Congenital Heart Diseases in Pregnancy

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A B S T R A C T

This research aims to shed light into congenital heart diseases, the pathophysiology, and the ultrasonographic findings of congenital heart diseases. Congenital heart diseases are a major health concern, affecting 1.35 million children born every year. Ventricular septal defect, atrial septal defect, and atrioventricular septal defect are found in 57.9% cases of congenital heart diseases. The risk factors include consanguineous marriage, family history of congenital heart diseases, old maternal and paternal age, and exposure to teratogens, and genetic factors. Missteps in cardiac development are the main pathophysiology of congenital heart diseases. Ultrasonography screening in 18–22 weeks gestational age is utilized to screen. Follow-up screening can increase detection rate to 80%. This study has limitation of only discussing most common congenital heart diseases and did not delve into rarer types of congenital heart diseases and did not discuss impacts or burden of congenital heart diseases in adulthood and health comorbidities associated. This literature review is beneficial for general practitioners and obstetricians focusing in maternal fetal medicine.

1. Introduction

Congenital Heart Diseases (CHD) affects 8 out of every 1,000 live births, or around 1.35 million children per year.[1,2] The incidence of congenital heart diseases is higher in Asia, with 9.3 cases per 1,000 live births.[2] According to the global incidence rate, 54.5 percent of congenital heart disease cases are Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), and Atrioventricular Septal Defect (AVSD).[3] Every five years, the incidence of congenital heart diseases increases by about 10%.[2,5]

From 1970–1974, the incidence rate of atrial septal defect, ventricular septal defect, and atrioventricular septal defect was 49.2%, increasing to 65.3% in 2010–2017.[3] Congenital heart diseases varied by region; Asian population studies revealed a higher incidence of pulmonal outflow obstruction and lower incidence of left ventricle outflow obstruction and Transposition of Great Arteries (TGA).[2]

Preliminary screening can detect up to 40% of congenital heart diseases before 22 weeks of gestation,

and additional screenings can detect up to 80% cases of congenital heart diseases.[1] Prenatal screening for congenital malformations, including congenital heart diseases, increasing in popularity since 1980s and is typically done at 18-22 weeks of gestation.[1,6,7]

Atrial septal defect, ventricular septal defect, and atrioventricular septal defect are typically shown as right-to-left shunts in ultrasonography and classified based on anatomical location of defects.[1,7] Because of placental circulation, which provides oxygen and nutrients, the majority of fetuses with congenital heart diseases showed no heart failure symptoms in utero. Following birth, with closure of the fetal circulation shunt, symptoms of heart failure is manifested clearly.[6]

Left side obstruction can manifest as systemic hypoperfusion with acidosis, particularly in ductus-dependent circulation, as in Hypoplastic Left Heart Syndrome (HLHS), aortic stenosis, and Coarctation of Aorta (CoA). These congenital heart diseases can be detected during antenatal care using three-vessel and tracheal view (3VT). In cases of ductus-dependent pulmonary circulation, such as in pulmonal atresia, right-sided obstruction can manifest as significant cyanosis.[6]

Intrauterine screening of otherwise normal four-chamber-view, such as Tetralogy of Fallot (ToF) and Transposition of Great Arteries (TGA), is possible with four-chamber-view with outflow tracts.[6] Closure or restriction of the foramen ovale can cause severe cyanosis and circulatory collapse in the transposition of great arteries where the systemic and pulmonal circulations work in tandem. Besides that, oxygenated and non-oxygenated blood are mixed.[6]

Intrauterine congenital heart diseases detection is difficult in present times because of gestational age, complex heart structure in ultrasonography, training and experience, fetal and maternal movement, maternal obesity, amniotic fluids, fetal position, and maternal tissues. This screening is usually done with ultrasonography and conducted by general practitioners or obstetrician and gynecologists. It consists of preliminary screening at 18□22 weeks of gestation and follow-up screening to improve the accuracy (with up to 80% of accuracy is achievable in congenital heart diseases-focused screening).[7]

Preliminary screening increases the likelihood of detection and intervention, with the ultimate goal of lowering congenital heart diseases morbidity and mortality. Even with trainings, some congenital heart diseases, such as Total Anomalous Pulmonary Venous Drainage (TAPVD), coarctation of aorta, and progressive valvular abnormalities are still difficult to detect.[6]

This literature review aims to describe the prevalence, anatomy, embryology, and ultrasonographic findings of congenital heart diseases, as well as other screening methods, like genetic polymorphisms, biomarkers, and artificial intelligence.

2. Prevalence and Causes

Congenital heart diseases are structural abnormalities of heart or major vessels that occur before birth. Ventricular Septal Defect (VSD), Atrial Septal Defect (ASD), Patent Ductus Arteriosus (PDA), pulmonary stenosis, Tetralogy of Fallot (ToF), Transposition of Great Arteries (TGA), Atrioventricular Septal Defect (AVSD), and Coarctation of Aorta (CoA) are the top eight congenital heart diseases globally.[3,8] Congenital heart diseases are found around the world and affect millions of babies every year. It is responsible for one-third of all congenital anomalies found each year.[2]

Congenital heart diseases prevalence varied over time. Congenital heart diseases were found in 0.6 births per 1,000 live births on 1930, rising to 9.1 births per 1,000 live births after 1995. Incidence rate rose sharply from 1930 to 1960, then plateaued at around 5.3 births per 1,000 live births from 1961 to 1975, before rising sharply again in 1975□1995.[2,3]

The three most common congenital heart diseases are ventricular septal defect, atrial septal defect, and patent ductus arteriosus. These three lesions account for 57.9% of congenital heart diseases cases worldwide, up from 49.2% in 1970-1974 to 65.3% in 2010□2017.[3] There is regional variation, with pulmonal outflow obstruction being more common in Asia than left ventricle outflow obstruction. Asia has also fewer TGA cases than in Europe, North and South America, and

Oceania.[2]

There are numerous risk factors for congenital heart diseases. Consanguineous marriage (OR 2.34; 95% CI 1.61–3.38), family history of congenital heart diseases (OR 9.43; 95% CI 3.30–27.02), maternal comorbidities (OR 3.9; 95% CI 1.2–5.6), and low birth weight (OR 3.11; 95% CI 1.84–5.29) were all identified as major risk factors in a study conducted in Pakistan.[9]

Table 1. Global Congenital Heart Disease Prevalence

Congenital heart diseases subtypes	Prevalence per 1,000 live births (95% CI)	Subtype percentage (95% CI)
Ventricular Septal Defect	3.071 (2.845–3.305)	35.568 (33.876–37.278)
Atrial Septal Defect	1.441 (1.215–1.687)	15.378 (13.492–17.363)
Patent Ductus Arteriosus	1.004 (0.803–1.228)	10.172 (8.519–11.954)
Pulmonary Stenosis	0.546 (0.485–0.611)	6.233 (5.703–6.784)
Tetralogy of Fallot	0.356 (0.326–0.387)	4.422 (4.064–4.794)
Transposition of Great Arteries	0.295 (0.269–0.322)	3.819 (3.446–4.210)
Atrioventricular Septal Defect	0.290 (0.265–0.316)	3.595 (3.302–3.900)
Coarctation of Aorta	0.287 (0.261–0.314)	3.570 (3.273–3.879)

Cited from: Liu et al., 2019

Meanwhile, a study in India found that paternal age above 25 years old (OR 1.943; 95% CI 1.421–2.658), no multivitamin intake in pregnancy (OR 2.853; 95% CI 2.089–3.895), first trimester fever history (OR 3.717; 95% CI 1.625–8.501), obstetric issues history (OR 2.454; 95% CI 1.565–3.848), and maternal age above 30 years old (OR 2.868; 95% CI 1.255–6.555) are congenital heart diseases risk factors.[10]

Similar findings were found in a study that was conducted in Shaanxi, China. Multiple pregnancy, family history of congenital heart diseases, old maternal age, and parity were all found to be risk factors for congenital heart diseases.[11] Genetic factors, including chromosomal and syndromic, are known to play a role. Table 2 shows genetic factors in greater detail.

Table 2. Congenital Heart Disease Genetic Factors

Syndrome	Abnormalities of genes/chromosomes	Lesions commonly found	Proportion
Down	Trisomy 21	AVSD, ASD, VSD, TOF	40–50%
Edwards	Trisomy 18	VSD, ASD, DORV, TOF, CoA, HLHS	90–100%
Patau	Trisomy 13	ASD, VSD, DORV, HLHS, L-TGA, AVSD, TAPVR, dextrocardia, PDA	80%
Turner	Monosomy X	CoA, AS, HLHS, PAPVR	25–35%
Klinefelter	47, XXY	ASD, PDA, MVP	50%
Cat eye	Tetrasomy 22p	TAPVR, PAPVR	50%
Pallister-Kilian	Tetrasomy 12p	VSD, CoA, PDA, ASD, AS	25%
Velocardiofacial	Del 22q11.2	IAA(B), TA, TOF, aortic arch anomalies	75–85%
Williams	Del 7q11.23	SVAS±PVS, PS, PPS	50–80%
Alagille	*JAG1, NOTCH1* (del 20p12)	PPS, TOF, ASD, PS	85–95%
Noonan	*PTPN11, SOS1, KRAS, RAF1*	PVS, ASD, CoA, HCM	80–90%
Holt-Oram	*TBX5*	ASD, VSD, AVSD, TOF	80%
Char	*TFAP2B*	PDA	60%
Ellis-van Creveld	*EVC, EVC2*	Primum ASD, common atrium, AVSD	60%
Smith-Lemli-Opitz	*DHCR7*	AVSD, primum ASD, VSD, PAPVR	45%
CHARGE	*CHD7, SEMA3E*	ASD, VSD, valvular abnormalities	50–80%
Kabuki	*MLL2*	CoA, ASD, VSD	40%
Heterotaxy	*ZIC3*	Dextrocardia, L-TGA, AVSD, TAPVR	90–100%

Cited from: Blue, et al. 2012.

Non-syndromic genetic mutations, in addition to syndromic genetic factors, play a role in congenital heart diseases; as shown on Table 3. Table 3 lists the mutations that have been linked to congenital heart diseases.

Table 3. Congenital Heart Diseases Non-syndromic Genetic Factors

Gene	Function	Lesions
NKX2-5	Transcription factor	ASD-AV block, TF, HLHS, TGA, DORV, Ebstein anomaly, VSD
NKX2-6	Transcription factor	TA
GATA4	Transcription factor	ASD±PS, TOF, VSD, DORV
GATA6	Transcription factor	TA, TOF, AVSD
TBX1	Transcription factor	IAA, aortic arch anomalies, VSD
TBX5	Transcription factor	ASD, VSD, AVSD, conduction anomalies
TBX20	Transcription factor	ASD, VSD, valvular disease, LVOTO
CITED2	Transcription factor	ASD, VSD, TOF, TGA
ZIC3	Transcription factor	Heterotaxy, ASD, AVSD, TGA, VSD, TAPVR, PS
ZFPM2	Transcription factor	TOF
FOXH1	Transcription factor	TOF, VSD
HAND1	Transcription factor	HLHS (somatic mutation)
TFAP2B	Transcription factor	PDA
NOTCH1	Membrane-ligand receptor	AS, BAV
NODAL	Membrane-ligand receptor	Heterotaxy, TGA
JAG1	Membrane-ligand receptor	PS, TOF
CFC1	Membrane-ligand receptor	Heterotaxy, TGA, DORV, TOF
MYH6	Sarcomere protein	ASD
MYH7	Sarcomere protein	ASD, Ebstein anomaly
MYH11	Sarcomere protein	PDA
ACTC1	Sarcomere protein	ASD, VSD
GJA1	Gap junction protein	HLHS (somatic mutation)
GJA5	Gap junction protein	TOF
CRELD1	Cellular matrix protein	AVSD, dextrocardia
ELN	Structural protein	SVAS
VEGFA	Mitogen	TOF

Cited from: Blue et al., 2012.

Furthermore, environmental and infectious factors can cause congenital heart diseases, as shown on Table 4 below, which lists environmental or infectious risk factors for congenital heart diseases.

Table 4. Congenital Heart Diseases Environmental and Infectious Factors

Teratogen	Lesions commonly found	Risks
Maternal diabetes	VSD, ASD, L-TGA, AVSD, TAPVR, CoA, TOF, TGA	5%
Maternal rubella	PDA, VSD, ASD, PS, TOF	30–60%
Maternal phenylketonuria	TOF, VSD, PDA, left heart lesions	15–50%
Systemic lupus erythematosus	Complete heart block	Unknown
Fever in pregnancy	PS, left-sided and right-sided obstruction defects, tricuspid atresia, VSD	Unknown
Thalidomide	TOF, ASD, VSD, TA	Up to 30%
Retinoic acids	TA, TOF, IAA, DORV	25%
Anticonvulsants	All common defects	Unknown
Lithium	Ebstein anomaly, tricuspid atresia	Unknown
Selective serotonin reuptake inhibitors	VSD, ASD, TOF	Unknown
Alcohol	VSD, ASD, TOF	Unknown
Marijuana	VSD, Ebstein anomaly	Unknown

ASD: atrial septal defect; AS: aortic stenosis; AV: atrioventricular; AVSD: atrioventricular septal defect; BAV: bicuspid aortic valve; CoA: coarctation of aorta; DORV: double outlet right ventricle; HLHS: hypoplastic left heart syndrome; IAA: interrupted aortic arch; LVOTO: left ventricular outflow tract obstruction; PDA: patent ductus arteriosus; PS: pulmonary stenosis; SVAS: supravalvular aortic stenosis; TA: truncus arteriosus; TAPVR: total anomalous pulmonary venous return; TGA: transposition of great arteries; TOF: tetralogy of Fallot; VSD: ventricular septal defect.

Cited from: Blue et al., 2012.

Methylenetetrahydrofolate reductase (MTHFR) is an important enzyme the metabolism of folate. Methylenetetrahydrofolate reductase converts 5,10-methylenetetrahydrofolate into 5-methylhydrofolate, which is folic acid's active form. Methylenetetrahydrofolate reductase is known to reduce folate bioavailability, which is necessary for homocysteine re-methylation into methionine. At 37oC, C677T polymorphism of MTHFR gene produces thermolabile enzyme that reduces activity of methylenetetrahydrofolate reductase.[13,14] MTHFR gene is located on the short arm of chromosome 1 (1p36.22), and it has 13 exons with total length of 20,373 base pairs.[15]

In Asian populations, the MTHFR C677T is known to be associated with congenital heart diseases. This polymorphism is thought to cause folate metabolic synthesis dysfunction, which leads to a decrease in methionine, an essential amino acid, synthesis.[15,16] The C677T polymorphism causes alanine to be substituted for valine in the catalytic domain of the enzyme, lowering enzyme activity by up to 35% in heterozygotic individuals and up to 70% in homozygotic individual due to decrease of enzyme thermostability.[15,17] Congenital heart disease risk is reduced with adequate maternal folic acid intake. Hyperhomocysteinemia is a known risk factor for congenital heart disease, methylenetetrahydrofolate reductase activity is known to affect homocysteine plasma concentration.[13,16] Congenital heart disease is more common in Asian population who have homozygous 677CC polymorphism.[16] MTHFR polymorphism causes DNA hypomethylation and raises plasma homocysteine, resulting in folic acid deficiency.[15] In a meta-analysis, the MTHFR C677T allele polymorphism was found to be a risk factor for congenital heart disease in Asians, while the A1298C polymorphism was found to be a risk factor in Caucasians.[18] According to another meta-analysis, the MTHFR C677T polymorphism is a significant risk factor

for congenital heart disease in Asian population, but not in Caucasian population. The MTHFR A1298C polymorphism does not appear to be a significant risk factor for congenital heart disease, according to the findings of this meta-analysis.[19] Another meta-analysis shows that MTHFR C677T polymorphism plays a significant risk factor for congenital heart disease in Caucasian population.[20]

3. Embryology of Heart

The heart begins to form in the third week of gestation. Cardiac cells emerge from mesodermal layers in cranial area, migrating to the primary heart field (cranial of neural folds), and begin to form parts of the atria and the entire left ventricle. The right ventricle and outflow tracts emerge from the visceral side of the mesoderm's secondary heart field.[21,22]
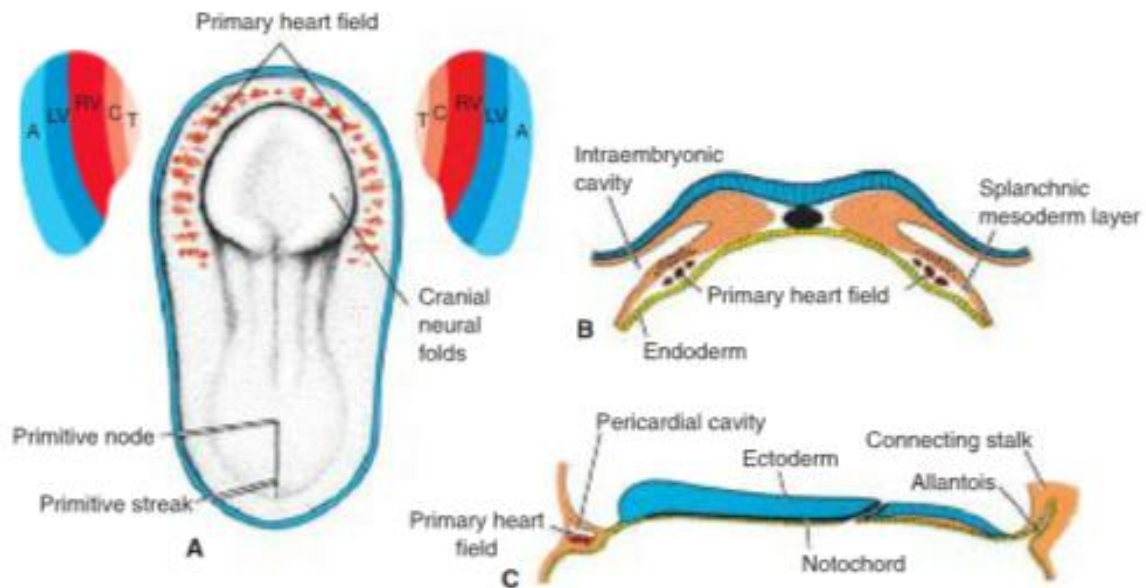

Figure 1. Heart embryology. (A) Dorsal view of 18-days old embryo. Progenitor cells of heart migrate and form primary heart field in the shape of a horseshoe. The primary heart field forms both the right and left sides of the heart, including both atrium and whole left ventricle. Secondary heart field gives rise to the right ventricle, outflow tract, and truncus arteriosus; (B) transverse view of primary heart field in visceral mesoderm; (C) lateral cut on embryo showing primary heart field.
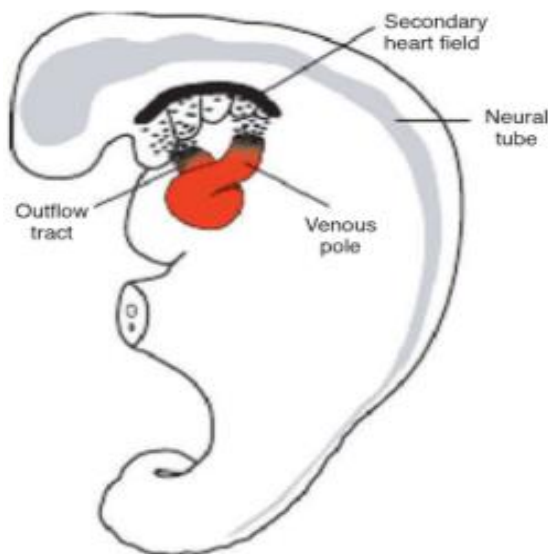
Cited from: Sadler, 2019

Figure 2. Secondary heart field in visceral mesoderm. The secondary heart field rises elongation of artery and vein poles, encompassing right ventricle and outflow tract (conus cordis and truncus arteriosus), atrium, and sinus venosus. Secondary heart field defect causes shortening and outflow defect.

Cited from: Sadler, 2019

At first, central part of cardiogenic area is located on the anterior of oropharyngeal membrane and neural plate. The oropharyngeal membrane pulls anteriorly and heart moves cervically during neural tube closure and brain formation, before migrating to the thorax.[21,22] During the period of cephalocaudal embryo development, the embryo also folds laterally, forming outflow and heart ventricles. During embryo development, the heart develops into a complete tube made of endothelial and myocardium cells. The middle section of mesocardium gradually disappears, leaving a transverse pericardial sinus that connects both sides of the pericardial cavity.[22]
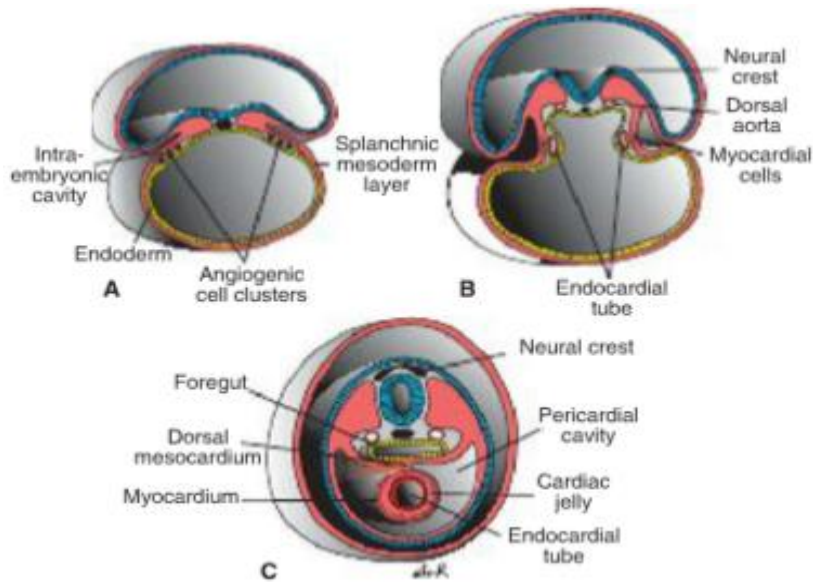

Figure 3. Cross-section of embryo in heart development; (A) 17-days old embryo; (B) 18-days old embryo; (C) 22-days old embryo. Caudal area of tube forms a fusion. Outflow and majority of ventricles are created from the expansion of the horseshoe-shaped area.

Cited from: Sadler, 2019

Heart undergoes elongation from cells arising from secondary heart field to create right ventricle and outflow tracts. Outflow defects, including ventricular septal defect, tetralogy of Fallot, pulmonary atresia, and pulmonary stenosis, come from disruptions in this stage.[22] During the outflow elongation, the cardiac tube begins to fold on the 23rd day to form cardiac loop, which finishes on the 28th day.[21,22]
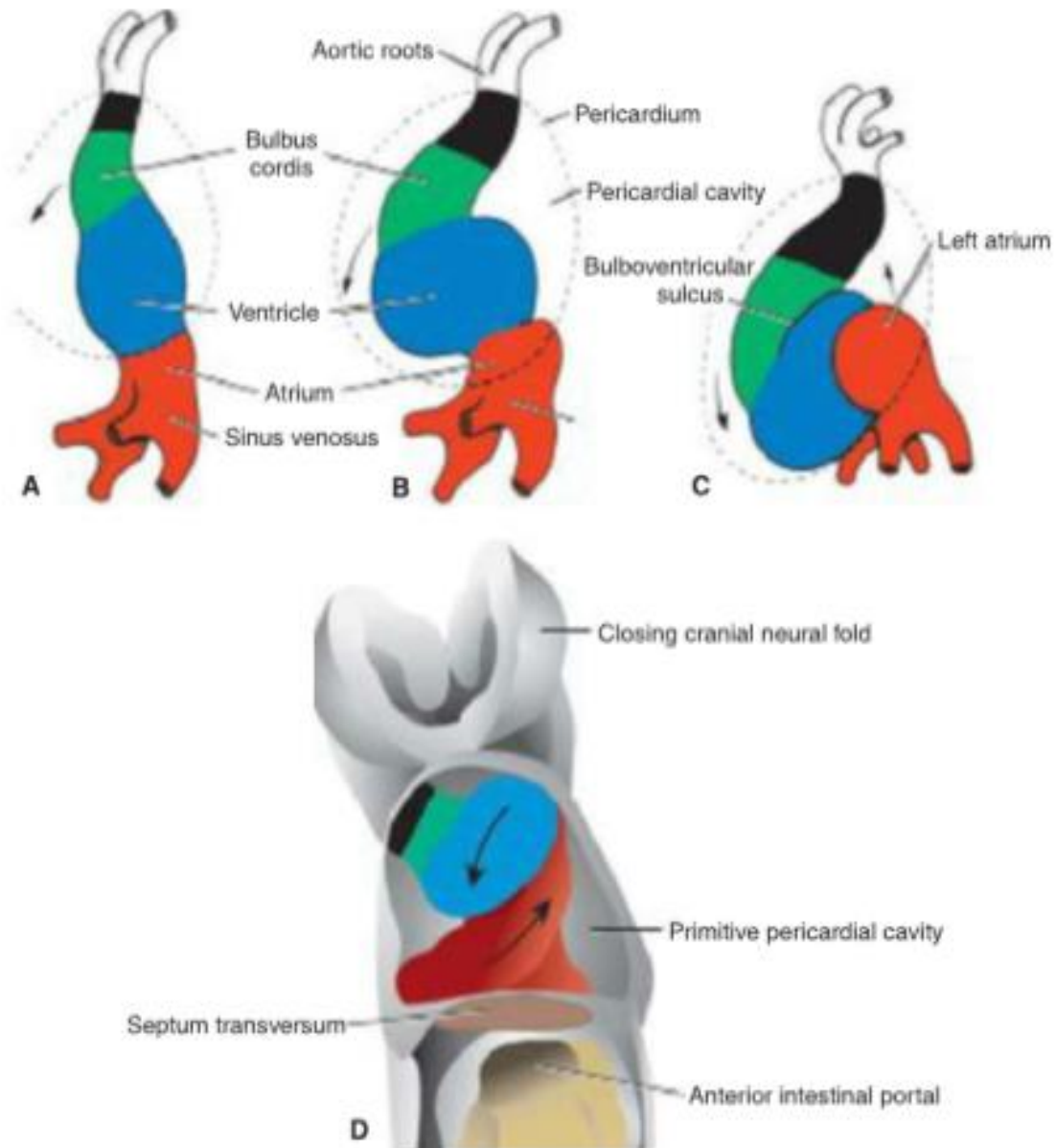
Figure 4. Formation of cardiac loop; (A) 22 days; (B) 23 days; (C) 24 days; (D) frontal view of looping heart tube. Primitive ventricles move ventrally and to the right, while atria move dorsally and to the left.

Cited from: Sadler, 2019

Cardiac septum develops on 27th day until 37th day. Endocardial cushions from around the atrioventricular and conotruncal area to form the septum of the atrium and the ventricles as the tissues develop. Atrioventricular canals and valves are formed by the same process. Atrial septal defect, ventricular septal defect, transposition of great arteries, and tetralogy of Fallot are all caused by the disruption of development at this stage.[21,22]
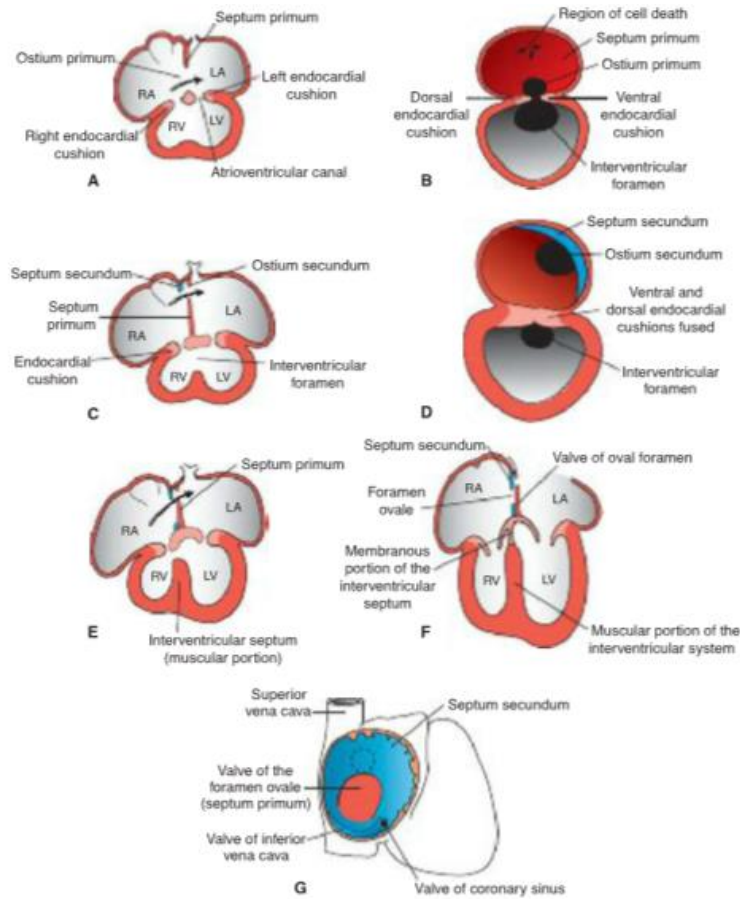
Figure 5. Septum on different development stages. (A, B) 30 days; (C, D) 33 days; (E) 37 days; (F, G) neonates.
Cited from: Sadler, 2019

Table 5. Lesions Associated with Various Developmental Stages

Tissues	Cellular processes involved	Normal process	Abnormalities
Primary heart field (16th day until 18th day)	Laterality and patterning	Formation of four heart chambers	Double outlet right ventricle, transposition of great arteries, atrial septal defect, ventricular septal defect, atrial isomerism, ventricular inversion, dextrocardia
Heart tube (22nd day until 28th day)	Genetic signal to create normal loop	Cardiac loop	Dextrocardia
Atrioventricular canal, endocardial cushions (26th day until 35th day)	Formation of endocardial cushions, proliferation and cellular migration	Division of atrioventricular canal to right and left canal, formation of mitral and tricuspid valve, formation of interventricular septum	Ventricular septal defect, mitral and tricuspid defect

Secondary heart field (22nd day until 28th day)	Visceral mesoderm from ventral pharynx and signals from neural crest cells	Elongation and separation of outflow into aortic and pulmonary canal	Tetralogy of Fallot, transposition of great arteries, pulmonary atresia, pulmonary stenosis
Outflow tract (36th day until 49th day)	Migration of neural crest cell, proliferation	Formation of conotruncal cushions and division of outflow tract	Common truncus arteriosus, outflow defect
Aortic arch (22nd day until 42nd day)	Migration of neural crest cell, proliferation	Formation of aortic arch	Anomalous right pulmonary artery

Cited from: Sadler, 2019

4. Ultrasonography in Congenital Heart Diseases

Ultrasonography is commonly used to screen for congenital heart diseases at 18-22 weeks of gestation.[23,24] In British Isles, detection rate of congenital heart diseases was around 35%. In United Kingdom, prenatal screening is able to detect 35% of congenital heart diseases, but only 32% in Northern Ireland. Scotland, had a 36% detection rate, while Wales had a 52% detection rate. The number is lower than the target of of 60% detection rate in British Isles.[24]

Around one-third of congenital heart diseases could be screened prenatally in a study in Czech. The detection rate for double outlet right ventricle was 77.3%, 50.6% for left heart hypoplasia, 50% for Ebstein anomaly, 42.9% for atrioventricular septal defect, and 42.5% for single ventricle. The rate of detection for atrial septal defect, ventricular septal defect, and pulmonary stenosis rate on the other hand were low; 0.8%, 2.4%, and 3.2%, respectively.[23]

Only 9.96% of congenital heart diseases were detected prenatally, according to a Brazilian study. Around 48.1% of the cases were complex (left heart hypoplasia, tricuspid atresia, Ebstein anomaly, truncus arteriosus), 18.5% were significant (tetralogy of Fallot, large ventricular septal defect, tricuspid dysplasia, large pulmonary stenosis), 7.4% were minor (small ventricular septal defect), and 26% were not classified (cardiomyopathy, dysrhythmia, and others).[25]

The four-chamber view can be used to screen for congenital heart diseases as early as 11 weeks of gestation. Following that, screening can be done from second trimester to monitor any septal or developmental abnormalities. In the 13th week of pregnancy, the sensitivity of congenital septal defect may approach 92%.[7]
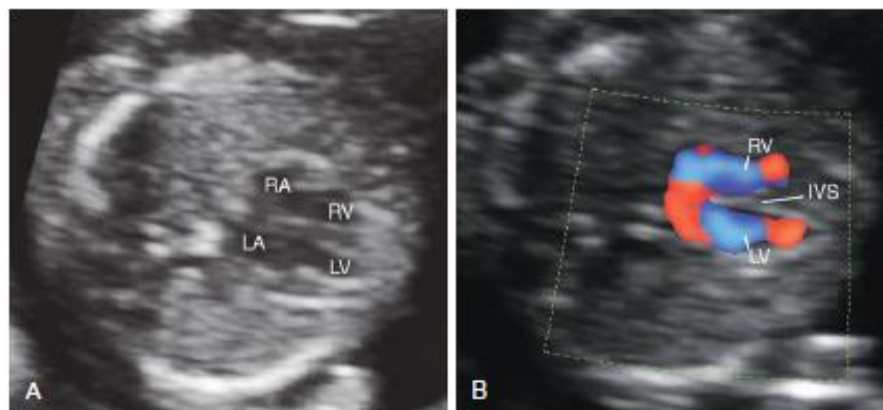

Figure 6. Four-chamber view in early gestation. (A) Four-chamber view in 13th week; (B) Four-chamber view with Doppler in 13th week.

Cited from: Norton, 2008

Congenital heart diseases can be detected during the second trimester screening. Screenings are usually performed between week 18-22 of gestation. The goal of screening is to assess heart rate, heart size, heart position, as well as four chamber of the heart, pericardium, atrium, ventricles, atrioventricular junctions, and ventriculoatrial junctions.[7] Because of the clinical complications that can arise shortly after birth, early detection of congenital heart diseases is paramount.

Because of its high sensitivity and specificity, safety, and noninvasiveness, Doppler echocardiography is becoming a primary diagnostic tool in congenital heart diseases screening.[6,26] Determination of heart location, followed by four-chamber view, left ventricular outflow tract view, right ventricular outflow tract view, and three-vessel view or three-vessel tracheal view are the steps of echocardiography.[6] The purpose of these examinations are to determine the cardiac shape and the cardiac abnormalities.[27]
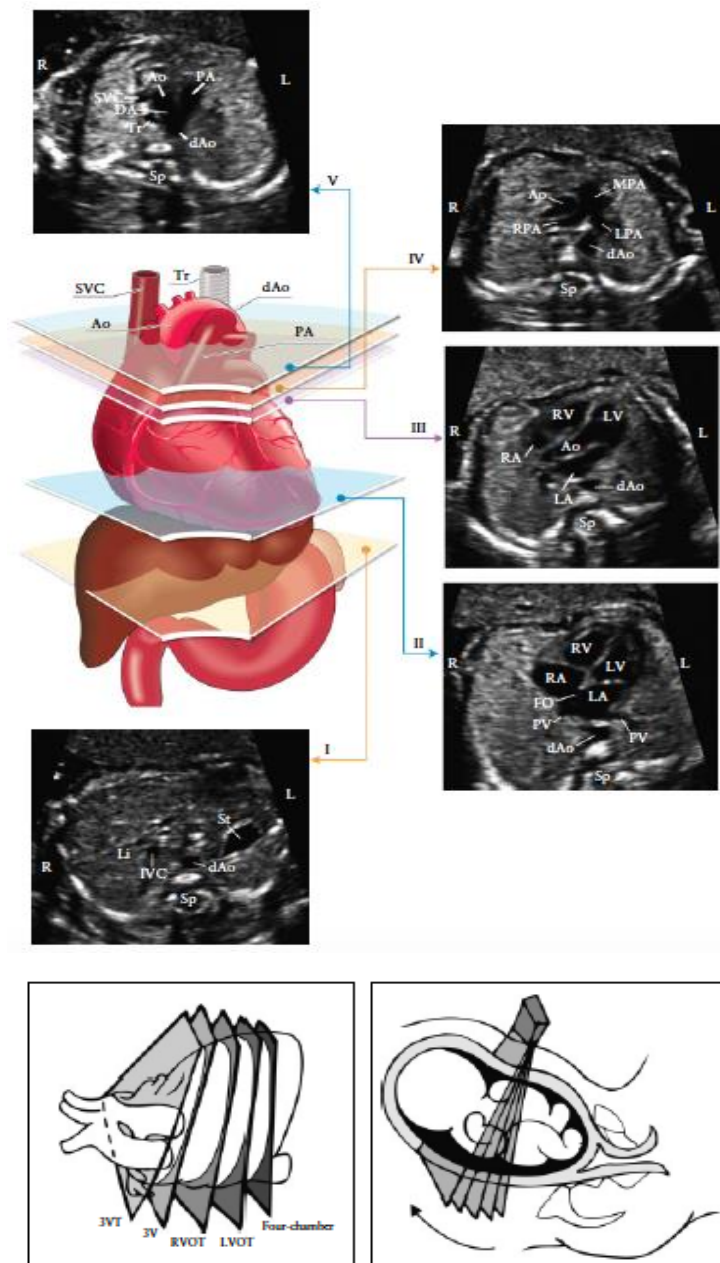

Figure 7. Main axis of fetal heart screening. I: most caudal plane, showing fetal stomach (St), descending aorta cross section (dAo), spine (Sp), and fetal liver (Li). II: four-chamber view of fetal heart, showing right and left ventricle (RV, LV), atria (RA, LA), foramen ovale (FO), and pulmonary veins beside descending aorta. III: left ventricular outflow tract view, showing aorta (Ao), LV, RV, LA, and RA with descending aorta cross section (dAo). IV: most cephalad position (right

ventricular outflow tract view) showing pulmonary artery (MPA) and its branches (RPA dan LPA), ascending aorta (Ao), and descending aorta (dAo). V: three vessels tracheal view show superior vena cava (SVC), pulmonary artery (PA), ductus arteriosus (DA), aortic arch (Ao-dAo), and trachea (Tr).

Cited from: The International Society of Ultrasound in Obstetrics, 2013

Cardiac location screening is required to determine cardiac orientation. Other lesions can sometimes be found in situs inversus, so more thorough screening is required. Four-chamber-view is used to determine the location and anomalies of the heart, as well as surrounding tissues lesions, tetralogy of Fallot, cardiomegaly, and septal or valvular defects.[6,28] Fetal heart rhythm and heart rate are also measured using the four-chamber view. Heart block can cause persistent bradycardia. Abnormalities in thoracal cavity, such as diaphragmatic hernia or pulmonary hypoplasia, can cause abnormal heart location.[27]

Valvular defect, aortal defect, and ventricular septal defect can be determined using the left ventricular outflow tract view. Right ventricular outflow tract view is used to determine right heart outflow, which includes pulmonary valve, pulmonary stenosis, and transposition of the great arteries.[6,26,28]

Three-vessels view and three-vessel tracheal view can be utilized to determine any congenital heart defects and to confirm defects detected in four-chamber-view ultrasonography. Three-vessel-view can also be used to help in determining the diagnosis of syndromic chromosomal abnormalities.[6,26,28]

A follow-up examination is sometimes recommended. Autoimmune antibody, family history of defects, in vitro fertilization, maternal metabolic disease, or teratogenic exposure are some of maternal indications. Abnormal screening results, a family history of congenital heart diseases, an abnormal heart rhythm, chromosomal abnormalities, extracardiac abnormalities, hydrops, or monochorionic twin pregnancy are some of fetal indications.[29]
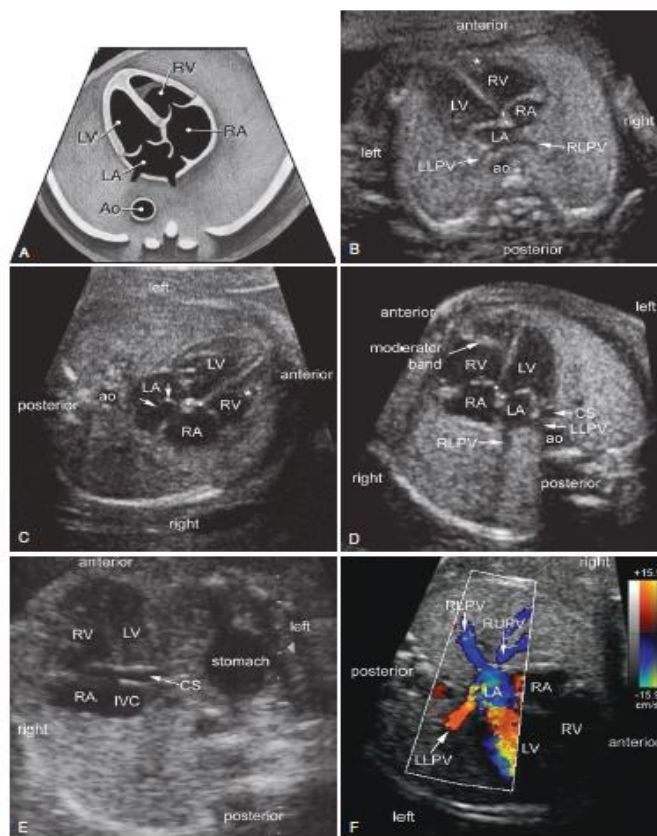

Figure 8. Four-chamber view on second trimester. (A) Diagram; (B-F) Ultrasonographic findings.

Cited from: Norton, 2008

5. Clinical Symptoms and Examination Required

Table 6. Clinical Symptoms of Congenital Heart Lesions

Lesions	Prevalence per 10,000 live births	Hypoxemia	Ductus arteriosus dependent
Tetralogy of Fallot	5.1	Majority	Rare
Transposition of great arteries	4.0	All	Rare
Double-outlet right ventricle	1.7	Some	Not
Truncus arteriosus	1.0	All	Not
Total anomalous pulmonary venous connection	1.2	All	Not
Ebstein anomaly	0.6	Some	Sone
Tricuspid atresia	0.5	All	Some
Pulmonary atresia with intact septum	0.8	All	All
Pulmonary stenosis/atresia	6.3	Some	Some
Right heart hypoplasia	3.3	All	All
Coarctation of aorta	4.7	Some	Some
Aortic arch atresia/hypoplasia	1.0	Some	All
Aortic valve stenosis	1.6	Rare	Some
Other defects	12.4	Some	Some

Cited from: Norton, 2008

Common lesions causing left-to-right shunts are atrial septal defect, ventricular septal defect, and patent ductus arteriosus. Shunt flow is affected by the size of defect and pulmonal resistance in an atrial septal defect. There are no cardiac enlargement are observed in small shunts; however, larger shunts can cause dilatation of right atrium and ventricle, mid-diastolic tricuspid murmur, and systolic murmur due to increased pulmonal flow.[30,31]

The pathophysiology of patent ductus arteriosus and ventricular septal defect is similar. The degree of the shunt is determined from the size of the defect and the pulmonary vascular resistance. Ventricular septal defect is more commonly found in six to eight weeks of birth because of decrease in pulmonary vascular resistance in this age. A small defect will not result in increase of cardiac size or changes in electrocardiogram, whereas a larger defect will result in the enlargement of left atrium and ventricle. Meanwhile, aortic arch elongation or enlargement can be found in patent ductus arteriosus. Cyanosis can be seen in the lower limbs as pulmonary vascular resistance increases.[30,31]

Thorax x-ray is crucial radiological examination. Cardiomegaly and pathognomonic heart shape can be assessed with thorax x-ray. Thorax x-ray can also be used to determine the size of large vessels. Echocardiography is utilized to evaluate cardiac shape, cardiac function (using Doppler echocardiography), and direct defect visualization. For surgical assessment and planning, MRI has been used to reconstruct three-dimensional cardiac shape.[30,32]

Proinflammatory cytokines, such as TNF-alpha, VEGF-D, and HB-EGF have been used to assess cardiac failure.[33,34] TNF-alpha has cut-off value of 68 pg/mL (sensitivity 50%, specificity 93.4%, positive predictive value 7.6, negative predictive value 0.5). Meanwhile, the cut-off value of VEGF-D is 1156 pg/mL (sensitivity 50%, specificity 93.4%, positive predictive value 7.6, negative predictive value 0.5). The cut-off value of other biomarker, HB-EGF, is 90 pg/mL (sensitivity 83.3%, specificity 83.6%, positive predictive value 5.1, negative predictive value 0.2). When combined, these three biomarkers have 100% sensitivity, 80.3% specificity, positive predictive value of 5.1, and negative predictive value of 0.[33]

6. Artificial Intelligence Role in Chd Screening

Artificial intelligence can help to increase diagnostic and therapeutic accuracy. Machine learning is capable

to analyze, manage, making decision based on the data available, and reflecting those decisions to improve accuracy in next step of the data process. Artificial intelligence is capable of making timely and effective decision with the help of additional data that has been gathered. The end result is a decrease in diagnostic errors.[35]

Machine learning is type of computer modelling that involves teaching a computer to perform a task with specific goal in mind without explicitly telling it to do some tasks.[36] Artificial intelligence can create and implement imaging protocols, reducing the amount of time and money spent required on imaging.[37] The medical team can use artificial intelligence to improve diagnosis, risk prediction, therapeutic decision-making, and workflow.[38]

When compared to the same ultrasonographic screening performed by a trained physician, computer-aided ultrasonography promises similar accuracy. Automatic echocardiography analysis can improve cardiac structures and anomalies recognition.[39,42] In 75% of cases, an automatic screening using neural learning-based computer program can diagnose tetralogy of Fallot with 76% specificity.[43]

There are two types of machine learning algorithm: supervised and unsupervised. Unsupervised learning can be taught using existing examples with the goal of recognizing pattern in a large amount of unrelated data. Supervised learning necessitates the preparation of prior ground truth, when the end goal of data processing is known, supervised learning is more commonly used. Whereas unsupervised learning is useful for data exploration and analysis.[36]
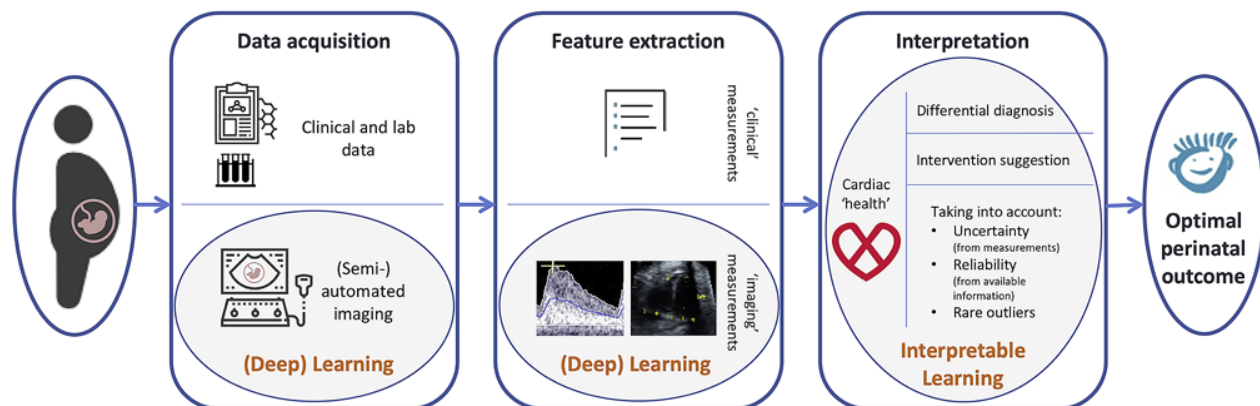

Figure 9. Machine Learning in Congenital Heart Disease. In the short term, machine learning can aid operators in fetal cardiac recognition, improving quality, and comprehension. Machine learning can extract key points from data, resulting in increased standardization and efficiency.

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Machine learning is capable of identifying fetal cardiac features, assisting segmentation and measurement of cardiac structures, and distinguishing normal cardiac shape from data pool, especially when used in a supervised learning format.[36] Artificial intelligence-based congenital heart defects recognition can recognize cardiac structures, distinguish them from surrounding tissues, and measure cardiac anomalies.[42]

7. Conclusion

Congenital heart diseases affect 1.35 million children born every year, making them a major public health concern. To achieve an acceptable detection rate, better screening and follow-up should be conducted as the increasing rate of congenital heart diseases. Ventricular septal defect, atrial septal defect, and atrioventricular septal defect are found in 57.9% cases of congenital heart diseases worldwide, and this number is growing. Consanguineous marriage, family history of congenital heart diseases, old maternal and paternal age, and exposure to teratogens are all known to be the risk factors of congenital heart diseases. Congenital heart diseases are known to be caused by genetic factors, such as chromosomal or syndromic abnormalities.

The main pathophysiology of congenital heart

diseases is flaws in cardiac development. Ultrasonography can be used to screen for developmental issues between 18 and 22 weeks of gestation. Follow-up screenings can be done to improve the detection rate to 80% or better.

Comorbidities associated with congenital heart diseases are one of the areas where more research can be conducted. Congenital diseases and cardiovascular risk factors in adulthood are also a promising field of research. Treatment options for congenital heart diseases, as well as risks and benefits associated with them, have emerged as a promising field of research.

8. Acknowledgment

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