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# Congenital Heart Disease: Genetic Aspect and Prenatal and Postnatal Counseling

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Additional information is available at the end of the chapter

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## Abstract

Cardiac malformation present at birth is an important component of pediatric cardiovascular disease. The etiology of congenital heart disease is multifaceted including environmental, genetic and stochastic factors. With the advancement of cardiac diagnostic and therapeutic techniques in the past decade, with relatively low morbidity and mortality, has led to more and more children with congenital heart disease living to adulthood. Therefore the role of prenatal and postnatal genetic counseling becomes even more paramount as there is a higher likelihood of these patients living to adulthood and having families of their own. Prenatal counseling allows for the expectant parents to understand the full ramifications of continuing the pregnancy and possible events after birth. It is a multidisciplinary approach to help parents reach an informed decision on how to best to proceed with the pregnancy. After the birth of the child with congenital heart defects, the course is significantly dependent on the type of cardiac lesion. Postnatally, if the lesion is amenable to surgery, therapeutic intervention is offered. The postnatal counseling session includes the possibility of performing advanced genetic testing to help determine the hereditary potential of the cardiac defect in future offspring.

**Keywords:** congenital heart disease, genetic syndromes, recurrence, counseling, genetic testing

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## 1. Introduction

Congenital heart diseases (CHD) are the most common major fetal structural defects and leading cause of neonatal morbidity and mortality among birth defects. The medical and surgical management of these children has continued to progress rapidly such that, most of these patients now survive to adulthood. The estimated incidence of moderate and severe forms of CHD is 6 per 1000 live births [1]. However, fetuses with heart disease show unique diagnostic,

therapeutic and sometimes ethical challenges. Treatment of the fetuses with CHD may expose the mother to significant risks, which may compete with the welfare of the mother [2, 3].

Advances in the field of prenatal imaging, and increasing experience in fetal cardiology and echocardiography over the last two decades has allowed for most heart defects to be well defined as early as the second trimester [4]. Pediatric cardiologists specializing in fetal medicine, play a critical role in help making an accurate diagnosis. In addition, these specialized physicians will be critical in providing prenatal counseling to help guide parents to understand the diagnosis and in the decision-making process. This counseling will give parents information about the fetus' heart defect and its expected outcomes. Fetal echocardiography has evolved since its inception, which now can provide precise details of cardiac structural and hemodynamic aberration in fetuses with CHD. During pregnancy, the sequential use of this modality can predict the evolution of disease in utero and transition to postnatal life. Such an approach allows for detailed prenatal counseling and detection of fetuses at high risk for morbidity and mortality. This allows for appropriate planning and postnatal management [5, 6]. Most CHD is well tolerated in utero, and does not present hemodynamic risks immediately. After birth, many of these babies, with simple cardiac lesion do not require specialized delivery care. However, some high-risk fetuses may develop hemodynamic instability soon after birth and may require immediate intervention [5]. With such infants it is highly recommended that these children be born at centers where a pediatric cardiac team and intensive care personnel are available to make appropriate therapeutics decisions and intervention, without delay.

Is the availability of a perinatal diagnosis of CHD is associated with improved surgical outcomes and less neonatal mortality? Some studies report a positive impact on outcomes while others showing no difference in outcomes compared to babies diagnosed with CHD after birth [7–19]. A recent meta-analysis evaluating the differences in pre-operative mortality rates between newborns with and without a prenatal diagnosis found that prenatal diagnosis of critical CHD improves neonatal pre-operative survival, and newborns with a postnatal diagnosis were more likely to die of cardiovascular compromise prior to planned cardiac surgery [20].

The etiology of CHD is multifaceted including environmental, genetic, and stochastic factors [21, 22]. Knowing the basis of the CHD will aid in the counseling of parents and help them to attain a complete understanding of the fetuses cardiac defect [23]. Although it will not change the course or management option, but it will allow for familial planning and future pregnancies.

## 2. Genetic syndromes

Genetic syndromes are defined as a consistent pattern of malformation caused by a genetic alteration. A malformation syndrome consists of multiple structural defects that are thought to be due to a single cause, even if the suspected cause has not yet been identified [24].

### 2.1. Noonan's syndrome

The Noonan phenotype includes characteristic facies (ptosis, hypertelorism, low set ears, and low posterior hairline), short stature, webbed neck and cardiac anomalies. Noonan syndrome occurs in 1 per 1000 to 1 per 2500 live births diagnosed clinically [25–27]. Cardiac anomalies are present in 80% of individuals [28]. In 70–80% of cases, the lesion is pulmonary stenosis, usually due to

dysplastic pulmonary valve leaflets [25]. In 20–30% of affected individuals, the cardiac anomaly is in the form of a cardiomyopathy, which may be present at birth or develop later [25, 29].

Most of the cases of Noonan syndrome are sporadic, although families with a pattern of autosomal dominant inheritance are well known. Mutation in the gene PTPN11 on the chromosome locus 12q24.1 was noted in 45% of cases. Gelb et al. demonstrated a positive association between those with PTPN11 mutations and pulmonary stenosis [30]. Maternal transmission of the gene is three times more common than paternal transmission [28]. Prenatal testing can be established by chorionic villus sampling or amniocentesis, fetal ultrasound can show increased nuchal translucency, increased nuchal thickening, pleural effusions and generalized hydrops [31]. Developmental delays are always present, and intellectual disability is typically in the range of moderate mental retardation [28, 29]. Diagnosis in newborn baby may be difficult unless the cardiac lesion is severe, with either significant pulmonary stenosis or severe cardiomyopathy. The diagnosis can only be confirmed genetically if there is an affected parent with a recognized mutation [25, 27, 30].

## 2.2. Turner's syndrome

The classical Turner's syndrome phenotype includes short stature, webbed neck, renal anomalies, congenital lymphedema, ovarian dysgenesis and cardiac anomalies. In many, the features are sufficiently subtle to be overlooked until the teenage years. The prevalence of Turner's syndrome is 1 in 2500 female births [32]. The phenotype depends on whether the X chromosome is absent (45, X in almost 50% of patient) or structurally abnormal [33].

The most common presentation is spontaneous abortion with hydrops or lymphatic malformation in the neck or mediastinum. Cardiac anomalies are present in 30% of patients with Turner Syndrome, bicuspid aortic valve (30%), coarctation of the aorta (10%) and hypoplastic left heart syndrome (HLHS); partial anomalous pulmonary venous connection is also associated with this syndrome. Aortic root dilatation is present in 5–10% of cases, associated with aortic root dissection in later life, this finding is mostly related to decreased numbers of smooth muscle and elastic fibers in the vascular walls [32]. Gotzsche et al. demonstrated a correlation between the precise karyotype and the form of congenital heart disease; 38% of patients with X0 had aortic valve anomalies and coarctation of the aorta, compared with 11% of individuals with mosaic X0 [34].

Fetuses with Turner's syndrome have been shown to have small hearts in 90% of the cases. Significant myocardial hypoplasia is thought to be associated with the high incidence of fetal death [32]. Neonatal diagnosis may be difficult but should be considered in females presenting with left-sided heart anomalies or lymphedema.

## 2.3. William's syndrome

The phenotype of Williams' syndrome is variable, but includes characteristic facies (flared eyebrows, bright stellate irides and wide mouth), specific personality and cognitive features, and infantile hypercalcaemia in addition to cardiac anomalies. The prevalence is 1 in 10,000–20,000. Children with Williams's syndrome can be diagnosed at different ages and present with a broad range of clinical features [35]. Early in life, feeding disorders and growth retardation are common. Hypercalcemia is seen in 15% of infants and usually resolves over

time [36]. Cardiac anomalies are present in 55–80% of individuals with Williams's syndrome, which typically include supra-avalvar aortic stenosis and/or supra-avalvar pulmonary stenosis [37, 38]. The degree of the cardiovascular involvement and the relative involvement of the pulmonary or aortic vessels varies widely. By 1 year of age 41% of the pulmonary lesions will have improved, whereas 73% of the aortic lesions will have progressed [38].

Approximately 90% of patients with the clinical diagnosis of Williams's syndrome have a deletion at chromosome 7q11.23, which can be detected by fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification (MLPA) and microarray technologies. The gene mapping to this region has been defined and includes the gene *ELN*, whose product is elastin. The deletion of this gene results in the connective tissue abnormalities associated with the CHD of Williams' individuals [39, 40]. Prenatal genetic testing can be performed on Chorionic villus sampling or amniotic fluid samples in the few pregnancies considered to be at increased risk. Neonatal diagnosis is challenging, and full features become more apparent with time. Williams's syndrome is transmitted in an autosomal dominant manner. Most cases are de novo occurrence and recurrence risks are 50% if a parent is affected but otherwise low (<5%) [41, 42].

#### **2.4. 22q11 deletion syndrome (DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome)**

Molecular studies demonstrate that the vast majority of patients with clinical diagnosis of DiGeorge, velocardiofacial, conotruncal anomaly face syndromes share a common genetic cause, namely a 22q11.2 deletion [43–45]. The prevalence is 1 in 4000 to 6000 live births, but the severity of the phenotype is variable and in some the features may go unrecognized [46]. CHD are estimated to occur in 75–80% of patients with a 22q11.2 deletion. The most common CHDs associated with 22q11.2 deletion include tetralogy of Fallot (TOF) and aortic arch anomalies. Other conotruncal lesions include pulmonary atresia with ventricular septal defect (VSD), and truncus arteriosus [47, 48]. In cases of truncus arteriosus, the truncal valve tends to be more dysplastic when the 22q11 deletion is present [49].

Identifying the cardiac patient with a 22q11.2 deletion early in life can provide substantial benefits to the child and family. Currently, it is recommended that infant with interrupted aortic arch type B, truncus arteriosus, TOF and isolated aortic arch anomalies undergo testing for a 22q11.2 deletion [22]. Prenatal diagnosis can be performed using FISH technology on samples obtained from chorionic villus sampling or amniocentesis if cardiac defects are present. Non-cardiac lesions are not easily diagnosed but, absent fetal thymus has been reported [50]. Many children initially present without cardiac symptoms in the form of recurrent infections. This may point to an underlying immunodeficiency associated with 22q11.2 deletion [51]. The risk of recurrence is in 50% as this is transmitted in an autosomal dominant inheritance if either parent carries the deletion. If neither parent carries the deletion, there may still be germline mosaicism, but the risk of recurrence is small (1%) [22, 48].

#### **2.5. CHARGE syndrome**

The CHARGE syndrome was previously referred as an association, however this was resolved after the discovery of causative mutations in chromodomain helicase DNA-binding gene7 (*CHD7*) on chromosome 8q12.1 [52, 53]. The phenotype is described by its acronym:

colobomata (79%), heart defects (85%), choanal atresia (57%), growth and developmental retardation (100%), Genital hypoplasia (34%) and Ear anomalies (91%). Additional problems include renal anomalies, facial clefts and esophageal atresia [54]. CHD has been always been part of the core phenotype.

The frequency of the CHD range from 74–92% in CHD7 mutation-positive cases [55, 56], as compared to 71% in CHD7 mutation-negative individuals in one report [55]. A wide range of CHD has been reported in CHARGE syndrome, including conotruncal and aortic arch anomalies consistently over represented in clinical series [56]. The frequency of the CHARGE syndrome has been reported to range from 1 per 10,000 to 1 per 15,000 live births, although one population-based study estimated a frequency of 1 in 8500 live births [57]. Most of the cases of CHARGE syndrome are sporadic in occurrence, but autosomal dominant inheritance and germline mosaicism, have now been confirmed by molecular testing [55].

## 2.6. VACTERL association

The phenotype is described by its acronym: Vertebral defects, Anorectal anomalies, Cardiac anomalies, Tracheoesophageal fistula with Esophageal atresia, and Renal and upper Limb anomalies. A general diagnostic guideline requires three or more defects to establish the diagnosis [58]. It is usually a sporadic occurrence of unknown cause. In rare cases an association can occur in trisomy 18 [59], or trisomy 21 [60]. A cardiac anomaly is present in at least 73% of affected individuals and includes atrial septal defect (ASD), VSD, double-outlet right ventricle, TOF and dextrocardia [58].

No definitive prenatal testing is available, but the diagnosis should be considered if antenatal ultrasound demonstrates a vertebral anomaly, absence of the fetal stomach and a cardiac anomaly with or without polyhydramnios. The management involves a multidisciplinary approach [61]. VACTERL has a low recurrence risk of 2–3%, although there are rare reports of familial cases, including one of a mother and son, both with typical features [62].

## 2.7. Alagille syndrome

Alagille syndrome was originally defined as the presence of bile duct paucity on liver biopsy in conjunction with three of the following five findings: cholestasis, congenital heart disease, skeletal or ocular abnormalities or typical facial features which give the face an inverted triangle appearance (broad forehead, deep set eyes, rounded tip and pear like shape of the nose and pointed chin) [63, 64]. Alagille syndrome is an autosomal dominant condition with high penetrance (94%) and variable expressivity, which is the result of mutations or deletions in the JAG-1 gene (locus 20p11.2). De novo mutations occur in 50–60% of cases [65, 66]. Alagille syndrome is now recognized to be a genetically heterogeneous disorder. Approximately 5% of the patients with a chromosomal deletion involving one copy of the entire JAG1 gene, whereas most will have various intragenic JAG1 mutations [67].

The prevalence is 1 in 70,000 to 100,000 live births [68]. Cardiovascular anomalies are present 90% of the cases [68]. The most common cardiac lesion is pulmonary artery branch stenosis (PABS), tetralogy of Fallot (in up to 10% of cases), pulmonary stenosis and coarctation of the aorta [69]. If the mutation or deletion is identified in a parent, prenatal diagnosis is available

on samples from chorionic villus sampling or amniocentesis. It is, however, not possible to predict the severity of the phenotype in an identified fetus [69]. The diagnosis needs to be considered in a baby with a cardiac defect and prolonged jaundice, and with at least three of the recognized features [61]. Alagille syndrome has a mortality rate around 10–20%. The risk of recurrence is low in the absence of a positive family history, but it is 50% if there is an affected parent [61, 68].

### **2.8. Holt-Oram syndrome**

The phenotype is characterized by the bilateral, asymmetrical upper limb anomalies of variable severity and is estimated to occur in 1 per 100,000 live births. There is a variation in the severity of the phenotype even within a family, and in some the upper limb anomalies may be so mild that X-ray can only diagnose them. A thumb anomaly is usually present [70]. Approximately 75% of the patients diagnosed with Holt-Oram syndrome have CHD. Atrial septal defects (secundum type) are present in 58% of these patients, in addition 28% have VSD. Up to 40% have conduction defects including a long PR interval, sinus bradycardia, atrial fibrillation and complete heart block [71]. Other types of congenital heart diseases in the form of total anomalous pulmonary venous drainage, TOF and truncus arteriosus have been associated with this syndrome [72]. There appears to be a correlation between the severity of the upper limb anomaly and the cardiac lesion [73].

Holt-Oram syndrome is an autosomal dominant condition with 100% penetrance and variable expression. New mutations make up 30–40% of the inheritance pattern. The affected gene is TBX5 on chromosome locus 12q24 [74]. The diagnosis should be considered prenatally when a cardiac lesion occurs in the presence of an upper limb anomaly. The risk to the offspring of an affected individual is 50% [61].

### **2.9. Trisomy 21 (Down's syndrome)**

The most familiar syndrome to cardiologists is Down's syndrome is trisomy 21 in which there is a complete extra copy of chromosome 21 in 94% of cases. Less commonly, partial trisomy of chromosome 21 (6% overall), is present owing to a chromosomal translocation or mosaicism. Common findings include: hypotonia, global developmental delays and moderate intellectual disability, microbrachycephaly, small ears, mouth and nose, protruding tongue, up-slanting eyes with epicanthal folds, transverse palmar creases, and sparse hair. Skeletal anomalies include fifth finger clinodactyly, brachydactyly, a gap between first and second toes, atlantoaxial instability, hypoplastic pelvis, and joint laxity. Additional problems involve the visual, auditory, endocrine, hematologic, reproductive, and gastrointestinal systems. Almost half of live born Down's syndrome individuals have a CHD, approximately 40% of whom have a complete atrioventricular septal defect (also known as atrioventricular canal defect or endocardial cushion defect) [75]. The association of Down syndrome and atrioventricular septal defects is underscored by the fact that approximately 75% of patients with a complete atrioventricular septal defect have Down syndrome. Other common CHDs include secundum atrial septal defect, conoventricular and muscular ventricular septal defect, tetralogy of Fallot (with and without atrioventricular septal defect), and hemodynamically significant patent ductus arteriosus [75]. The overall prevalence of Down syndrome is 1 in 700 live births [76].

The risk of conceiving a child with aneuploidy (an extra chromosome), including Down's syndrome increases with maternal age. Overall survival has improved, although prenatally diagnosed CHDs and/or growth retardation may predict a poorer outcome [77]. The largest survey study to date reported that the frequency of CHDs in patients with Down syndrome mosaicism was similar to the complete trisomy 21 comparison group (~42 and 50%) [78]. Prenatal screening programs providing risk figures for Down's syndrome in individual pregnancies are widely available. Definitive testing involves an invasive procedure, either chorionic villus sampling or amniocentesis, and a rapid result can be obtained by FISH. The diagnosis is suspected clinically and confirmed by karyotyping. The risk of recurrence is about 1% for women aged 39 or less [61].

### **2.10. Trisomy 18 (Edward's syndrome)**

It is a rare syndrome with a prevalence of 1 in 6000, and a male to female ratio of 1:4. Majority of this syndrome is caused by maternal meiotic non-disjunction. Greater than 90% of cases have trisomy 18, the remainder having trisomy 18-mosaicism or partial trisomy of 18q. All cases have cardiac anomalies: mal-aligned VSD is the most common finding; ASD and patent ductus arteriosus are also common findings in these patients. Polyvalvular dysplasia, usually without stenosis or regurgitation, is usually present [79, 80]. Karyotyping is indicated if prenatal screening detected structural anomalies on ultrasound. The risk of recurrence is low, at around 1 in 200 [61].

## **3. Counseling**

### **3.1. Prenatal**

The process of prenatal counseling and its recommendations, should be based on the best available current evidenced-based practice. This process may require more than one consultation due to its emotional nature of the situation and complexity of information being delivered. Any prenatal counseling should include the suspected cardiac diagnosis in detail based on the fetal ultrasound findings. The purpose of this is to give the most accurate and up to date information about the prognosis and outcome of the pregnancy and fetus. This will allow the parents to make the best-informed decision for them and the fetus.

In regards to the screening ultrasound, all relevant information available needs to be given prior to the examination. Ideally, all prescreening information should be made available to the referring hospital. It needs to be emphasized that not all cardiac defects can be detected in the initial ultrasound examination [81, 82]. Whenever a cardiac abnormalities is detected this will require prompt referral for specialist examination. The general screening detection rates for congenital heart disease (CHD) vary between 14–45% [83]. A standard 4-chamber view can detect 40–50% of major CHD [84], while a 4-chamber view and outflow tract detects 70–80% of major CHD [85]. In dedicated fetal cardiac centers the diagnostic accuracy is close to 100% [86, 87]. Thereafter a referral for specialized echocardiography and cardiology consultation should be done. If there are suspected cardiac abnormalities on the screening fetal ultrasound, there should be minimal time delay in referring the mother for a fetal echocardiogram

and cardiology consultation. Delays in referral for further evaluation increase parental stress [88], and may prohibit the option of early termination of pregnancy. At the referral center, before the scan, the physician should make sure that the parents have consented to the examination and understand why they have been referred. A detailed review of past maternal history, including health wellbeing, previous pregnancies outcomes and similar conditions in the family need to be determined. In addition, any previous genetic screening has been performed or suspected in the family.

Ideally, the parents should be counseled by a pediatric cardiologist specialized in fetal cardiology, once the fetal echocardiogram is complete. The counselor needs to have full knowledge of the anatomy, physiology, gestational age, and association with extra-cardiac malformations and its natural history. In addition, the discussion should include the short and long-term management and possible outcomes. If possible a multidisciplinary meeting with the parents should be conducted. This conversation should include the most accurate information and include prenatal and postnatal management. Ideally this discussion should include fetal cardiologist, obstetrician, neonatologist, geneticist, pediatric cardiac surgeon and a psychologist or social worker. In addition to the physicians, a fetal nurse coordinator or midwife should be involved from the first counseling visit to delivery of the baby or termination of the pregnancy. This is to provide continuous support and ongoing resources for follow up with the family [89]. There is little research on performing prenatal counseling for CHD or determining the most effective strategies for providing family support. Therefore, it is important that counselors have good communication skills, show empathy, and be perceptive in assessing how the information is being received. The counselor must assess parental understanding and emotional status throughout the discussion.

A structured explanation focused on assessing the parents understanding is very important at this stage. Highlights of the counseling of session needs to be repeated and the expected parent should be made to verbalize understanding in their own words. This may need to be repeated to ensure complete understanding of the situation and implication for treatment and intervention. Throughout this process, the counselor needs to assess and give feedback to the treating team on how the information is being received. Particularly at the first visit, the initial shock and grief reactions to an abnormal finding may inhibit the parents' ability to retain information. Therefore, it may be necessary to repeat information on subsequent encounters and assess understanding. A common issue that complicates counseling in today technological age, is the access and availability of the vast amount of information on the Internet. At times such recourses can be beneficial, but more often than not, this information is misleading, biased and inappropriate for the precise circumstances. Unfortunately, none of this information is subject to review and can be a source of major confusion for the parent [90].

Complications of the cardiac abnormality and its progression in utero, and the results of surgery or any intervention also figure in to the discussion. There is a need to describe possible poor outcomes, so that they have been informed of all possible scenarios, even though unlikely to happen. This information allows the parents to decide how best to proceed with knowledge of the worst-case scenario [91]. One of the most important points which needs to be mentioned during the consultation is that the risk of intrauterine death is low in fetuses with CHD who are in sinus rhythm with good myocardial function [89]. Characterization of the cardiac defect and its association with genetic syndrome or not will guide the counselor on how best to give

the information to the parent [92]. The parent should be counseled after each scan, and should be given enough time for questions and follow up information [89]. If the amniocentesis detects a chromosomal abnormality, advance cytogenetic testing may be warranted. These testing include FISH, chromosomal microarray and whole exome sequencing [93]. The next step in the counseling, should mention the possibility of chorionic villus sampling or amniocentesis, as this knowledge may help determine prognosis and guide postnatal care. The finding of an associated chromosomal abnormality may also strongly influence decisions about pregnancy termination [94, 95]. Whatever the parental decision is made, the counselor should express full support.

In the final step, the counselor needs to identify and discuss the prenatal options and parental decision-making. This stage is crucial, because the counselor will be discussing the management options with the parents in regards to the outcome of the pregnancy. The management options include: pregnancy continuation, pregnancy termination (if legally allowed) and prenatal intervention if available [96].

If the decision is to continue with the pregnancy, there will be further decisions to be made as to where the infant will to be delivered, mode of delivery and the need for postnatal care and intervention [97]. Delivery at a tertiary care facility with access to pediatric cardiac care is recommended for ductal-dependent lesions and any heart defect that is expected to require neonatal and surgical interventions. Transfer is usually between 30 and 34 weeks gestation to allow the mother to become familiar with the new obstetrician and hospital in the time of her delivery. At the same time, it can be useful to have parent meet the surgeon. The fetus can be delivered at the local hospital, depending on the nursery's comfort level in dealing with such newborns. However, continued communications between the referral hospitals is vital for optimal outcome [98]. Delivery after 39 weeks is typically recommended because of high morbidity, and mortality has been reported in babies born before 36 weeks. Particularly in those with extracardiac and genetic abnormalities [99]. Parents should be counseled that IUGR is associated with increased morbidity after cardiac surgery [100]. Similarly, lower weight (<2.5 kg) is associated with higher mortality after cardiac surgery [101]. Mode of delivery is not typically altered in the setting of fetal CHD, and high rates of vaginal delivery can be achieved [102]. Cesarean section is almost never indicated for cardiac reasons and should be avoided if possible if the cardiac malformation is associated with a high mortality [103]. When the parents make an informed decision to continue the pregnancy, it may be useful for them to meet and speak with parents who have had a child with similar cardiac abnormalities. This will allow for them to have a better understanding of what is to be expected of the journey ahead.

If the decision is to terminate the pregnancy, parents should be counseled and supported fully, as this can cause guilt and emotional stress. Counselor should appreciate the mixed feelings of the parents when it comes to such decisions. It is very important to highlight that termination of pregnancy is never recommended nor absolutely indicated in any circumstances. Termination of pregnancy is a legal option in most of the developed world, but the gestational age limit is variable. In general, it is allowed up to 24 weeks of gestation in most countries all over the world, but late termination, even up to term, can be obtained in some countries like the United States of America for fetal malformations. The counselor must be able to discuss the options of termination of pregnancy and its risks, regardless of their personal beliefs. The earlier the diagnosis of fetal malformation can be reached (possible from as early as 12 weeks of gestation) the more safely termination of pregnancy can be accomplished. This will create

the least amount of physical and emotional trauma for the mother and family [90, 96, 104]. In one center experience, over 2000 sets of parents were counseled, half of them chose termination and the other half continued with pregnancy. Those who accepted termination of pregnancy recovered from it and with time ended up as normal healthy family. However, many of those who continued with the pregnancy, eventually lost the affected child, which was associated with increase grief and agony. In addition, break-down of the whole family unit after many years was reported [90].

Outcomes in terms of rate of termination, after prenatal diagnosis of heart defects vary between countries and even between centers within the same country [105, 106]. The reason for this may be due to differences in social/religious elements and in the local laws and practices. Termination rates are greatly influenced by the gestational age at the time of diagnosis [107], by the presence of the chromosomal abnormalities and other extracardiac malformations [25]. Severity of the cardiac malformation also influences the termination rate like hypoplastic left heart syndrome [81, 105].

Intrauterine interventions may be available for some cardiac malformations like Balloon aortic and pulmonary valvuloplasty. Currently there is a conflict between American College of Obstetricians and Gynecologists and the American Academy of Pediatrics (AAP) regarding the issue of fetal interventions [108]. The AAP favors fetal intervention if available, and puts less weight in maternal decision that is recommended for fetal benefits. This approach may place the mother at greater risks and decrease autonomy [96, 109]. If the intervention considered are questionable and carry a high risks to the mother, it is prudent to respect the mothers autonomy and giving her priority [96], until further research and consensuses are definitive in this regards.

In case of multiple pregnancies with one fetus with a serious congenital anomaly need to be highlighted in this step of the counseling. These risks and benefits of continuing or terminating the pregnancy of affected twin needs to be considered and balanced. The expectant parents need to understand that the death of the normal twin can occur if the twin pregnancy is continued. This is particularly true when there is a monochorionic twin pregnancy [96, 110].

The prenatal counseling should discuss the anticipated postnatal course, intervention and outcome/survival. In most cases, the infant born with cardiac malformation will require immediate medical and/or surgical intervention. Medical intervention to ensure patency of the ductus arteriosus will include starting Prostaglandin for duct-dependent lesions for either pulmonary blood flow (e.g., severe TOF or pulmonary atresia) or systemic blood flow (e.g., HLHS, interrupted aortic arch). Once these patients are stable medically, they may require cardiac catheterization and/or surgical repair. Parents should be counseled on what to expect in the delivery room. Management will vary, depending on the severity of the cardiac defect. Decision such as, where the baby will be admitted and how much time they will have the baby, will be decided prior to the delivery date. Parent should be made aware that the postnatal cardiac diagnosis might be modified after birth. Emphasis on the possibility of modification of the postnatal course, including change in the interventions and length of stay needs to be discussed. Helping the parents understand and deal with changes that may occur and be contrary to what they might have been told [98].

The outcomes and long-term survival (20 years) are profoundly dependent on the type of defect in babies born with CHD. Majority of these babies, approximately 85% are expected

to reach adult age. For example, infants with simple CHD such as VSD or ASD have survival rate of 95%, whereas moderate severity such as TOF reach 90%, and complex CHD such as single ventricle reach 80%.) [111]. A follow up study of 1000 Fontan patients by d'Udekem et al. showed 97% 10-year survival rate [112]. Although there are relatively good survival many of these patient may manifest other complications, including dysrhythmias, need for pacemaker and thromboembolic events [98]. Parents have to be informed about that there is an increased risk of neurodevelopmental delay in children with cardiac malformations. The severity of cardiac defect correlates with the degree of developmental delay [113]. In a recent meta-analysis, fetuses with severe cardiac malformation showed signs of impaired fetal cerebral development as shown by fetal MRI or ultrasound. However, correlations of fetal brain findings with neurodevelopmental outcome have been inconclusive and more long-term data are needed [114].

### 3.2. Postnatal

The advancement of cardiac diagnostic and therapeutic techniques in the past decade, with relatively low morbidity and mortality, has led to more and more children with congenital heart disease living to adulthood. Therefore, the role of genetic counseling becomes even more paramount as there is a higher likelihood of these patients living to reproduce and that they may have families of their own [22]. It is very important to help elucidate the genetic basis for patients' congenital cardiac malformation for the reason mentioned, as there may be important reproductive risks that the families need to know about [22, 115, 116]. Recent analysis indicate that adults now constitute roughly two-thirds of the congenital heart disease population, representing a nearly 60% increase in congenital heart disease among adult patients since the year 2000 [115, 116]. The greatest increase in congenital heart disease survival has occurred among the 18-year old to 40-year-old demographic, which has clear implications for heritability [116].

One of the obstacles, in performing genetic testing in patients with congenital heart disease is that there are no standardized recommendations or protocols incorporating, newer genetic testing technologies at present. The literature is sparse with guidelines, and there is evidence that there is under use even of those modalities of testing that are available [22, 115]. However, there has been an emphasis from the American Heart Association in the recent past, in obtaining genetic testing in these patients [117].

#### 3.2.1. *Genetics in congenital heart disease*

Cardiac malformation present at birth are an important component of pediatric cardiovascular disease. Defects can range from simple ventricular septal defects to complicated cyanotic lesions, requiring complex interventions shortly after birth. With the possibility of myriad of presentations, it begets one to ask, what is the percentage of pediatric cardiac defects are a result of a genetic anomaly. CHD is estimated that the prevalence of cardiac malformation at birth ranges from 4 to 10 live born infants per 1000. The true incidence, perhaps maybe higher as there are silent cardiac malformations that are only found later on in life [115]. As most calculations do not include bicuspid aortic valves, mitral valve prolapse and conduction problems, such as prolonged QT syndrome and complete atrio-ventricular block [115, 116]. The care of the pediatric patient with cardiac malformation is multifaceted, ranging from simple reassurance and observation to advanced surgeries and

interventional techniques shortly after birth. The primary focus of treatment of the patient with cardiac malformation is diagnosis and best course of treatment. However an important and integral part of the care of these patients is to have genetic counseling with their parents in regards to possible etiologies of the congenital heart disease. In the past, it was believed that the recurrence of congenital cardiovascular malformations in the same family was low, with expert quoting recurrence rate of only 3–5%. However currently it is known that for a family with autosomal-dominant 22q 11 deletion syndrome, the risk is up to 50% with a variable phenotypic expression [117, 118].

Etiology of some cardiac malformation that are known to have genetic components, where they make up approximately 5–17% are part of a genetic syndrome. Environmental factors need to be considered and a detailed family history needs to be elicited [119]. The role of the primary care giver is paramount, in detecting possible associated cardiac genetic syndromes. When genetic syndromes are a possibility, intervention requires referral to a genetic counselor for accurate diagnosis and possible future pregnancy. Since approximately, 75% of currently known cardiac malformations have no identifiable cause or underlying condition, the necessity for genetic counseling may appear unwarranted. However with the advent of advanced genetic testing such as whole exome sequencing, once unrecognized features are now being associated with syndromes [120–123]. Postnatal, the purpose of the genetic evaluation is to help establish a diagnosis and educate the family about future risk recurrence and expected outcomes. Parents need to be counseled and educated on both the numeric risk and the variable expressivity that makes predicting severity difficult.

### 3.2.2. Genetic evaluation of congenital heart disease

The role of genetic evaluation in patients with cardiac malformations, as patients live longer is becoming increasingly important. In the past, where genetic testing was limited to research laboratories, in today clinical practice this is no longer the case. The current clinical practice allows for the physician to obtain chromosomal analysis and request FISH testing when looking for specific deletions [22, 121–123]. The yields of these testing becomes higher when a genetic counselor is consulted prior to obtaining specific test. However even with the advancement on genetic testing, not all patients with congenital heart disease will be identified to have a genetic cause. The recommend approach for newly diagnosed patients with cardiac malformations includes the routine evaluation of all available relatives for a potential genetic contribution [22], and obtaining an accurate and complete medical history and documenting and extended pedigree. If from the information a syndrome is recognized, then evaluation and counseling of other family members becomes extremely important. Depending on the suspected diagnosis or syndrome, other consultation will need to be obtained such as neurology, ophthalmology, and others subspecialties.

Cytogenetic testing should be obtained in the following situations (from AHA Scientific Statement):

1. Any child or infant with the phenotype of a recognizable chromosomal syndrome (e.g., Trisomy 21 or 18)

2. Because not all chromosomal abnormalities result in a clinically recognizable syndrome, any infant or child with congenital heart disease combined with (a) dysmorphic features (b) growth retardation that cannot be explained by the heart defect (c) developmental delay or mental retardation or (d) multiple congenital anomalies.
3. Infant or children with a family history of multiple miscarriage and/or sibling with birth defects
4. If major cardiac and/or other visceral organ malformations are documented by prenatal ultrasound and/or fetal echocardiogram.

Review of the literature shows that chromosome abnormalities were present in 12% of patients with TOF, 26% in tetralogy of Fallot/pulmonary atresia, 44% in interrupted aortic arch, 12% in truncus arteriosus, 5% in double outlet right ventricle, and 60% in absent pulmonary valve. With certain cardiac defect, chromosomal analysis should be considered. In patients with conotruncal defects or interrupted aortic arch, FISH should be used looking for 22q11 deletion. Also analysis of the 8p region should be included [124].

### 3.2.3. Types of genetic testing

#### 3.2.3.1. Karyotype

Prior to the advent of advanced cytogenetic testing, the standard chromosomal analysis (i.e., karyotype) was widely used. Chromosome testing using standard metaphase karyotype is the traditional method and remains standard for the detection of aneuploidy (Trisomy 13, 18 and 21 and Turners 45 XO) and detecting gross changes such translocation and duplications [22, 117, 125]. A more sensitive karyotype is also available, which allows for the visualizations of greater number of bands. However, standard karyotype has an estimated 3% detection rate for pathogenic chromosome abnormalities. Conventional chromosome analysis detects well-known chromosome aneuploidies in about 10% of cases of CHDs [126]. with the advent and feasibility of newer technology, karyotype maybe used less and become replaced.

#### 3.2.3.2. Florescence in situ hybridization (FISH)

More advanced cytogenetic techniques such as FISH and chromosome microarray are required to diagnose more subtle structural abnormalities, such as microdeletions, tiny duplications and/or subtle translocations. This technology can be used to detect small deletions and duplications in chromosomes that cannot be detected with standard analysis as it looks specifically at the one area of the chromosome. A final FISH analysis will report on how many chromosomes of a certain type are present, in addition confirm suspected rearrangements. FISH technology uses probes of DNA that have been labeled with a fluorescent dye, that bind to complementary parts of a DNA, when it is heated. These probes are able to attach to their complementary DNA sequence [127]. The classic examples that uses this technology is the diagnosis of DiGeorge Syndrome with 22q11 deletion and William Syndrome with 7q11.23 deletion. The drawback of fluorescence in situ hybridization (FISH) lies in its targeted approach to detect chromosomal defects, rather than a genome-wide screening method like microarrays [128].

### 3.2.3.3. *Chromosome microarray*

Chromosomal microarray (CMA) testing looks for extra (duplicated) or missing (deleted) chromosomal segments, sometimes called copy number variants (CNVs). It refers to a microchip-based testing platform that allows high-volume, automated analysis of many pieces of DNA at once. CMA chips use labels or probes that bond to specific chromosome regions [129]. The resolution of conventional karyotype analysis is limited to 5 Mb or larger genomic imbalances. Chromosome Microarray Analysis (CMA) is a routine technique in clinical molecular testing nowadays, which contains two types of arrays: oligonucleotide arrays and Single Nucleotide Polymorphism arrays (SNP arrays). Computer analysis is used to compare a patient's genetic material to that of a reference sample. A difference between a patient's DNA and the reference sample is called a variant. These include chromosomal microdeletions and micro-duplications that are too small, abnormalities of chromosome number like the trisomies. In addition other variants include unbalanced rearrangements of chromosome structure such as translocations and triploidies.

Both the arrays could detect genome-wide CNVs. Moreover, SNP arrays can detect mosaicism, triploid, loss of heterozygosity and uniparental disomy. In 2010, the American College of Medical Genetics issued practice guidelines for CMA, and pointed out that CMA was recommended as a first-tier test for postnatal patients with multiple congenital anomalies, intellectual disabilities/developmental delay (ID/DD) and autism spectrum disorders [127, 129]. Recently, CMA has been successfully applied to detect CNVs in patients with CHD, which confirmed the relationship between chromosome microdeletion/microduplication and CHD [128].

### 3.2.3.4. *Whole exome sequencing*

Whole exome sequencing is part of next-generation sequencing. With this technology, it is now possible to sequence large amounts of DNA that provide genetic code for making proteins, which are called exons. All the exons in a genome are referred to as the exome, hence this method of sequencing them is known as whole exome sequencing, which allows for the identification of variations in the protein-coding region. It is known that most mutations that cause disease states, occur in these regions. Therefore, the use of this technology allows an efficient way to detect possible disease-causing mutations [130]. Whole exome sequencing has been successfully applied to patients with CHD. Many de novo mutations involved in cardiac related genes to the developing heart have been detected. [22, 130, 131]. This finding helped better elucidate understanding of overall CHD and its developmental pathways. However, more research needs to be done to determine a causal relation and best therapeutic interventions in these cohort of patient studied [130].

### 3.2.4. *Preimplantation genetic diagnosis*

In the current era of in vitro fertilization, preimplantation genetic diagnosis is possible. PGD provides chromosomal and mutational analysis of blastocyst that results from in vitro fertilization before implantation [22]. In assisted reproductive technology, PGD is becoming a

treatment option for some inherited disorders. The application of PGD can be used in some conditions present at birth, in addition to prevent carrier states that may or may not present later on in life. Holt-Oram syndrome (HOS) was the first heart disease in which PDG was used successfully [125, 132]. The features of HOS include ASD and cardiac conduction disorder, which has a variable penetrance. Currently there is no treatment prospect as it may manifest later on in life. Clinical manifestations may be extremely variable, and may not be present at birth, or present subtly as a sinus bradycardia, as the only clinical sign. So PGD may provide a treatment option to prevent offspring with this genetic diagnosis [117, 125, 132].

### 3.2.5. *Impact on patients and families*

The identification of genetic cause in congenital heart disease can prove to be very beneficial. Firstly it allows for the physician to be confident of the diagnosis and explain the mechanism of disease and other prognostic factors.<sup>1</sup> When the cardiac malformation is part of a genetic syndrome, it allows for the care team to look for other associated anomalies in other organ system. A genetic basis for disease may also necessitate evaluation into other family members [22, 117]. This will help further characterize the extent of the disease in the family and monitor risks and assess ability to pass on to future offspring [117]. Patients and families need to be made aware of both the numeric risk, as in Marfan and William Syndrome, an affected person has a 50% risk. However when the cardiac malformation has variable expressivity, predicting severity becomes extremely difficult [118].

## 4. Conclusion

Since approximately, 75% of congenital heart diseases have no identifiable cause or underlying condition, the notion of formal genetic evaluation may appear unwarranted [123]. However with the development and feasibility of genetic evaluations improving, more and more cardiac malformation are being linked to underlying genetic anomalies. Therefore the need to look for a genetic link become more crucial, as more patient with congenital heart disease live into adult age, it is very important that families understand their recurrence risk [120–122]. Unfortunately genetic counseling is not an integral or compulsory part of the treatment plan for families at many centers. Too many times, parents are exhausted from the complex interventional procedures and surgeries and its subsequent complications, the need for such counseling is forgotten and pushed aside [22, 117]. There are likely to be approximately 400 genes involved in the causation of congenital heart disease, many of which are yet to be identified [119]. Therefore the role of genetic counselors, with specialized skills in cardiovascular genetics is of utmost importance in the adult patient with congenital heart disease. Such genetic counselors play a crucial role in providing accurate recurrence risk, facilitating appropriate genetic testing, interpreting of results and appropriate subspecialty referrals. Phenotypic heterogeneity and incomplete penetrance complicate our understanding of the genesis of congenital heart disease. However it seems more likely than ever that our gaps in understanding the causes of congenital heart disease are primarily genetic and that the mechanism are multifactorial [117].

It is known that the prenatal diagnosis of moderate to severe CHD is associated with improved outcomes and reduction in the morbidity in select cardiac defects. Prior knowledge of the cardiac lesion allows the delivery room team to be prepared with appropriate resources to help minimize hypoxemia and metabolic acidosis. The likely need of invasive ventilation can be assessed prior to delivery. Therefore the prenatal counseling allows for an accurate diagnosis of the cardiac defect, with parents educated on the possible interventions and expected outcomes after birth. Counseling and the availability of a multidisciplinary team will give the expectant parents support and allows for them to make informed decision before and after delivery.

### Conflict of interest

None.

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