of association with consanguinity, but most investigators have not addressed the association with specific diagnostic categories of CHD such as Patent Ductus Arteriosus and Tetralogy of Fallot, nor quantifying the magnitude of the effect sizes simultaneously attributed to gender, maternal age and maternal diabetes.

Methods: Using Saudi Arabia CHD registry data, we compared the odds of having Patent Ductus Arteriosus (PDA) and Tetralogy of Fallot (TOF) for families with consanguineous marriages and those of unrelated parents. Since maternal age is a possible confounder the comparisons are made by first constructing maternal age strata and then pooling the estimated odds ratio across age strata. The data included (n=429) mothers with (n=259) consanguineous marriages.

Results: The prevalence of CHD was significantly higher for boys in consanguineous marriages (OR=3.7, 95% CI: 1.05-12.78). The prevalence of CHD for girls was also higher in consanguineous marriages, but the difference from that of non-related marriages did not reach significance (OR=1.84, 95% CI: 0.758-4.490). The joint effect of the risk factors on the CHD was assessed using the logistic regression models.

Conclusions: The association between CHD and consanguinity may be due to underlying genetic factors and/or environmental factors common among siblings of the same family.

Keywords: Congenital heart diseases; Consanguinity; Risk factors; Odds ratio; Attributable risk.

Introduction

Most chd have a multifactorial etiology, involving interactions between genetic and non-genetic factors as cause of elevated probable risk. Approximately 15% to 20% of CHD cases have been linked to known genetic disorders such as Down syndrome, Turner syndrome, and 22q11.2 deletion. Maternal conditions such as diabetes, obesity, phenylketonuria, and rubella infection are established risk factors for chd [1,2]. Other risk factors that are implicated include consanguinity, gender, maternal age, and gender [3].

Briefly, chd is defined as a malformation of the heart structure and or cardiac great vessels that happen during intra uterine life and present from birth. [4] defined chd as a gross structural abnormality of the heart or intra thoracic great vessels that is actually or potentially of functional significance. Most congenital anomalies are caused by chd, representing a major global health problem. Twenty-eight percent of all major congenital anomalies consist of heart defects [5]. The incidence of congenital heart disease at birth (sometimes referred to as birth prevalence) depends on how a population is studied [6]. The most practical measurement of chd occurrence is birth prevalence per 1,000 live births [7]. Factors that contribute to the variations in estimates of disease incidence are, age distribution of the study population, inclusion and exclusion criteria, the level of expertise and training to detect minor defects and the advances in treatment modalities that took place over the last 20-30 years [8,9].

Epidemiologically, pre-maturity increases the incidence of PDA, mostly due to physiological factors rather than inherent abnormality of the ductus [10,11]. The incidence of PDA has been reported to be approximately, 1 in 2000 births, which accounts for 5% to 10% of all congenital heart diseases with female to male ratio of almost 2: 1 [4]. The PDA was found to occur with increased frequency in several genetic syndromes, which precise mechanisms resulting in persistent PDA are not yet clear [12-14]. TOF is a very common cyanotic congenital heart defect and is estimated to account for 4% to 9% of congenital heart defects overall, or in the range of 0.262 to 0.392 per 1000 live births [15].

Preliminary steps to understand the genetic etiology of inherited diseases is to conduct carefully planned family studies. Early studies of familial clustering of congenital heart defects suggested either polygenic or

multi factorial inheritance [16]. Patterns of recurrence of congenital heart diseases in one or more affected first-degree relative were studied, and it was shown that exact concordance rate was seen in 37% of cases. Other studies to detect different patterns of chd among siblings and twins have concluded that the pattern of inheritance was supported by a monogenic or oligogenic model, [17]. It has been reported that in a family having 1 sibling with PDA, there is almost 3% chance of having PDA occurrence in a subsequent offspring [18]. It is also reported that PDA is more common among females than among males [19,20].

This paper has two-fold objectives. Firstly; we identify the joint occurrence of PDA and TOF as the chd of interest and investigate the influence of potential risk factors on their co-occurrence. Investigating the joint effect of consanguinity and other risk factors on the co-occurrence of both conditions has not been investigated in the Saudi population. Secondly; we use several statistical analyses both at the univariate and multivariate levels to adjust for the possible confounding of maternal age through appropriate stratification. To quantify the effect of absence of consanguinity as the main risk factor of interest on the extent of the disease, we compare the attributable risk (AR), as a measure of amount of disease, with the commonly used effect size measured by the odds ratio.

Risk factors

In this section we shall review the literature on the associations between chd, and four risk factors of interest namely; consanguinity, maternal age, maternal diabetes, and gender.

Consanguinity

Arab countries are notorious of consanguineous marriages, with first cousin types being the most common. For example in Jordan the prevalence of consanguinity was reported by Khoury et al. [21] as 51.3% , Yemen, 40% as reported by Jurdi et al [22], and almost 57% in Saudi Arabia as reported by El-Hazmi et al. [23]. In one comparative study from Saudi Arabia, researchers found that first-cousin consanguinity is significantly associated with some congenital heart defects. They concluded that, in a population with a high degree of inbreeding, first-cousin consanguinity may exacerbate underlying genetic risk factors for some types of congenital heart diseases [24].More recently, a survey of Saudi families conducted by El Mouzan et al. [25], estimated the prevalence of consanguinity to be as high as 56%.

Maternal diabetes

While improvements in fetal surveillance and perinatal management have led to a reduction in diabetes related complications including perinatal mortality, the incidence of associated congenital anomalies remains high relative to the general population. Congenital heart defects occur in up to 8.5 per 100 live births of infants of diabetic mothers, and cardiac defects predominate [26, 27]. It was shown by Carrigan et al. [28] that fetal cardiac defects are associated with raised maternal glycosylated hemoglobin levels and are up to five times more likely in infants of mothers with pre-gestational diabetes compared with those without diabetes. Other studies emphasize the frequency with which the offspring of diabetes-complicated pregnancies suffer from complex forms of congenital heart disease [29]. Earlier Towner et al. [30] found a correlation between oral hypoglycemic agents during early pregnancy and the increased risk of congenital malformations in infants of mothers with non-insulin-dependent diabetes mellitus (NIDDM), independent of maternal metabolic control. Schaefer et al. [31] estimated the prevalence of congenital anomalies in offspring of women with gestational and type 2 diabetes and found that there is no preferential increase in involvement of specific organ system and is similar to that previously described in pregnancies complicated by type 1 diabetes. In Saudi Arabia, data published by the Institute for health Metrics and Evaluation in 2013 (http://www.healthdata.org) indicate that female diabetes prevalence is about 14.8%. However studies on Saudi population to establish association between maternal diabetes and chd are lacking.

Maternal age

Although several reports proved that maternal age is with a number of birth defects in different populations, the literature on the association of this risk factor with isolated congenital heart defect chd phenotypes is an interesting issue that warrants independent investigation. Over the past decades, different study designs were used for testing the significance of the maternal age as a main risk factor that contributes to the increasing prevalence of chd. Many of these studies reported significant associations between maternal age 35-40 and the increased occurrence of chd cases. However, there are differences in individual chd pattern of distribution [32,33,19]. Similar results based on a cross sectional study [34] involving children with chd diagnosed at the National Hospital of children (HNN) were reported. Miller et al. [35] conducted a population-based surveillance study and their findings suggested that the birth prevalence of specific isolated chd phenotypes, such as coarctation of the aorta, valvar pulmonic stenosis might be associated with advanced maternal age, especially among offspring of mothers in the 35 years of age or older [36].

Gender

In many population-based family studies, interest is focused in detecting gender differences in the risk of developing a chronic disease. For example, a study conducted by [37] aiming at examining sex-specific associations between cardiovascular risk factors and type 2 diabetes mellitus showed that there are gender-related dissimilarities that are apparently involved in disease development. Another study conducted on a sample of families from South Australia [38] found that men and women face different challenges in the management of diabetes and its associated complications. An exploratory assessment of a large international database found evidence that gender differences exist in morbidity and mortality among adult patients with congenital heart disease. It is recommended that future studies in adult congenital heart disease should always take into account the effects of gender [39]. Further results on gender effects were reported in [40] where a relationship between gender and elevated risk of death among heart disease patients was established.

Material and Methods

The Saudi Arabian the chd registry was established in 1998, and in 2003 the registry has evolved into Multi Institutional research collaboration with. The prime aim was to develop a registry whereby data from major referral hospitals across the country participate and provide patients information. The participating hospitals were from regions that cover the country making the registry a nationwide data repository for the Kingdom of Saudi Arabia [41]. This registry is an ongoing registration system where data on live birth infants with heart conditions are continuously collected, entered and summary statistics are annually reported.

The main objective of the study is to evaluate the relationship between the joint occurrence of PDA and TOF and four potential risk factors namely; consanguinity, maternal age, maternal diabetes, and gender.

All registered live birth chd patients, from both sexes who have positive family history for chd in one or more than one sibling will be included. The main risk factor of interest was parental consanguinity. Exposure to this risk factor parameter is documented through face to face interview with the parents during registration. As well, information regarding maternal diabetes was determined during a face-to-face interview of mothers whose children were registered. Parental Consanguinity is classified as first degree cousins (60.4%).

Study design

This was a nested case–control study. The target population was all live birth chd patients registered between 1998 and 2013 in the Saudi multi-institutional chd registry.

Sample selection

Registered families that had complete information regarding maternal age, maternal diabetes, consanguinity, and child's gender were included in the study. The total number of families was 429, of whom 259 had first cousin marriages, and 170 did not. Within these families we define cases as registered patients with both PDA and TOF. Non-cases (controls) were registered patients that belonged to any of the following sub-groups:

1. Patients with PDA but TOF free.
2. Patients with TOF but PDA free.
3. Patients with neither PDA nor TOF.

We restricted the definition of consanguinity to first cousin marriages. Measures of disease exposure associations such as odds ratio are commonly used in medical, epidemiological and clinical research. This measure of effect size is symmetric and has good statistical properties when the sample size is moderate to large. Less frequently used is the concept of "attributable-risk" (AR). We shall follow an approach proposed by [42] to calculate pooled estimates of this measure and compare it with the odds ratio estimates. Analyses were performed using SPSS, version 21 [SPSS, Inc., Chicago, Illinois], and [SAS version 9.4, Carey, North Carolina]. The logistic regression model was used to analyze the data. A generalized estimating equation was used to analyze comparisons between cases and controls, using an exchangeable correlation structure, with robust empirical standard errors. Odds ratio with 95% confidence intervals were computed. We use the ROC curve to identify the maternal age cut-off point (maternal age > 40 years, or maternal age ≤ 40) at which we can discriminate between the two types of marriages. In addition to the well-known odds ratio as a measure of disease risk association, we used the attributable risk (AR) to quantify the amount of disease that can be attributed to consanguinity. This measure combines relative risk and the prevalence of consanguinity to measure the population burden of this risk factor by estimating the proportion of PDA and TOF that would have not simultaneously occurred in the absence of consanguinity. Walter et al. [43] derived the asymptotic distribution of the attributable risk from single stratum. We followed an approach due to [42] to find an over-all estimate of AR, pooled over the maternal age strata, for boys (AR_{boys}) for girls (AR_{girls}). The study was approved by the Ethics Committee of the Office of Research Affairs (ORA) of King Faisal Specialist Hospital and Research Center.

Results

Throughout the entire registration period (1998-2013), the chd registry had 12602 males of whom 3124 with PDA and 606 with TOF. During the same period, the registry had 12135 females, of whom 3454 PDA and 472 TOF. In general the female to male ratio is 1: 1.04. In our study the total number of patients (satisfying the case definition) with both PDA and TOF was 45 (4.1%). First cousin marriages accounted for 60% of all marriages. Among first cousin consanguineous marriages 26% had PDA, while only 5.4% had TOF. The mean age at diagnosis of TOF male was 2.7 years (95% CI: 2.3-3.2) and 3.6 years (95% CI: 3.1-4.1) for females. The mean age at diagnosis of PDA male was 0.8 years (95% CI: 0.6-0.9) and 1.4 years (95% CI: 1.2-1.7) for females. Cases and controls that satisfied the inclusion criteria covered 429 families, out of which259 (60%) were of consanguineous marriages (group-1) and 170 (40%) were unrelated (group- 2). After the removal of two outlying observations of maternal age (12 years and 88 years), the mean maternal age was 26.2 ± 6, with range (16-42), and 26.4 ± 6with range (16-54) in group-1 and group-2 respectively (p-value=0.767). Dichotomizing the maternal age at 40 years, 230/259 (89%) women whose age is ≤ 40 were in group-1, and 139/170 (82%) were in group-2 (p-value=0.040) (Table 1). Consanguinity was present among 16/19=84% of the affected boys (OR=3.7, 95% CI: 1.05-12.78). On the other hand, consanguinity was present among 19/26=73% of the affected girls (OR=1.84, 95% CI: 0.758-4.49) (Table 1).

We also investigated the effect of maternal age on the affected children. For affected boys, 17/19=(89%) were born from younger mothers (OR=1.401, 95% CI: 0.315- 6.1), and affected girls 24/26=(92%) were born from younger mothers (OR=2.02, 95% CI: 0.46-8.8) (Table 2).

Of the affected boys, 1/19=5% were from diabetic mothers (OR= 0.382, 95% CI: 0.05-2.9), and of the affected girls the rate was 3/26=11.5% among diabetic mothers (OR= 0.921, 95% CI: 0.27-3.18) (Table 3).

	Consanguinity		
	Yes (*n=259*)	No (*n=170*)	p-value
Mean maternal age Range	26.2 ± 6 (14-42)	326.4 ± 6 (14-54)	0.767 (NS)
Maternal age ≤ 40	230 (89%)	139 (82%)	
>40	29 (11%)	31 (18%)	0.040*
Affected Boys			
Yes	16 (6.2%)	3 (1.8%)	
No	243 (93.8%)	167 (98.2%)	
OR=3.7			0.030*
95% CI(1.05, 12.78)			
Affected Girls			
Yes	19 (7.3%)	7 (4.1%)	
No	240 (92.7%)	163 (95.9%)	
OR=1.84			0.172 (NS)
95% CI (0.758, 4.490)			

Table 1: Effect of Consanguinity on the CHD stratified by the maternal age
*Significant at 5 % Type I error rate. (NS =non-significant)

	≤ 40	>40	
	(*n=370*)	(*n=59*)	p-value
Affected Boys			
Yes	17 (4.6%)	2 (3%)	
No	352 (95.4%)	58 (97%)	
OR=1.401			0.676 (NS)
(0.315,6.1)			
Affected Girls			
Yes	24 (6.5%)	2 (3%)	
No	345 (93.5%)	58 (97%)	
OR=2.02			0.340 (NS)
(0.46,8.8)			

Table 2: Effect of Maternal Age on the CHD stratified by gender

	Diabetic		p-value
	Yes (*n=53*)	No (*n=376*)	
Affected Boys			
Yes	1 (2%)	18 (4.8%)	
No	52 (98%)	358 (95.2%)	
OR=0.382			0.337 (NS)
(0.05,2.9)			
Affected Girls			
Yes	3 (5.7%)	23 (6.1%)	
No	50 (94.3%)	353 (93.9%)	
OR=0.921			0.369 (NS)
(0.267,3.18)			

Table 3: Effect of Maternal Diabetes on CHD stratified by gender

Furthermore we stratified the data according to maternal age and gender in order to disentangle the confounding effect of gender and maternal age on consanguinity. Disease incidence among boys born to younger mothers with consanguineous marriages was 6/87=6.9% (OR=8.21, 95% CI: 0.45-148). The reason for this wide interval is that the cell (disease, non-consanguineous) was zero in this stratum. For the young maternal age, the disease incidence for girls was 5/87=5.7% (OR=0.975, 95% CI: 0.22-4.27).Boys born to older mothers had a disease incidence in the consanguineous group as 10/162=6.2% (OR=2.38, 95% CI: 0.64-8.87).For girls this incidence was 14/172=8% (OR=2.55, 95% CI: 0.82-7.98).

Tables (1-4) summarize results of the univariate and stratified analyses of the data. To investigate the joint effect of the three risk factors under consideration we fitted a multivariate logistic regression model, separately for boys and girls (Table 5). It is interesting to see that the results are not much different from the univariate analyses. This means that there is no effect modification (no interactive effect) for the covariates on the main risk factor (consanguinity).

The estimated attributable risk pooled over the two age strata are given by:

$AR_{boys} = 32\%$ and $AR_{girls} = 33\%$.

Table 6 shows the per-stratum estimate of the odds ratios and AR.

Mother's Age		Consanguinity	
Age ≤ 40		Yes (*n*=259)	No (*n*=170)
Affected Boys	Yes	15	2
	No	215	137
		OR=4.78	p-value=0.024
Mother's Age			
Age >40			
Affected Boys	Yes	1	1
	No	28	30
		OR=1.071	p-value=0.962
Mother's Age			
Age ≤ 40			
Affected Girls	Yes	6	18
	No	133	212
		OR=1.88	p-value=0.185
Mother's Age			
Age >40			
Affected Girls	Yes	1	1
	No	28	30
		OR=1.071	p-value=0.962

Table 4: Consanguinity and disease stratified by gender and maternal Age

Parameter	Boys		Girls	
	OR	p-value	OR	p-value
Consanguinity	3.6	0.045*	1.8	0.203 (NS)
	(1.03, 12.6)		(0.73, 5.0)	
Maternal age	1	0.850 (NS)	0.532	0.0513 (NS)
	0.98, 1.02		(0.121, 2.33)	
Diabetes	0.38	0.999 (NS)	1.15	0.893 (NS)
	(0.05, 3.13)		(0.144, 9.222)	

Table 5: Multivariate Logistic Regression Analysis including consanguinity, maternal age and maternal diabetes as potential risk factors

Stratum	Boys	Girls
	AR	AR
Maternal Age	54%	35%
≤ 40	OR=8.21	OR=0.975
Maternal Age	5%	5%
>40	OR=2.38	OR=2.55

Table 6: Attributable Risk measuring the association between CDH and consanguinity stratified by maternal age

Discussion

There are several advantages to the use of the nested case-control study design. First, it is efficient-not all members of parent cohort require diagnostic testing. Second, it is flexible-allows testing of hypotheses not anticipated when the cohort was drawn. Third we may achieve reduction in selection bias since cases and controls sampled from same population. However, a major disadvantage of the nested case-control study is the reduction in power because of the reduction in the sample size.

Based on this nested case-control study, our findings from both the univariate and the multivariate data analyses showed an almost 4-fold increase in the disease prevalence for boys from consanguineous families relative to non-related marriages (OR=3.7, 95% CI: 1.05-12.78) . On the other hand there is a 2-fold increase in the prevalence for girls from consanguineous families relative to non-related marriages (OR=1.84, 95% CI: 0.758-4.49) (Table 1). The difference is not statistically significant because the sample size is not large enough. Although the sample size is small, the study included information on potentially confounding variables (maternal age and maternal diabetes). The disease groups showed higher prevalence among younger women, and we have demonstrated that consanguinity is more prevalent among younger women. These findings do not provide conclusive evidence of genetic component between chd and the risk factors. There are differences across studies with respect to the risk factors and the defined chd included within each study population. One obvious source of variation is our focus on the subtype used in this study. This emphasizes the need for further investigation using more accumulated data in the chd database from the Saudi population. One important finding in our study is when the AR was used to quantify the association between the exposure variable (consanguinity), the pooled gender difference disappeared (AR=32% for boys and AR=33% for girls). As general observations, it seems that males are diagnosed at a younger age than female patients. Moreover, regardless of consanguinity, the mothers of cases are more likely to be young. All our findings were based on the use of the OR as an effect size, which is known to be a versatile measure of association under many study designs.

The study has several limitations. Firstly; the chd registry was the only source of data. This registry collects information on reported cases contributed by the participating centers, information on patients' geographical distribution, and complete follow-up information on their vital status. Therefore, the registry should be considered an active system of surveillance. However, due to the absence of national mandate for data collection there is no guarantee that complete ascertainment of chd cases is achieved. Therefore, estimation of measures of disease etiology such as odds ratio using this data will be biased, and supplemental information from cohort studies will be needed. Secondly; the sample size is not as large as it should be. Thirdly, we restricted our definition of consanguinity to first degree cousins. We may relax the inclusion criteria and extend the definition of consanguinity to include second and third degree cousins.

As a final remark; we should note that the epidemiology of chd is quite complex and in fact is changing. With early intervention the mortality rate is declining and patients are living longer. In the meantime we observe a decline in the incidence which may be attributed to the early screening of the Saudi children. The registry should become the tool for active surveillance to ensure that complete disease ascertainment is achieved and that accurate data cover the entire country. Therefore, on using the incidence data together with important risk factors measured at both maternal and paternal levels we should be able to construct of statistical models that can be utilized to predict the disease burden, improve patient's care and control the cost of interventions

Conflict of Interest

The authors declare that they have no conflict of interest

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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