The epidemiology of congenital heart diseases in Saudi Arabia: A systematic review

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Several studies have been conducted on congenital heart disease in different regions of Saudi Arabia. However, no recent systematic review has examined the growing scientific evidence with respect to the epidemiology of CHD in the Kingdom. The aim of this review is to provide a comprehensive summary of CHD incidence, prevalence, burden and impact on the Saudi population. A literature search was conducted through PubMed and Google Scholar using relevant keywords to identify studies performed in Saudi Arabia regarding CHD from 1993 to December 2013. Articles written in English that described or investigated the epidemiology, etiology, distribution, impact and burden of CHD in the Saudi Arabian population were included. Twenty one articles met these criteria. Cross-sectional studies found the prevalence of CHD ranging between 2.1 and 10.7 per 1,000 persons. The most prevalent type of CHD was the ventricular septal defect ranging from 29.5 to 39.5% of all diagnosed CHDs, followed by atrial septal defect (8.9 to 18.1%) and pulmonary stenosis (6 to 12.4%). Overall, the incidence of severe CHD was approximately 5.4 per 1,000 live births per year. Occurrence of CHD in Saudi Arabia was significantly associated with Down’s syndrome, consanguinity and maternal diabetes. Studies on the burden of these anomalies on children, families and society are scarce. This systematic review found that prevalence of CHD is comparable to that in other developing countries. Several modifiable risk factors have been identified emphasizing the importance of public health programs that are aimed at tackling such potentially preventable risk determinants.

Keywords: Heart, congenital, defect, epidemiology, prevalence, Saudi.

INTRODUCTION

Congenital Heart Disease (CHD) has been defined as “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance” (Mitchell et al., 1971). The range of defects
RESULTS

The 21 studies included were conducted in a variety of geographical areas in Saudi Arabia. The supplementary search by cross-referencing and searching in local journals did not identify any additional papers. Of the 21 articles, five reported on prevalence and pattern of CHD and seven reported on the association of CHD with Down’s syndrome and its prevalence. Nine studies reported on risk factors only such as consanguinity, maternal diabetes, maternal obesity, the social impact of CHD and fetal outcome (Table 1).

Prevalence and pattern of CHD

A study investigated the clinical features of 320 patients diagnosed with CHD at a Saudi hospital in the period between 1988 and 1991 found that both sexes were equally affected. Relative frequency of VSD was higher than Atrial Septal Defect (ASD), Pulmonary Stenosis (PS), Patent Ductus Arteriosus (PDA) and Atrioventricular Septal (AVSD) with percentages of 38.5, 11.5, 9, 8% and 5%, respectively (Jaiyesimi et al., 1993). Bhat et al., (1997) screened all children referred to the cardiology clinic at the Madina Maternity and Children Hospital for three years and documented very similar findings with VSD representing 29.7% of all CHD diagnoses, ASD (26%), PS (16.1%) and PDA (13.2%) (Baht et al., 1997). Abbag (1998) documented that the most common defect was VSD 32.5% (Abbag, 2006). Likewise, Alabdulgader (2001) studied the prevalence of CHD using a cross-sectional design and concluded that VSD was the most common defect (39.5%), followed by ASD (11.5%), PS (8.9%), PDA (8.6%), AVSD (3.5%), Tetralogy of Fallot, TOF (4.2%), Coarctation of Aorta COA (2.7%), Aortic Stenosis (AS) (3.5%) (Alabdulgader, 2001). Few studies estimated the prevalence of CHD at the population level. Greer et al. (2005) showed that Southwestern region had the highest burden of CHD with a period prevalence of 748 cases per 100,000 persons (Greer et al., 2005). Alquirashi et al. (2006) determined the prevalence of CHD in children and adolescents by randomly sampling households in all regions of Saudi Arabia. The results found the prevalence of CHD over all as 21 per 10,000 persons. VSD was the most common defect with 10 cases per 10,000 (Alquirashi et al., 2006). Alnajjar et al., (2009) found that CHD represents 34.4% of all cardiac problems diagnosed at Al Madina city. Ventricular septal defect period represented 34.5% of all CHD diagnoses, followed by ASD (8.9%), PS (7.9%), PDA (6%), AVSD (3.8%), TOF (3%), AS (3.5%), COA (3.4%), Transposition of the Great Arteries (TGA) (3.5%),

METHODOLOGY

An electronic search was conducted from January 3 to January 25, 2014 using PubMed, Google Scholar and local Saudi journals. The following keywords: “Heart”, “Cardiac”, “Congenital”, “Defect” and “Epidemiology”, “Prevalence”, “Incidence”, “Risk”, “Impact”, and “Saudi Arabia” were used in the search strategy. The articles included in the study were from PubMed and local journals, written in English and they describe or investigate the epidemiology, etiology, distribution, impact or burden of CHD in Saudi Arabia. Treatment or interventional studies were excluded. The search identified 108 articles. Titles, abstracts and at a later stage full texts were reviewed independently by two researchers to identify articles that met the predefined inclusion criteria. After mutual consensus of the two researchers 21 articles met the inclusion criteria with publication dates ranging from 1993 to 2013. Figure 1 shows a flow chart of the search with justification for exclusion at each stage. A supplementary search for articles by the primary investigator was conducted by cross-referencing and reviewing locally published journals that were not indexed in PubMed.
and others (26%) (Alnajjar et al., 2009). Almawazini and Al-Ghamdiin (2011) studied the proportion of CHD among all diagnoses in the Southwestern Albaharegion. Of all cardiac patients, 26.8% were diagnosed with CHD (Almawazini and Al-Ghamdiin, 2011). Al-Mesned et al., (2012) reported on the incidence of severe CHD in Al-Qassim. The incidence of severe CHD was 5.4/1,000 live births/year. VSD defect was the most common lesion 22.5/1,000 live births/year (Al-Mesned et al., 2012).

**Figure 1.** Flow chart of the literature review search.

**Risk factor studies**

**Down syndrome (DS)**

Alabdulgader, (2001), reported that Down syndrome was found in 6% of all patients with CHD. Down syndrome patients with CHD presented with higher proportion of non-cyanotic lesions, than cyanotic lesions (Alabdulgader, 2001). Al-Jarallah (2009) reported a 49%
Table 1. Summary of studies included in the systematic review.

| Study                  | Sample Size | Study setting | Year of data collection | Prevalence/incidence | Other findings                                                                 |
|------------------------|-------------|---------------|-------------------------|----------------------|-------------------------------------------------------------------------------|
| **Prevalence/incidence and relative frequency Studies** |             |               |                         |                      |                                                                                |
| Jaiyesimi et al. (1993)| 320 cases of CHD | Hospital      | 1988-1991               | -                    | Relative frequency of VSD was 38.5% followed by ASD (11.5%), PS (9%), PDA (8%) and finally AVSD (5%). A relatively high incidence of trisomy -21 was found in 10%. |
| Bhat et al. (1997)     | 1209 CHD cases | Hospital      | 1992-1995               | -                    | Frequently detected types of CHD were VSD (29.7%) followed by ASD (26%), PS (16.1%) and PDA (13.2). DS was found in 79% of patients with AVSD                        |
| Abbag (1998)           | 608 cases of CHD | Hospital      | 1994-1996               | -                    | Relative frequency of VSD (32.5%), followed by PDA (15.8%), ASD (10.4%), PS (10.1%), AVSD (3.6%), TOF (4.5%), AS (2.7%), COA (2.7%), and TGA (1.5%) |
| Greer et al. (2005)    | 5,865 cases of CHD | National Registry | 1998-2002               | 748/100,000          | The southwestern region having the highest burden of CHD                                                                                     |
| Alqurashi et al. (2007)| 95 cases of CHD | Household     | 2004-2005               | 21/10,000            | The Central region had the highest prevalence with 27 cases per 10,000 persons; the Northern and Eastern region had prevalence of 25 cases per 10,000 persons each, and Southwestern Region prevalence of 21 cases per 10,000 persons. The VSD was the most common defect with 10 cases per 10,000 |
| Alnajjar et al. (2009) | 4348 cases of CHD | Hospital     | 2007-2008               | -                    | Relative frequency of VSD 34.5%, followed by ASD (8.9%), PS (7.9%), PDA (6%), AVSD (3.8%), TOF (3%), AS (3.5%), COA (3.4%), TGA (3.5%), and others (28%) |
| Almawazini et al. (2011)| 2610 cases of CHD | Hospital   | 2005-2010               | -                    | VSD (29.6%), PDA (9.5%), ASD (9.3%), PS (7.9%), AVSD (6.0%), TOF (4.7%), COA (3.4%), AS (3.0%), and TGA (1.9%) |
| **Down Syndrome as a risk factor** |             |               |                         |                      |                                                                                |
| Alabdulgader (2001)    | 740 CHD cases | Hospital      | 1997-2000               | -                    | VSD was the most common defect (39.5%), followed by ASD (11.5%), PS (8.9%), PDA (8.6%), AVSD (3.5%), TOF (4.2%), COA (2.7%), AS (3.5%). DS patients with CHD presented with higher proportion of non-cyanotic lesions (VSD-30%, AVSD - 25%, PDA -20%, ASD-16%), than cyanotic lesions (TAPV -5%, TOF -4%). |
| Abbag (2006)           | 98 DS cases | Hospital      | 1994-2005               | -                    | VSD being the most common (33.3%) followed by AVSD (22.8%), ASD (21.1%), PDA (14%) and TOF (5.3%). Sixteen patients (16.3%) died at a mean age of 19 months of which 15 of them (93.8%) had anomalies. |
| Al-Jarallah (2009)     | 110 DS cases | Hospital      | 2001-2004               | -                    | Incidence of CHD in DS was 49%, the incidence of VSD was the highest (43%), followed by ASD (25%), AVD (15%), PDA (7%), and finally TOF (4%). |
| Al-Mesned et al. (2012)| 316 DS cases | Hospital      | 2008-2010               | 5.4 /1,000 live birth (incidence) | VSD was the most common lesion (22.5%), COA (14.9%), AVSD (8.5%), PS (7.6%), and TOF (5.7%). 15% of the subjects suffered from other syndromes of which DS was the most common (14.2%). |
| Study | Sample Size | Setting | Year | Incidence/Prevalence | Findings |
|-------|-------------|---------|------|----------------------|----------|
| Al-Aama et al. (2012) | 130 DS cases | Hospital | 2007-2011 | 7.1 per 1,000 live births | 86.8% children with DS had CHD, PDA (47.8%), followed by ASD (41.3%), trivial tricuspid regurge (33.7%), VSD (29%), and PFO (28.3%). |
| **Consanguineous marriage as a risk factor** | | | | | |
| Al-Abdulkareem and Ballal (1998) | - | PHCC and the Maternity and Children's Hospital | 1998 | - | No significant differences between children of consanguineous and non-consanguineous marriages with respect to rates of inherited diseases and reproductive wastage. |
| Becker and Halees (1999) | 949 | Congenital Heart Disease Registry | 1998 | - | The prevalence of CHD which was significantly higher among first-cousin marriages (41.6%) as compared to the general population (28.4%). Down's syndrome was found in 49 patients (5.2%) with 23 from consanguineous marriages. |
| Seliem et al. (2007) | 37 families | Hospital | 1996-2000 | - | Consanguineous marriages resulted in twenty-three of these families (62%). The prevalence of dilated cardiomyopathy was considerably higher between consanguineous cases, 26 vs. 2 in non-consanguineous marriages. |
| El Mouzan et al. (2008) | 11,554 | Community-based survey | 2004-2005 | - | 56% of the respondents were in consanguineous marriages and CHD to be the only statistically significant disease associated with first cousin consanguinity. |
| Becker (2012) | 891 | Congenital Heart Disease Registry | - | - | Consanguinity was significantly higher in the sample (40.4%) compared to the general population (28.4%). Consanguinity was found to be significantly associated with some types of CHD such as VSD, ASD, AVSD, PA, and PS while no significant relationship was found with TOF, TA, AS, COA, and PDA. |
| **Diabetic Mothers** | | | | | |
| Abu-Sulaiman and Subaih (2004) | 100 | Hospital | 2000-2001 | - | Incidence of CHD in children of diabetic mothers was determined to be higher than in the general public; 150 per 1,000 live births, (after excluding PDA and hypertrophic cardiomyopathy). The predominant lesions were PDA (70%) followed by PFO (68%), HCM (38%), ASD (5%), VSD (4%), MVP (2%). |
| **Maternal Obesity** | | | | | |
| Khalil et al. (2008) | - | Registry data | 1998-2005 | - | No significant association in incidence of CHD and maternal obesity. |
| **Social Impact** | | | | | |
| Almesne et al. (2013) | 41 parents | Hospital | 2011-2012 | - | Families of children with complex CHD had significantly higher IFS score, 62 vs. 51 (p=0.005) with a significant difference in both the family impact and mastery domains. |
| **Fetal outcome** | | | | | |
| Bader et al. (2013) | - | Hospital-based database | 2002-2012 | - | Overall mortality rate for fetuses with AVSD was 48%. Extra-cardiac anomalies are an independent risk factor for prediction of mortality. |

VSD: Ventricular Septal Defect, ASD: Atrial Septal Defect, PS: Pulmonary Stenosis, PDA: Patent Ductus Arteriosus, AVSD: Atrio-ventricular Septal, TOF: Tetralogy of Fallot, AS: Atrial Stenosis, CoA: Coarctation of Aorta, TGA: Transposition of the Great Arteries, IFS: Impact on Family Scale, and DS: Down syndrome.
prevalence of CHD among DS patients (Al-Jarallah, 2009). Al-Aama et al. (2012) described the prevalence of CHD among DS patients in a prospective hospital-based study conducted between 2007 and 2011. A total of 130 DS patients aged 0 to 33 years (mean 5 ± 4.9) were included. The results found CHD in 86.8% of the patients with a prevalence of 7.1 per 1,000 live births (Al-Aama et al., 2012). Abbag et al., in 2006 documented that CHDs was found in 61.3% of DS patients (Abbag, 1998). Al Massned et al., found that DS is the most commonly encountered syndrome among children with CHD (Al-Mesned et al., 2012).

Consanguineous marriage

Al-Abdulkareem and Ballel, (1998) documented a non-significant difference for rates of inherited diseases between families of consanguineous and non-consanguineous marriages (Al-Abdulkareem and Ballel, 1998). Becker and Al Halees (1999) studied the relationship between CHD and consanguineous marriages (Becker and Al Halees, 1999). First-cousin marriages among families of children with CHD (41.6%) were significantly higher than that in the general population (28.4%) (Becker and Al Halees, 1999). Becker et al. (2001) documented the prevalence of various CHD lesions in patients who were the product of first-cousin marriages and found consanguinity was significantly higher in the sample (40.4%) compared to the general population (28.4%). Consanguinity was found to be significantly associated with some types of CHD (Becker et al., 2001). Seliem et al., (2006) investigated the influence of consanguinity on the pattern of familial aggregation in CHD. Consanguineous marriages resulted in twenty three of these families (62%) (Seliem et al., 2006). El Mouzanet et al. (2008) observed the role of consanguinity in genetic disorders and found that 56% of the respondents were in consanguineous marriages and that CHD to be the genetic disease most significantly associated with first cousin consanguinity (ElMouzan et al., 2008).

Diabetes and obesity

Abu-Sulaiman and Subaih, (2004) used a prospective cohort to investigate the relationship between CHD and insulin dependent diabetic mothers. Incidence of CHD in children of diabetic mothers was determined to be higher than in the general public; 150 per 1,000 live births (Abu-Sulaiman and Subaih, 2004). Khalil et al. (2008) conducted a retrospective study and documented no significant association in incidence of CHD and maternal obesity.

Impact and mortality studies

Almesned et al. (2013) measured the social impact of CHD on families of children with a complex CHD. Results showed that families of children with complex CHD had significantly higher Impact of Family Scale (IFS) score, 62 vs. 51 (p = 0.005) with a significant difference in both the family impact and mastery domains (Almesned et al., 2013). Bader et al. (2013) evaluated risk factors for prediction of outcome in fetal of AVS defect through retrospective design documented that overall mortality was 48% for fetus with AVSD (Bader et al., 2013).

DISCUSSION

There were 21 articles included in the review. Of those, the prevalence of CHD in Saudi Arabia was addressed in two studies. Alqurashi et al. (2006) conducted a community-based national prevalence study and reported approximately 21 cases per 10,000 persons. While Greer et al. (2005) and Alqurashi et al. (2006) used the CHD registry of KFSH and found it to be three fold at 74.8 per 10,000 persons. International studies have reported prevalence rates ranging from 10 to 119 per 10,000 persons (Samánek et al., 1989; Marelli et al., 2007; Dolk et al., 2010; Koshnood et al., 2010; van der Bom et al., 2012). Various factors may contribute to the differences in prevalence and relative frequencies of CHD between these studies including the study setting. Hospital based studies, for example, will often report a higher prevalence than community based studies due to the higher relative frequency of VSD, the most common type of CHD, which often closes spontaneously in early childhood and would not be detected in most studies outside of hospital. In addition, minor forms of CHD, such as small PDA and ASD, may go undetected outside of hospital settings due to their subtle clinical signs. On the other hand, children with severe forms of CHD may die before one year of age thus reducing prevalence in community based studies. Nonetheless while the study methodology must be taken into consideration when making any comparisons, community based studies in China and India have reported higher prevalence's of 50 and 42 per 10,000 persons, respectively than that conducted in Saudi Arabia (Chadha et al., 2001; Jiang et al., 2005). Another important factor is the definition used for CHD as some studies excluded structural abnormalities that were not of functional significance (Abbag, 2006; Alqurashi et al., 2006; Alnajjar et al., 2009; Almawazini and Al-Ghamdiin, 2011).

Bhat et al. (1997) for example, did not exclude ASD in neonates and reported a relative frequency of 26% while in other studies in Saudi Arabia they ranged from 8.5 to11.5% (Bahl et al., 1997). The sensitivity of the diag-
nistic tools used is another factor affecting detection rates of CHD between studies as echocardiography was used in all studies in Saudi Arabia but was not available in previously conducted international studies. The most common cardiac congenital lesion reported in KSA was VSD ranging from 29.5 to 39.5% which is consistent with other parts of the world (Rose et al., 1964; Hoffman et al., 2004; Koshnood et al., 2010). The order of frequency of other forms of CHD however is less consistent. The second most common type of CHD in Kingdom of Saudi Arabia was ASD, which was the second most frequently reported disorder in terms of incidence in the US, Canada and Bohemia while other studies found it to be less common; the fourth most common form in Hungary at 10.4% and the fifth most common type in Sweden at 4.3% (Rose et al., 1964; Mitchell et al., 1971; Mészáros et al., 1975; Samánek et al., 1989; Sípek et al., 2010).

Variation in frequencies has been attributed to methodology and sensitivity of diagnostic tools, particularly as older studies have not used echocardiography, which was used in all of the studies in KSA. The cause of congenital heart disease is largely multifactorial and occurs through a combination of genetic and environmental factors. However, the role of chromosomal abnormality is conspicuous with approximately 20% of cases attributed to chromosomal anomalies (Blue et al., 2012). The association of CHD with DS was first described by Evans in 1950 (Carlgren, 1959). Since then a number of studies have consistently shown an association between the two conditions (Evans, 1950; Granzotti et al., 1995; Wells et al., 1994; de Rubens Figueroa et al., 2003; Vida et al., 2005; Roizen et al., 2014). As CHD is the greatest cause of death in infants and young children with DS, describing the prevalence and types of defects found in DS is relevant in facilitating early intervention and appropriate management (Evans, 1950).

Presence of CHD in children with Down's Syndrome in central KSA was reported as 49% while in the Southwest region where CHD is more prevalent, it was higher (61%) (Abbag, 1998 and Al-Jarallah, 2009). Al-Aama et al. (2012) reported a greater prevalence of 86.6%, possibly due to the study being conducted from a genetic referral center. International studies ranged from 40 to 55% (Evans, 1950; Wells et al., 1994; de Rubens Figueroa et al., 2003; Vida et al., 2005; Al-Aama et al., 2012; Roizen et al., 2014). Similar to CHD in the general population, VSD was the most common lesion in DS, which is also consistent with most international studies (Abbag F, 1998; Al-Jarallah, 2009 and Al-Aama et al., 2012). Relative frequency of other types of CHD, however, varied among the studies due in part to the variation in method used for categorization. For example when multiple types of CHD were detected, Al-Jarallah (2009) reported only on the dominate one while Al-Aama (2012) reported on them both in isolation or in combination, therefore PDA, for example, was only 7% in the former and 47.8% in the latter. The role of consanguinity in recessive diseases is well known, however, its potential role in certain common birth defects is unclear. Most studies support the view that consanguineous marriages increase susceptibility of CHD, particularly at first cousin level (Shieh et al., 2012). This is particularly the significant as consanguineous marriages are common in Saudi Arabia (Al Husain and Al Bunyan, 1997; Al-Abdulkareem et al., 1998 and Shieh et al., 2012).

Prevalence of consanguineous marriages was found to be as high as 51% in Riyadh, 47 and 52% in the Eastern province (Al-Abdulkareem and Ballal, 1998). El-Hazmi screened 3212 families in all regions of KSA and found 57.7% were consanguineous with first cousin marriage the most common type (28.4%) (El-Hazmi et al., 1995). In Kingdom of Saudi Arab first cousin marriages were significantly associated with VSD, ASD, AVSD, PS, and PA (Becker et al., 2001). Similarly, septal defects (VSD and ASD) were consistently found to be associated with consanguinity especially at first cousin level, in several international studies (Shieh et al., 2012). The less common forms of CHD with lower incidence (AVSD, PS, PA) may not have achieved enough power to determine the effect of consanguinity in international studies and may require large population based trials to accurately determine this relationship. The relationship of DM and CHD has been well established in Type 1, Type 2 and gestational DM (El-Hazmi et al., 1995; Narchi and Kulaylat, 2000 and Schaefer-Graf et al., 2000). Loffredo found a strong association between maternal diabetes and CHD (OR = 4.7, 95% CI 2.8 to 7.9) with all-cause mortality of children with CHD more than double in diabetic mothers than in non-diabetic (39 and 17%, respectively) (Loffredo et al., 2010). Similarly, Lukas A. also had identified a strong association of CHD and the offspring of diabetic mothers (p-value < 0.05) (Lisowski et al., 2010). Schaefer-Graf et al., (2000) reviewed 4,180 pregnancies complicated by gestational or type 2 DM and found the initial fasting serum glucose levels were significantly higher in the mothers of children born with anomalies.

The most common major anomalies were cardiac (37.6%) (Schaefer-Graf et al., 2000). Narchi and Kulaylat, (2000) estimated that CHD occurs in 5% of infants born to diabetic mothers with the highest relative risk for major defects occurring in mothers with gestational diabetes and developing insulin resistance in the 3rd trimester (Narchi and Kulaylat, 2000). In Saudi Arabia, Abu-Sulaiman and Subaib (2004) reported incidence of CHD in mothers with insulin dependent DM as 150 per 1,000 live births. This is significantly higher than the incidence
reported in the general population (2.1 to 10.7 per 1,000 live births) (Greer et al., 2005; Alqurashi et al., 2006). The detection and inclusion of minor forms of CHD may have contributed to this higher incidence. The limitations of this review includes limiting our search for articles in English. However, most if not all studies by research institutes and universities are in English in the Arab world. We might have missed some articles as we did not search into different databases like KoreaMed and Embase but local journals were reviewed to include all the study related to the Saudi Arabia. Publication bias, which is the tendency for publishing manuscripts positive finding is a potential limitation of all systematic reviews including our review, and certainly might explain, partially the significant association between CHD and some factors like maternal diabetes and advanced age. Limitations of this systematic review derive also from limitations of the individual studies included. Most of the studies conducted in Saudi Arabia were cross-sectional with an aim of characterizing patients diagnosed with CHD in terms of defect type or associated factors with very few follow-up studies that aims to know the prognosis, burden and consequences of these conditions on the society and healthcare services.

CONCLUSION

The results of this systematic review give a general understanding of the CHD epidemiology in Saudi Arabia. These diseases, that pose a considerable impact on children and their families, have higher prevalence than that in Western countries and comparable to those reported in other developing countries. Consanguineous marriages, maternal age, diabetes and Down syndrome and were among risk factors related to CHD in studies conducted in Saudi Arabia. Identified risk factors are potentially modifiable, emphasizing the importance of public health programs that are aimed at tackling such determinants. Studies that explored the prognosis and burden of these diseases on the Saudi society and healthcare services are scarce and should be the focus for future research.

Conflict of interest

The authors declare that they have no conflicts of interest.

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