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U.O.C. Cardiochirurgia Pediatrica e delle Cardiopatie Congenite

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DIDAS Salute della Donna e del Bambino

TESI DI LAUREA

The role of a multidisciplinary approach in prenatal counseling for congenital heart disease and its effects on the prevalence of termination of pregnancy

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ABSTRACT

Background: The diagnosis of congenital heart disease (CHD) during pregnancy can be a disquieting experience for parents, which relates to stress and a broad spectrum of variable emotional responses. This poses the medical and ethical obligation of accurate and sensitive counseling to patients, who should be extensively informed about the diagnosis, its implications for pregnancy, post-natal prognosis and available treatment options as well as termination of pregnancy (TOP).

Therefore, early detection of congenital heart disease is advantageous to allow anticipated prenatal counseling and with it a suitable time frame for parents to decide whether to continue or end pregnancy. Today an early diagnosis is possible thanks to progress in ultrasound diagnosis, continuous formation of doctors and updated cardiac screening guidelines.

Aim of the study: This experimental study has the aim of evaluating the effects of multidisciplinary prenatal counseling in the diagnosis of fetal CHD and on the parental choice of termination of pregnancy (TOP).

Materials and methods: In 2023 the Obstetrics and Gynecology Division of Padua introduced a new multidisciplinary integrated clinic for CHD. Fetal echocardiography is performed on expectant mothers by an obstetrician specialized in maternal-fetal medicine and a pediatric cardiologist, who then explain to parents the features of the malformation, its prognosis and possible treatment options. Regarding specific technical aspects of surgery treatment, parents are given the opportunity to speak to a pediatric cardiothoracic surgeon, in a separate and dedicated room.

A single-center and retrospective comparison was made within the registry of fetal echocardiography performed in 2022, when the multidisciplinary clinic was yet to open, and those performed in 2023 and 2024, focusing on the number of CHD diagnoses, severity of diagnosis and prevalence of termination of pregnancy.

Results: Since the introduction of the multidisciplinary clinic, the number of fetal echocardiography performed annually increased, with a corresponding rise in the detection of congenital heart diseases. In 2022, 595 FE were conducted, with 84 CHDs identifies (14.1%) and corresponding pregnancy termination rate 17.9%. In

2023, this rate decreased to 15.2% (92 CHDs among 668 FEs) and further declined to 14.0% in 2024 (100 CHDs among 683 FEs).

When stratified by severity, distinct trends emerged. For minor CHDs, a statistically significant reduction in the TOP rate was observed, declining from 9.4% in 2022 to 0% in the 2023–2024 period (*p*-value 0.03). In contrast, trends among major CHDs were more heterogeneous. A significant decline in the TOP rate was limited to atrioventricular septal defects (AVSDs), from 66.7% in 2022 to 0% in 2023–2024 (*p*-value 0.02). Although not statistically significant, a trend toward higher TOP rates was observed for complex lesions with poor postnatal prognosis, such as Hypoplastic Left Heart Syndrome (HLHS). Other malformations, including Transposition of the Great Arteries (TGA) and Double Outlet Right Ventricle (DORV), exhibited a fluctuating pattern over the study period.

Conclusion: A multidisciplinary approach to prenatal counseling for congenital heart disease can have a variable influence in the reduction of parents' choice of pregnancy termination, depending on the severity of the prognosis, available medical and surgical treatment, parent's background and personal resources (emotional, cognitive, economic).

RIASSUNTO

Introduzione: La diagnosi di cardiopatia congenita (CC) durante la gravidanza è percepita come un evento traumatico da parte dei futuri genitori, legato a forte stress emotivo per l'incertezza sulle conseguenze della anormalità riscontrata. Questo pone l'impegno medico ed etico ad una consulenza prenatale accurata e sensibile verso i bisogni del feto e dei genitori. Quest'ultimi devono infatti essere informati sulla natura della malformazione e le sue conseguenze sulla vita fetale, sulla prognosi post-natale, sulle possibilità di trattamento e sul percorso di interruzione volontaria di gravidanza (IVG).

Dunque, è auspicabile svolgere una diagnosi in epoca gestazionale precoce che permetta un'anticipata consulenza prenatale e garantisca al genitore una maggiore finestra temporale per la decisione di proseguimento o interruzione di gravidanza. Questo è permesso grazie al continuo progresso delle tecniche di indagine diagnostica, le sempre maggiori competenze dei medici coinvolti nella diagnosi e l'aggiornamento delle linee guida internazionali di inclusione.

Obiettivo dello studio: Questo studio sperimentale ha l'obiettivo di valutare gli effetti dell'introduzione di un team multidisciplinare in sede di consulenza prenatale in termini di numerosità di diagnosi prenatale di cardiopatie congenite ed interruzione volontaria di gravidanza.

Materiali e Metodi: Nel 2023 la divisione ostetrica e ginecologica dell'Azienda Ospedaliera – Università di Padova ha introdotto un ambulatorio integrato per le diagnosi di cardiopatie congenite. Le pazienti in visita sono sottoposte a ecocardiografia fetale in presenza di un medico ginecologo ostetrico e un cardiologo pediatrico che, a fronte della diagnosi, forniscono ai genitori le informazioni riguardo la cardiopatia riscontrata, la prognosi e le possibilità di trattamento. Successivamente, per rispondere a domande specifiche sulle modalità di chirurgia e gestione post-operatoria viene data ai genitori l'opportunità di confrontarsi con i cardiochirurghi pediatrici, in una stanza separata e dedicata a tale colloquio.

Per valutare gli effetti dell'ambulatorio multidisciplinare sono state confrontate le numerosità di diagnosi di cardiopatie congenite e delle relative interruzioni volontarie di gravidanza nel periodo antecedente all'introduzione dell'ambulatorio, anno 2022, e conseguente, biennio 2023 e 2024.

Risultati: A seguito dell'istituzione dell'ambulatorio integrato, il numero di ecocardiografie fetali (EF) eseguite annualmente è aumentato, con un conseguente aumento nella diagnosi di cardiopatie congenite. Nel 2022 sono state eseguite 595 EF, con 84 CC diagnosticate (14,1%); il tasso corrispondente di interruzione volontaria di gravidanza (IVG) è stato del 17,9%. Nel 2023, tale tasso è diminuito a 15,2% (92 CC su 668 EF) ed ulteriormente a 14,0% nel 2024 (100 CC su 683 EF).

Nella stratificazione per gravità, sono emerse tendenze distinte. Per le CC minori, si è osservata una riduzione statisticamente significativa del tasso di IVG, variato dal 9,4% nel 2022 allo 0% nel biennio 2023-2024 ($p = 0,03$). Al contrario, gli andamenti tra le CC maggiori sono risultati più eterogenei. Un calo significativo del tasso di IVG, dal 66,7% nel 2022 allo 0% nel periodo 2023-2024 ($p = 0,02$), è stato circoscritto ai difetti del setto atrioventricolare (CAV). Sebbene non statisticamente significativo, si è osservata una tendenza a tassi di IVG più elevati per le lesioni complesse con prognosi postnatale sfavorevole, come la Sindrome del Cuore Sinistro Ipoplasico (HLHS). Altre malformazioni, tra cui la Trasposizione delle Grandi Arterie (TGA) e il Ventricolo Destro a Doppia Uscita (DORV), hanno mostrato un andamento fluttuante nel corso del periodo di studio.

Conclusioni: Un approccio multidisciplinare al counselling prenatale per le cardiopatie congenite può influenzare in misura variabile la decisione dei genitori per l’interruzione volontaria di gravidanza, in relazione alla gravità della prognosi, alle opzioni terapeutiche mediche e chirurgiche disponibili, nonché alle risorse personali (emotive, cognitive, economiche) dei genitori.

I. INTRODUCTION

Congenital heart diseases (CHD) are the most common type of congenital malformation and occur in nearly 1% of live births. (1) These diseases are associated with a higher risk of perinatal and long-term morbidity and mortality; implications which may be improved with prenatal diagnosis.(1)(2) Over the past two decades important advances in imaging technology, including fetal echocardiography, have been witnessed, leading to an improvement in the diagnostic rate of congenital heart disease. (3) Echocardiography screening conducted at an early gestational age, between 18 and 22 weeks, has the aim to detect congenital malformation at an early age allowing to identify its severity, implications in utero, post-natal prognosis and treatment options, always considering the time limit allowed for possible termination of pregnancy (TOP). According to Italian's current legislation *(Italian Law No. 194 of May 22, 1978),* TOP after the first 90 days of pregnancy is possible only if there is evidence of fetus's malformations which are dangerous for the woman's physical and psychological health and if the fetus would not have possibility of life at birth for its underdeveloped status. These conditions are conventionally fixed at a limit of 22 weeks and 6 days of gestational age. (4)

1. Epidemiology

Congenital heart disease is defined as an anomaly in the structure of the heart present at birth which interferes with the physiological septation of the cardiac segments, valves' functionality and/or venous drainage. (5) As previously said, congenital heart conditions present worldwide an approximate prevalence of 5-11/1000 live births (incidence of 1%). (6) Within this population, the most frequent types of congenital disorders are: ventricular septal defect (VSD), atrial septal defect (ASD), patent foramen ovale (PFO) and patent ductus arteriosus (PDA). (7)

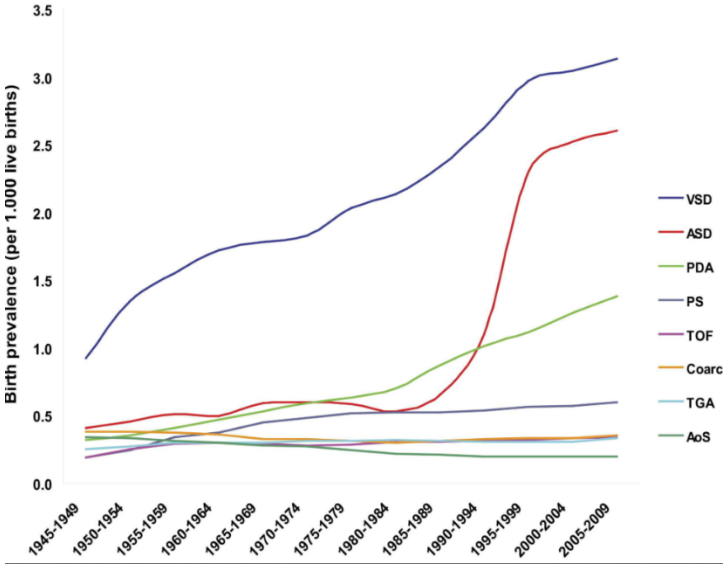

Figure 1 – Birth Prevalence of CHD subtypes over time (8)

Furthermore, of all newborns with CHD, 75% present a non-critical heart disease (NCCHD), most represented by isolated ventricular septal defects (VSD). (9) On the other hand, the remaining 25% present critical congenital heart diseases (CCHD) that require intervention in the first year of life and for which improvements in cardiothoracic surgery, catheter and medical therapies have widely extended life expectancy. (10) In 2020, survival trends from 1980 to 2017 in children with CHD were nationwide investigated through the Swedish health registries. Completing proportional regression models and survival analysis among 64 396 patients with CHD and 639 012 matched controls, healthy at birth, the study proves a substantial increase in survival rate among patients with congenital heart malformations. Overall, since the 1980s, 97% of survivorship was measured, however with no significant improvement between 2010 and 2017. (*Figure 2)* (11) These findings speak positively for the improvement of CHD's treatment and highlight the need for life-time management.

Furthermore, survivorship is not the only parameter that has been reported as increased over time. In 2011 the first meta-analysis on worldwide CHD's birth prevalence was published. (8) The study highlights the proportional connection between improvements in diagnostic methods and screening modalities and increase in CHD's birth prevalence.

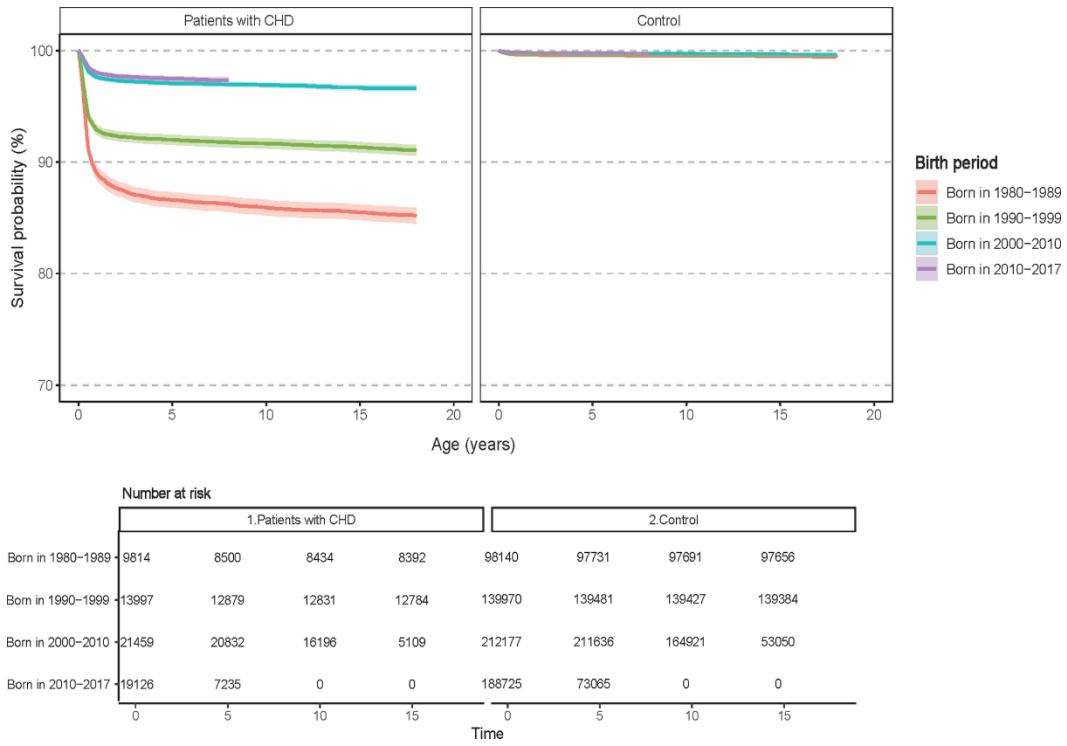

Figure 2- Comparison between survival trends for patients with CHD and matched controls for the years 1980-2017 (11)

2. Etiology

The causes of congenital heart diseases are complicated and multifactorial and approximately half of the pathogenesis patterns remain unknown. Firstly, because of improvement in survival rate, patient population with grown up congenital heart (GUCH) is expanding, meaning their offspring present an increased risk of developing congenital heart defects, higher when the mother is affected rather than the father (general recurrence risk ranges from 2-50%). (7) For this reason, prognostic values such as ventricular function, severity of the defect and history of previous cardiac events should be examined before pregnancy time as prognostic value of maternal and neonatal outcomes. Furthermore, genetic counseling should be suggested since 10-30% of all structural CHD have a genetic etiology. Marked recurrence risks are associated with single gene disorders and/or chromosomal abnormalities found in Marfan, Noonan, DiGeorge syndrome and Holt-Oram syndrome while isolated CHD have a 1-21% presentation rate. (12)

As for non-inherited risk factors, currently available literature shows that low periconceptional intake of multivitamins and folic acid as well as prenatal maternal conditions, such as maternal rubella infection, febrile illness, diabetes mellitus and phenylketonuria, can be associated with a higher risk for cardiac defects.

Furthermore, modifiable risks linked to maternal organic solvents and therapeutic drug exposure (Thalidomide, Retinoids, Lithium) as well as cigarette smoking inhalation and alcohol consumption are also to be taken into consideration. In addition, delayed childbearing is becoming more diffused in developed countries and higher maternal age represents a proven risk factor for the development of congenital abnormalities. (13)

3. Classification

Congenital heart diseases can be classified according to different parameters including anatomical and physiological characteristics, severity, survival rate and treatment options. Following natural history, categories can be divided as follows: (14)

Category	**Implications for survival and treatment**	**Examples**
Critical CHD	Incompatible with survival without specific intervention in newborn period or early infancy	Transposition of the great arteries (TGA). Obstructed total anomalous pulmonary venous connection (TAPVC). Duct-dependent pulmonary or systemic circulation.
Major CHD	Intervention is required, often in early infancy, for an optimal long-term outcome	Tetralogy of Fallot (TOF). Double Outlet Right Ventricle (DORV). Large VSD and PDA. Atrioventricular Septal Defect (AVSD). Truncus arteriosus. Single ventricle physiology.

		Severe outflow tract obstructions.
CHD that typically manifests at an older age	Diagnosis is seldom made in early childhood; intervention required to prevent long-term sequelae in adulthood	Moderate or large ASD. Moderate aortic and pulmonary valve stenosis. Some forms of coarctation.
Minor CHD	Long-term, symptom-free survival can be expected without any specific intervention in most cases	Small left-to-right shunts (ASD, VSD, PDA). Bicommissural aortic valve.

Table 1 - Broad Categories of Congenital Heart Disease, classified according to Natural History (12)

In addition, based on the underlying anatomy and hemodynamic impact, categories of severity can also be divided into: (9)

1. Severe CHD
    a. Cyanotic heart disease:
        i. D-TGA.
        ii. TOF including pulmonary atresia and absent pulmonary valve.
        iii. Hypoplastic right heart.
        iv. Hypoplastic left heart (HLHS).
        v. Single Ventricle (SV).
        vi. DORV.
        vii. Truncus arteriosus.
        viii. Total anomalous pulmonary venous connection.
        ix. Critical Pulmonary Stenosis (PS).
        x. Miscellaneous uncommon lesions.
    b. Acyanotic lesions:
        i. AVSD.
        ii. Large VSD.

iii. Large PDA.
iv. Critical Coarctation of the aorta.
v. Severe PS.
vi. Critical or severe aortic stenosis (AS).

2. Moderate CHD:
    a. Mild or moderate AS or aortic incompetence.
    b. Moderate PS or incompetence.
    c. Non-critical Coarctation of the aorta.
    d. Large ASD.
    e. Complex forms of VSD.
3. Mild CHD:
    a. Small VSD.
    b. Small PDA.
    c. Mild PS.
    d. Small or spontaneously closed ASD.
    e. Bicuspid aortic valve without AS or aortic incompetence.

4. Pathophysiology

When understanding congenital heart disease, it is helpful to evaluate the presence of a shunt between arterial and venous blood, the manifestation of cyanosis and circulation's variation after birth.(6)

4.1. Circulation during fetal life

Fetal circulation is markedly different from adult circulation, reflecting the unique physiological circumstances needed for the growing fetus. Blood and nutrients are exchanged through fetal-placental circulation. Oxygenated blood is directed from branches of the maternal uterine artery to the placental space. Here, thanks to concentration gradient, it is brought to multiple villi, located on the fetal side of the placenta. These villi contain capillaries that unite to form the umbilical vein, a vessel that delivers oxygen and nourishment to the fetus. After its distribution to the fetus, deoxygenated fetal blood and waste products are carried to the mother through the two umbilical arteries. (15)

Moreover, during pregnancy, when the lungs and the liver are not functioning yet, the fetal circulation is organized with shunts, managing to bypass the two organs.

The first important structure is the ductus venosus. This represents one of the two branches (ductus venosus and portal sinus) of the umbilical vein, which divides itself after entering the fetal umbilicus. While the portal sinus carries oxygenated blood to the liver, the role of the ductus venosus is to bypass this organ and deliver oxygenated blood directly into the inferior vena cava (IVC). This latter vein therefore receives a major oxygenated blood supply from the ductus venosus, mixed with a minor amount of deoxygenated blood from the hepatic vein (which drained deoxygenated blood from the liver). Therefore, the right atrium is reached both by the blood carried from the IVC and by the poorly oxygenated blood collected from the superior structures of the fetus by the superior vena cava (SVC). At this point, in the right atrium, based on the oxygen saturation, the blood flows follow different paths.

In particular, the less-oxygenated blood from the hepatic vein and SVC flows on the lateral side of the chamber into the right ventricle. Subsequently, via pulmonary arteries, a minor percentage of the right ventricle output reaches the lungs, while the remaining flow is shunted to the descending aorta, through the ductus arteriosus (the second physiological shunt between the pulmonary artery and aorta). This guarantees 60% oxygen saturation in the blood destined to the abdominal organs and lower body.

Instead, the well-oxygenated blood from the ductus venosus courses mainly in the medial part of the right atrium where the foramen ovale is located. Through this communication, better oxygenated blood is directed from the ductus venosus to the right atrium first and to the left atrium secondly, in a right-to-left shunt. This blood mixes with a minimal quantity of blood from the pulmonary veins and heads then to the left ventricle and the ascending aorta, giving supply to the carotid and coronary arteries. From the moment that this source of blood gathers the better oxygenated one, brain and heart receive blood with oxygen saturation of approximately 65%, higher percentage than the one measured in post ductal aorta. (16)

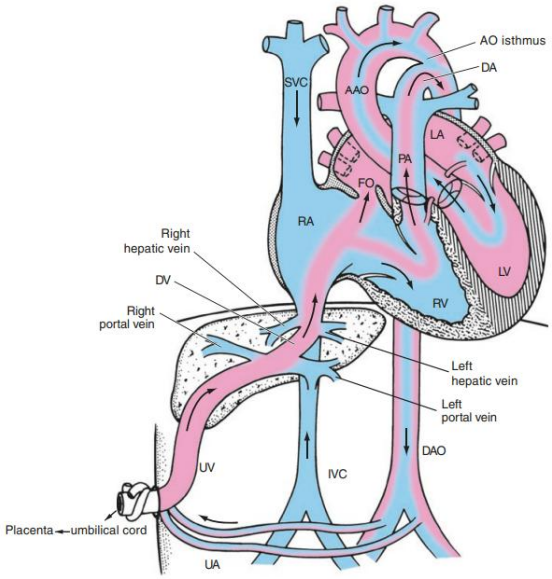

Figure 3 - Fetal circulation (17)

4.2. Circulation after birth

After birth, adaptation to extra-uterine life is necessary and fetal circulation undergoes a rapid transition, led by two major factors: the stop in placental blood flow and the beginning of respiration. When the umbilical cord is cut, systemic vascular resistance rises and the blood flow in the umbilical vein decreases, leading to the closure of the ductus venosus. In synergy, the lung expansion and consequent increase of alveolar oxygen tension leads to a vasodilatation of the pulmonary artery and pulmonary vascular system, with reduction in its resistance. In this way, lung perfusion is guaranteed and continuously increased through protracted pulmonary arterioles maturation in the following days, up to 8 weeks. This process can be hindered by CHD causing inadequate oxygenation, bringing persistent pulmonary hypertension.

Furthermore, the obliteration of the ductus arteriosus is allowed by the contribution of many factors such as adequate oxygen tension, prostaglandin E2 levels, acidosis and newborn's maturity. The closure happens primarily around 48 hours after birth, when medial smooth muscle constrict and secondarily, with enduring modifications in the endothelium and subintimal layers. (6)

Because of the increase in pulmonary blood flow, the left atrial pressure increases and the septum primum is forced against the septum secundum, initiating the process of fusion of the two layers and closure of the foramen ovale. (16)

4.3. Intracardiac shunts

A shunt is an irregular communication among two cardiac chambers or vessels that occur from derangements in the heart's development in embryologic age, mainly in the first trimester of pregnancy. (18) The result is a deviation of blood from high pressure chambers to low pressure ones. The direction is therefore dependent on pressure gradient and can be described as left-to-right, right-to-left or bidirectional. (6) Furthermore, intracardiac shunts can be divided into two major categories, cyanotic and acyanotic, based on the existing impairment in oxygenation by the pulmonary system or not.

Since the heart's left chambers have higher pressures, in left-to-right shunts, additional oxygenated blood is sent into the lungs, therefore these lesions are defined as acyanotic. Defects in incomplete separation of right and left-sided structures, such as ASD, VSD and PDA are representative for this group of pathologies. As previously mentioned, these are among the most frequent CHDs and small defects can close independently with time. Acyanotic defects are often asymptomatic at an early age but can manifest in time with dyspnea, exercise intolerance and easy fatigability. These symptoms are a consequence of the protracted blood overload of the right chambers, which causes increased pulmonary artery pressure and pulmonary vascular resistance, leading to pulmonary hypertension and, later, to pulmonary vascular obstructive disease. When pulmonary hypertension increases, to the point that it approaches or exceeds systemic vascular resistance, the shunt reverses in right-to-left, in a cyanotic condition known as Eisenmenger syndrome.

On the other hand, cyanotic shunts describe the disorders where an anatomic defect obstructs deoxygenated blood from reaching the lungs, leading to low partial oxygen's pressure in arterial circulation. Because of the poor oxygen supply, these defects manifest generally early after birth with cyanosis, dyspnea, poor weight gain, clubbing of fingers and toenails and recurrent infections. Furthermore, higher morbidity and mortality rates are registered within this group. (18)

5. Diagnosis

The International Society of Ultrasound in Obstetrics and Gynecology's (ISUOG) 2023 guidelines suggest that cardiac examination is to be performed as screening method between 18- and 22-week's gestation, or in the first trimester for high-risk pregnancies. Prenatal diagnosis of CHDs can improve birth and long-term neurodevelopmental outcomes and allows organization and preparation for specialized care afterbirth. Nevertheless, early detection permits appropriately timed counseling and parental education. (19)

5.1. Cardiac examination

The cardiac screening examination includes the study of the fetal situs and the four-chamber, outflow-tract and great-vessel views.

5.1.1 Situs

The first step in the ultrasonographic evaluation of the fetal heart is assessing the visceral situs. The laterality of organs is obtained at the level of the standard abdominal circumference measurement with the stomach on the left side and cross-sectional views of the descending aorta and inferior vena cava respectively on the left and right side of the spine. (19) Situs solitus refers to normal arrangement while situs inversus is characterized by mirror-image arrangement of organs. A third outcome, situs ambiguous, or heterotaxy, is complicated by complex congenital heart disease, anomalous venous drainage, bowel malrotation and abnormal bronchial, splenic and biliary tree.

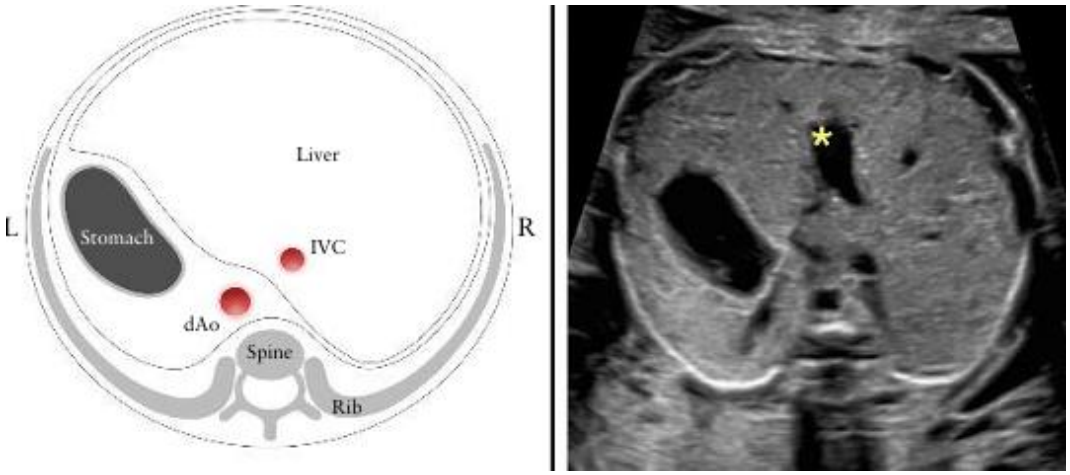

Figure 4 - Situs solitus: schematic diagram and corresponding grayscale (20)

5.1.2. Four-chamber view

The four-chamber view is possible from a transverse position of the fetal abdomen and requires the following anatomic markers: one complete rib on each side of the fetal lateral chest wall, two inferior pulmonary veins along the posterior wall of the left atrium and the heart's apex.

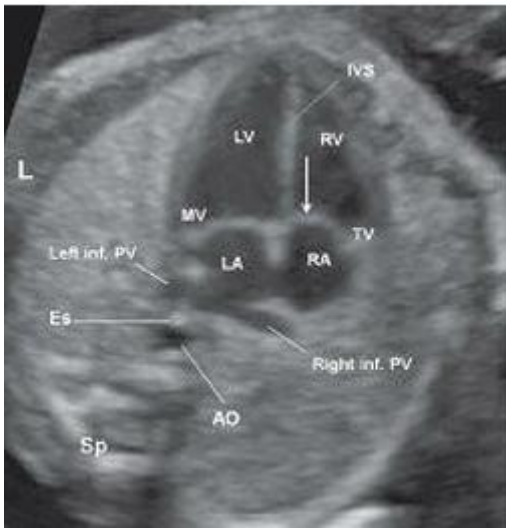

Figure 5 - Apical four-chamber view of the fetal heart: right atrium (RA), left atrium (LA), right ventricle (RV), left ventricle (LV) and interventricular septum (IVS). (20)

This projection is useful to highlight the inlet of the heart and the cardiac axis, where abnormal axis increases the risk of malformation, especially involving outflow tracts. (19)

5.1.3. Outflow-tract, three-vessel and three-vessel-and-trachea views

The cardiac screening examination is completed by the investigation of the right and left outflow-tract (RVOT, LVOT) and the three-vessel (3VV-pulmonary artery, aorta, superior vena cava) and three-vessel-and-trachea (3VTV) view on grayscale.

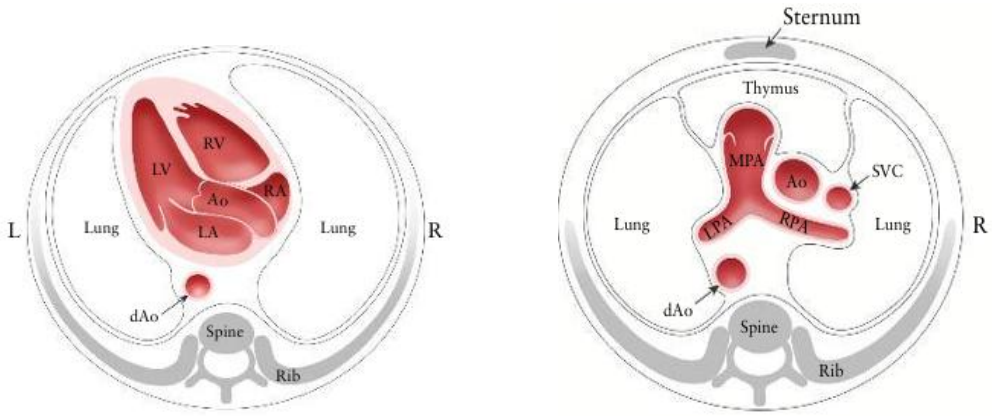

Figure 6 - Schematic diagram of LVOT and RVOT (guidelines ISUOG)

Color Doppler, which allows a more specific description of the aortic arch and systemic veins, is also performed. These projections allow us to identify the anatomy of the two great arteries and their connection to the corresponding ventricle, their size and position and the functional opening of the semilunar valves. Normality is ascertained when, in a regular LVOT, the first great artery exits from the left ventricle and its anterior wall is in continuation with the ventricular septum. On the right side, the pulmonary artery, that exits the RV, is recognized thanks to its bifurcation. These two great vessels should then cross each other in the normal 'crossover'. (19)

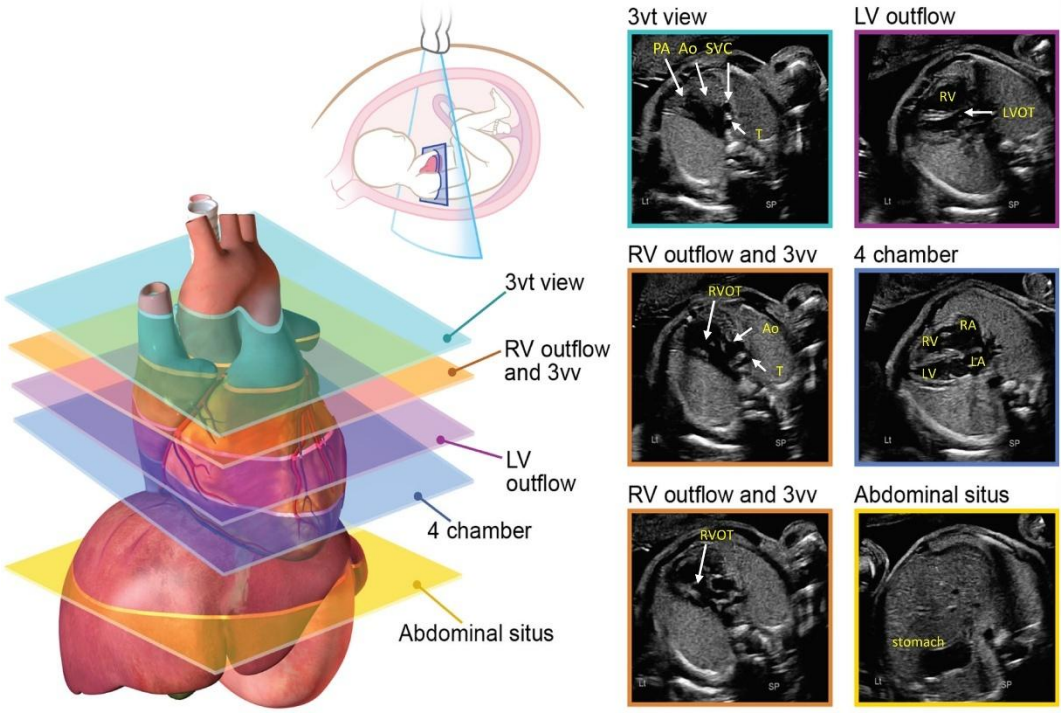

Figure 7 - Axial planes suggested for screening during echocardiography. Source: Journal of the American Society of Echocardography

5.2. Fetal echocardiography

Fetal echocardiography is performed in fetus with suspected abnormality in routine cardiac ultrasound and those presenting high risk factors for CHD. Conditions that present indication to further investigation can be distinguished in fetal or patient factors. The first include: nuchal translucency ≥ 3.5 mm; hydrops fetalis, persistent fetal tachycardia (≥ 180 bpm) or bradycardia (≤110 bpm), frequent episodes or persistently irregular cardiac rhythm, confirmed or suspected genetic abnormality and monochorionic twinning.(19) Early investigation is suggested also in presence

of reverse flow in the ductus venosus or the detection of tricuspid and mitral regurgitation in early screening. (20)

Further indications to echocardiography include patient and familiar disease or environmental exposure such as first-degree relatives with CHD; pregestational and gestational diabetes, Anti-Ro/SSA antibodies, phenylketonuria, retinoid exposure and confirmed fetal infection (TORCH and Parvovirus-B19) and conception by in vitro fertilization (IVF), including Intracytoplasmic Sperm Injection (ICSI). (19)

5.3. Evaluation of first-trimester ultrasound screening

The performance of a potential standardized first-trimester ultrasound screening strategy was assessed in early 2025 by a large retrospective single-center study, involving 74 839 mixed-risk pregnancies from 2015 to 2023, conducted at the Maternal and Child Healthcare Hospital of Guangxi Zhuang, China. Fetus with ultrasound markers suggesting CHD in first trimester (nuchal translucency (NT) thickening, reversed a-wave in the ductus venosus, tricuspid regurgitation, extracardiac abnormalities, fetal edema and chromosomal abnormalities), underwent first-semester ultrasound cardiac screening. On the other hand, fetus with normal ultrasound results at 11 + 0 to 13 + 6 weeks' gestation underwent mid-trimester screening at 20–24 weeks. Based on this study, the detection rate of CHD in the first trimester was 70.52% (586/831), with a sensitivity of 70.52%, specificity measuring 99.99% and false-positive rate and false-negative rate respectively of 0.01% and 29.48%. (21)

This data, along with evidence from other retrospective studies, for example those conducted by Helmbæk et al.(22), highlights how first-trimester screening could be standardized in the future to spot CHDs earlier in gestational age, it being advantageous in time for prenatal consultation and decision-making, reducing complications caused by these procedures at advanced gestational age. (21)

However, as reported in the ISUOG guidelines, first-trimester ultrasound screening for CHD should not replace the echocardiographic views used in the second trimester. This is because many structures in primitive views are limited by the small size of the heart, especially on grayscale ultrasound imaging and because the spectrum of cardiac defects encountered in early gestation differs from the one in the second and third trimester (VSD, valve stenosis,…). (19) A further disadvantage is that early echocardiography requires a skilled and experienced operator and may

be time consuming if the transabdominal approach shall be combined with the transvaginal one, mainly due to the incomplete development of the anatomical structures.

Potential false-positive diagnoses in early gestational age include VSD due to Doppler artifacts, irregular ventricular size in tricuspid regurgitation which may resolve autonomously in the second trimester, and ASD in fetus with left superior vena cava and dilated coronary sinus.

On the other hand, false negative may occur in TOF with mild stenosis of the pulmonary valve, TGA, ASD, VSD, HLHS and anomalies of the aortic arch. (20)

5.4. Effects of CHD diagnosis on parents

Diagnosis of CHD during pregnancy exposes expectant parents to emotional, psychological and financial stressor.

Mental health problems are referred as the most frequent complication of pregnancy, involving up to 22% of expectant women in physiological pregnancy and almost double the incidence in high-risk ones. (23–25) Complications associated with prenatal psychological distress include pre-eclampsia, spontaneous abortion, preterm delivery, lower birth weight and neurodevelopmental problems. A recent longitudinal case-control study conducted by Yao Wu et co. on 140 fetuses studied the connection between psychological distress in pregnant and impaired fetal cerebellar, cortical, amygdale and hippocampal development. (26)

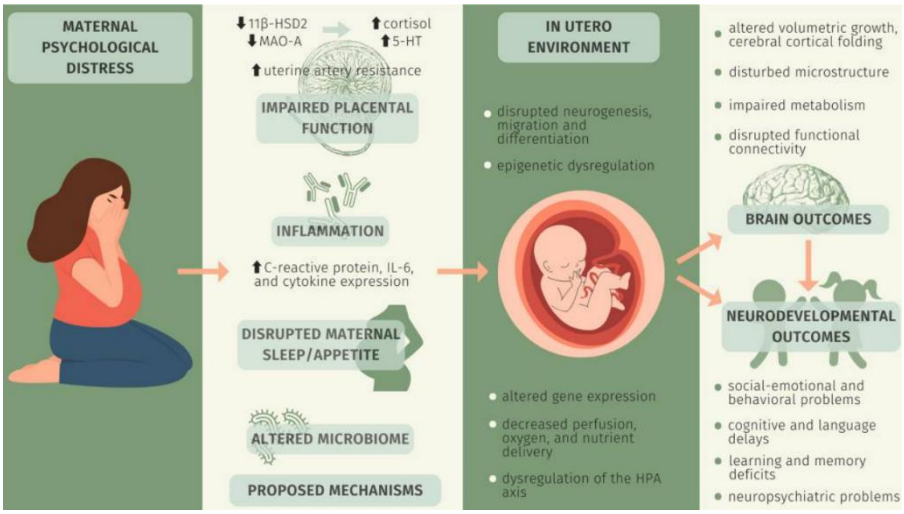

Figure 8 - Brain and neurobehavior developmental outcomes of prenatal maternal psychological distress and possible mechanism (24).

These findings suggested that psychological distress among women carrying fetuses with CHD is prevalent and underline the importance of universal screening for maternal psychological distress, integrated prenatal mental health support, and targeted early cognitive-behavioral interventions given that stress is a potentially modifiable risk factor in this high-risk population. (26)

6. Severe CHD

Here follows a description of the most frequent congenital heart diseases that have been encountered in this study.

6.1. Hypoplastic left heart syndrome (HLHS)

Hypoplastic heart syndrome (HLHS) is a rare spectrum of complex malformations characterized by an underdevelopment of left-sided cardiac structures (left ventricle, aorta, aortic arch) along with mitral atresia or stenosis. The mitral and aortic valve can present stenosis or atresia in different combinations, and an ASD is required to survive.

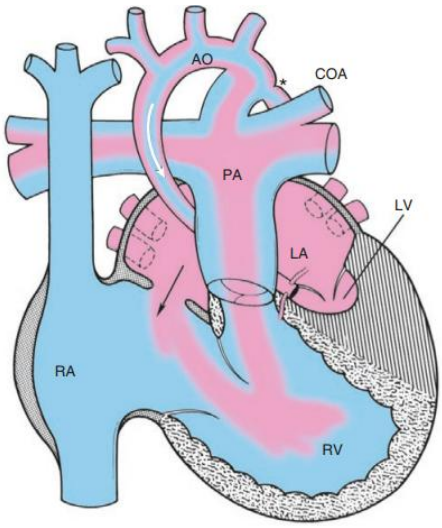

Figure 9 – HLHS: ascending aorta, aortic arch, and LV extremely hypoplastic (17)

Considering the incidence rate of 0.1-0.25/1000 live births, more prevalent in males, and termination of pregnancy rate 12-48% (27), HLHS accounts for 3.8% of all congenital heart disease and is one of the most frequently diagnosed congenital malformation in utero. (20)

The prenatal diagnosis of HLHS is characterized by a markedly small and hypokinetic left ventricle. This underdeveloped chamber appears typically globular and may present a bright echogenic inner wall of endocardial fibroelastosis. The

left atrium presents smaller dimensions than the right ventricle with a paradoxal movement of the leaflet of the Foramen ovale from the left to the right atrium, leaving space for a left-to-right shunt across it. The left ventricle hypo-functionality is confirmed by the minimal to absent filling at the color Doppler. This technique in a 3-VTV view shows flow across the aortic isthmus and transverse aortic arch, while in the longitudinal view it highlights a retrograde flow from the pulmonary artery to the aortic root through the ductus arteriosus.(20)

While HLHS is compatible with intrauterine life due to the right ventricle's compensation through the ductus arteriosus; after birth, death occurs in 70% of cases within the first week if left untreated. (28) If the ductus arteriosus is not kept patent through intravenous prostaglandin E1 infusion, a critically impaired systemic circulation will present, leading to early respiratory symptoms: respiratory distress, tachypnea and mild cyanosis which can evolve in shock and severe cyanosis. For this reason, early prenatal diagnosis is crucial to guarantee the best treatment therapy for the newborn.

The surgical approach consists in three consecutive operations: Norwood, Glenn and Fontain procedures. Firstly, the Norwood procedure connects the aorta to the main pulmonary artery with the aim of paving an unobstructed way for the systemic blood flow from the right ventricle to the aorta. (29) An atrial septectomy is made to secure good atrial communication, to allow pulmonary venous return to reach the right ventricle. By the end, the right ventricle is the main pumping chamber, and the two circulation systems are in parallel. A hybrid procedure can be preferred in patients with extracardiac risk factors: a stent in the ductus arteriosus guarantees systemic perfusion, a surgical or balloon atrial septostomy maintains the pulmonary venous return and pulmonary artery bands are performed to control the pulmonary blood flow.

At 4-6 months, a second operation is conducted to unload the right ventricle and limit the exposure of pulmonary vessels to systemic pressure, either with the bidirectional Glenn or the hemi-Fontan procedure. The superior vena cava is separated from the right atrium and connected to the pulmonary artery to direct deoxygenated blood to the lungs.

Finally, between 1 and 2 years of age, a total cava - pulmonary connection is made through the linking of the inferior vena cava to the right pulmonary artery. (30)

6.2. Tetralogy of Fallot (TOF)

The tetralogy of Fallot is caused by an anterior and cephalad displacement of the conal or infundibular septum that leads to a right ventricular outflow tract obstruction (RVOTO). (31) As suggested by the name, it presents four anatomic features: anteriorly misaligned VSD, pulmonary stenosis (subvalvar, valvar, supravalvar), aorta's root overriding the VSD and right ventricle hypertrophy (RVH). (20) The pulmonary valve annulus is variably hypoplastic, usually bicuspid and within the TOF spectrum severe forms can be found: TOF with absent pulmonary valve or TOF with pulmonary atresia. (31)

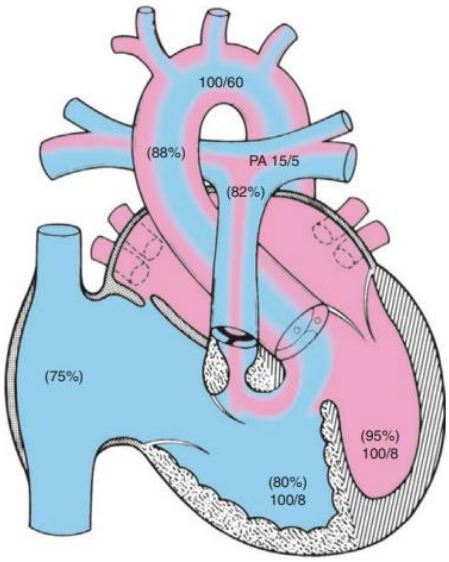

Figure 10 - TOF with a large VSD, almost normally sized pulmonary artery (PA), overriding aorta, and RVH. Pressures in RV and LV are the same. Aortic saturation is lower than normal (17)

TOF is generally detected in the five-chamber view which gives evidence of the perimembranous subaortic VSD and overriding of the aortic root, which dilates itself because of receiving blood from both the RV and LV. These anatomical modifications are confirmed by the color Doppler at the 3-VTV which sees the blood shunting across the VSD and blood draining from both ventricles in the aorta.(20)

6.2.1. TOF with pulmonary stenosis

It is the most frequent cyanotic congenital cardiac malformation presenting 5-8% of incidence. (32) The direct cause is unknown but marked association with DiGeorge syndrome (22q11.2 deletion) is proven. (31) The pulmonary stenosis occurs due to annular hypoplasia combined with thickened and dysplastic valve leaflets.

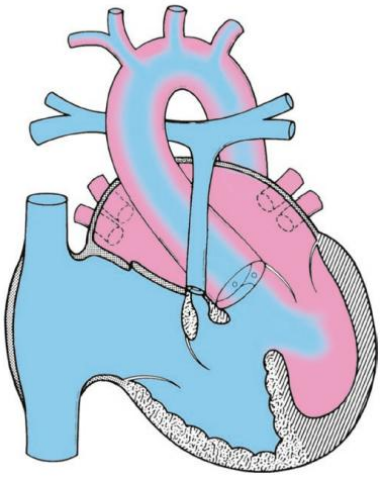

Figure 11 – TOF with pulmonary stenosis (17)

Cyanosis is the main feature, but its severity varies based on the degree of RVOTO. For mild obstruction, the VSD guarantees a left-to-right shunt that allows lung perfusion and no cyanosis verifies. Instead, in severe degrees of obstruction, blood flows from the right to the left ventricle leading to evident cyanosis. In the first months of life, adrenergic stimulus such as crying or decreases in systemic vascular resistance can trigger infundibular muscle spasm, enhancing the right-to-left shunt and causing cyanosis crises. If neurological compromise shall occur, the phenomenon is called cyanotic spells. (33) In asymptomatic or stable patients, an elective correction is made at 3-6 months of age. Surgical treatment includes the closure of mal-aligned VSD and relief of RVOTO. For this latter aim, the dimensions of the pulmonary valve and annulus are crucial. If dimensions are adequate, a valve sparing repair technique (VSR) is preferred: via trans atrial, transpulmonary approach the pulmonary valve is repaired with commissurotomies and delamination of leaflets. Nevertheless, the transannular patch approach (TAP) remains the most frequent RVOTO enlargement technique: an incision from the main pulmonary artery to the infundibular area is performed together with right ventricle muscle bundles excision. Subsequently, the infundibular area is

approached, the pulmonary valve leaflets are partially or fully removed and patch material is used up to the bifurcation of the pulmonary artery to expand the RVOT. (34) (35)

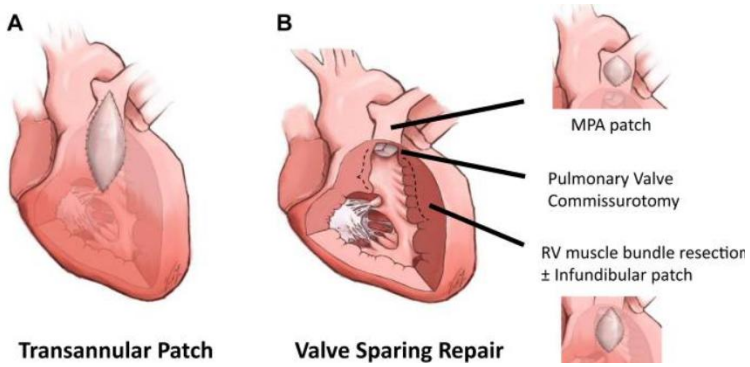

Figure 12 - Options for RVOTO relief in surgical treatment (34)

6.2.2. TOF with pulmonary atresia and VSD

Pulmonary atresia with VSD (PAVSD) is characterized by extreme deviation of conal septum and severe hypoplasia of subpulmonary infundibulum. It results in no right ventricular outflow and complete dependence of the pulmonary circulation on the systemic arterial circulation. Lung perfusion, and with it blood oxygenation, is possible through the ductus arteriosus and collateral arteries from the descending aorta to the lungs (MAPCA). (20)

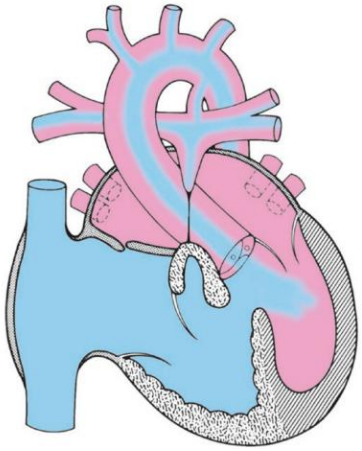

Figure 13 - Pulmonary atresia with VSD (PAVSD)(17)

This heart abnormality is well detected on the LVOT-view, which shows the VSD with a large overriding aorta, while the three-vessel view gives evidence of the main pulmonary artery's absence. The color Doppler confirms missing blood draining from the RV into the pulmonary trunk, retrograde filling of the right and left pulmonary arteries as well as the reverse flow in the tortuous ductus arteriosus.

Lower Doppler velocity give evidence of MAPCAs, arising from the descending aorta. (19)

PAVSD repairment involves ventricular septation and a valved right ventricular-pulmonary artery conduit. (31) Furthermore, MAPCA can be connected to either the RV-PA conduit or a central shunt with the aim of increasing the pulmonary flow. A staged repair strategy may be undertaken if the pulmonary arteries are severely underdeveloped. (33)

6.2.3. TOF with absent pulmonary valve

In the rare malformation of absent pulmonary valve syndrome (APVS), pulmonary valve leaflets are absent, dysplastic or rudimental. This leads to the valve's insufficiency and consequent overload of the right ventricle and pulmonary artery dilatation with possible tracheobronchial compression and bronchomalacia.

A dilatated RV is evident in the four-chamber view of echocardiography, while the five-chamber view reveals the VSD with the overriding aorta, which doesn't present a dilated root (differential diagnosis with the classic form of TOF). Furthermore, from a short-axis or 3-VTV view, a massive dilatation of the right and left pulmonary arteries can be seen. (20)

Within a mild dilatation of the pulmonary vessel APVS presents with growth retardation and frequent respiratory infection, while severe dilatation causes respiratory failure. (36) The goal of surgical treatment is first TOF's correction and secondly airway decompression. The latter aim is achieved by plication and reduction of the anterior and posterior wall of the pulmonary artery or by replacing the aneurysmatic vessels with homograft or direct reconstruction. In alternative, the pulmonary vessel can be translocated anterior to the aorta and away from the trachea and the bronchial tree, in the so called LeCompte maneuver. (37)

6.3. Transposition of the great arteries (TGA)

Transposition of the great arteries is a congenital heart disease characterized by atrioventricular concordance and ventriculoarterial discordance: the pulmonary artery arises from the LV, the aorta from the RV and the two circulations run in parallel. The total incidence is 5-7% (20-30/100.000 live births), and the most common form is dextro-TGA (d-TGA) which sees the aortic valve to the right of the pulmonary valve. By contrast, in congenitally corrected transposition (ccTGA), both atrioventricular and ventriculoarterial discordance are present and the aortic

valve is generally anterior and to the left of the pulmonary valve (L-transposition). Furthermore, VSD and left ventricular outflow tract obstruction are frequently common.

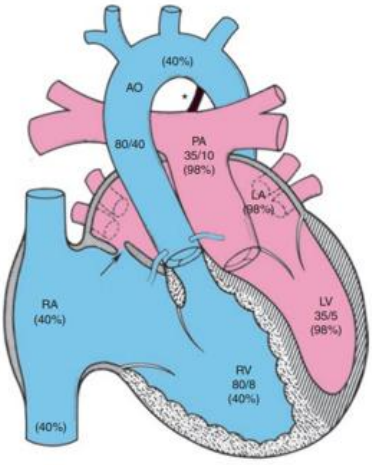

Figure 14 - Complete TGA with intact ventricular septum (17)

Prenatal diagnosis of TGA is possible with a five-chamber view by following the great vessel originating from the LV and noticing its bifurcation, characteristic for the pulmonary artery. The aorta is noted to arise from the RV in an anterior and parallel course to the former vessel. This orientation reflects on the 3-VTV which sees the aorta positioned anteriorly and superiorly to the pulmonary artery. (20) (17)

In TGA anatomic setting, life is only possible in the presence of communication among the circulatory systems, via PDA or interatrial shunt. Because of this parallel circulation, oxygenation of the blood is markedly insufficient leading to a significant hypoxemic status and cyanosis manifestation. However, the clinic can be milder with cyanosis triggered by stress such as by crying or agitation. This is the case of a large VSD and no obstructive lesions which allow adequate mixing of blood flow. Yet following excessive ventricular workload can manifest with congestive heart failure signs: tachypnea, tachycardia, diaphoresis and poor weight gain up to hepatomegaly later during infancy.

The initial management includes intravenous prostaglandin E1 infusion to keep the ductus arteriosus patent and eventual pre-operative support of balloon atrial septostomy (Rashkind procedure) if the interatrial communication is to be expanded. Subsequently, physiological and anatomical repair is possible through the arterial switch operation. Within the first month of life both aorta and pulmonary trunks are transposed and anastomosed at their distal extremities and coronary

arteries are translocated to the neo-aorta. If intact ventricular septum is present at birth, operation should be anticipated within 14 days of life due to the complications deriving from the lack of mixing blood flow. (38)

6.4. Coarctation of the aorta (CoA)

Coarctation of the aorta (CoA) is defined as a narrowing of the aorta, which can be divided into juxtaductal coarctation, if located in the aortic isthmus, or diffuse aortic arch hypoplasia, if the aortic arch is widely involved. Most commonly the aorta constricts at the site of the ductus arteriosus suggesting that the coarctation is a result of an extension of the ductus's closure. This fetus' shunt structure presents a different tunic organization in comparison to the pulmonary artery and descending aorta. In particular, the media is arranged with longitudinally and spirally smooth muscles fibers and the intima presents intraluminal intimal cushions which guarantee its contraction and functional closure after birth. CoA might therefore be a consequence of abnormal tissue ingrowth from the ductus arteriosus into the aorta.

This congenital heart disease occurs in 5-7% heart malformations and is frequently associated with bicuspid aortic valve (50% of cases), VSD, aberrant right subclavian artery and Turner syndrome. (39)

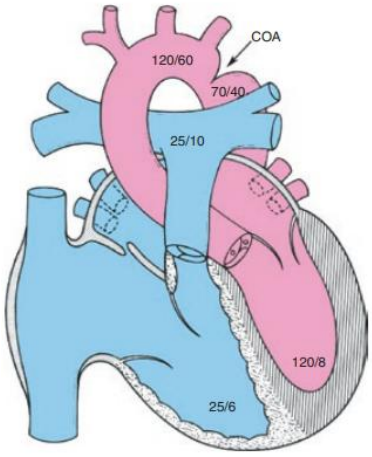

Figure 15 - Coarctation of the Aorta (17)

Coarctation of the aorta behaves as an obstruction to the physiological blood flow leading to significantly increased afterload of the LV, which results in ventricular hypertrophy and hypertension, especially in the upper extremities. Clinically, this critical and sudden narrowing in newborns leads to LV dysfunction, systemic hypoperfusion and rapidly to congestive heart failure. In less severe cases, CoA manifests as upper extremity hypertension with long term complications such as coronary artery disease, aortic aneurysm and cerebrovascular events. (39)

This aorta's abnormality is often associated with disproportion of the LV compared to the RV, evident at the four-chamber view. Thus being, the LV maintains its contractility, the mitral valve is patent and applying color Doppler to this view, normal ventricular filling is seen, allowing the differential diagnosis with HLSH. Further evidence is given in the 3-VTV where a narrowed diameter of the aortic arch can be measured, resulting in a great vessel disproportion as well as the ventricular one. (20)

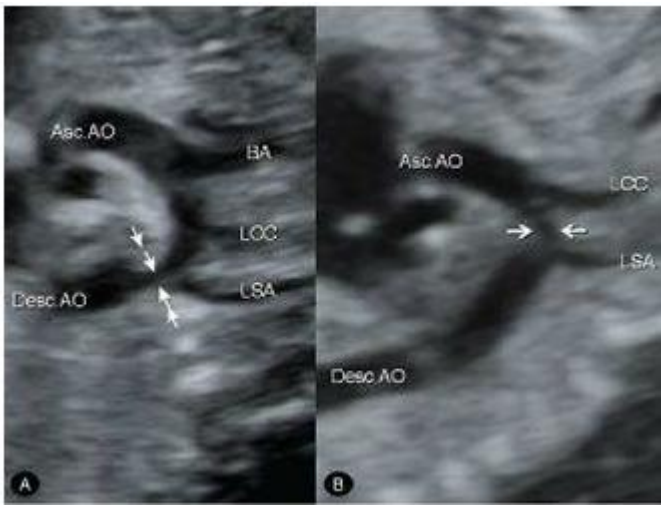

Figure 16 - Sagittal views of the aortic arch with coarctation. (20)

Surgical treatment is necessary to restore the normal blood flow. If acute shock signs are present, initial stabilization with prostaglandin E1 infusion is began and diuretics can be useful for congestion. Operative treatment includes PDA ligation, resection of the coarctation and arch reconstruction. As for the latter step, several surgical techniques have been developed. In juxtaductal coarctation, the arch repairment can be done through an end-to-end or an extended end-to-end anastomosis (when both the inferior wall of the arch and the lateral wall of the descending aorta are incised), with the second option being associated with a lower risk of re-coarctation (4-13% vs. 41-51%). Instead, if the narrowing is diffused along the arch, a longitudinal incision and subsequent patch aortoplasty is preferred. Moreover, older patients can be treated with an interposition graft technique, which replaces the coarcted segment with a Dacron tube graft or aortic homograft, or less invasive approaches such as balloon angioplasty or stent placement via percutaneous catheter. (39)

Although these surgical techniques are specific for the grade of extension of the malformation, extracorporeal circulation is commonly used. This support can as

well present differences in cannulation technique among hospitals and equipes. In Padua, aortic arch surgery is led during selective vital organs perfusions. In particular, the ascending aorta is clamped distally to the coronary arteries which receive blood perfusion from the first cannula. Subsequently, the brachiocephalic trunk is cannulated while the left common carotid artery and the left subclavian artery are clamped. Ongoing studies are evaluating whether this selective perfusion approach might be advantageous for surgery's outcomes. (39)

6.5. Interruption of the aortic arch (IAA)

Interruption of the aortic arch is a malformation characterized by the absence of continuity between the aortic arch and the descending aorta. This aortic defect can be classified into three types based on the position of the interruption:

- Type A: distal to the origin of the left subclavian artery.
- Type B: between left common carotid and left subclavian artery. This is the most common type (55% of IAA cases).
- Type C: between the brachiocephalic and left common carotid artery.

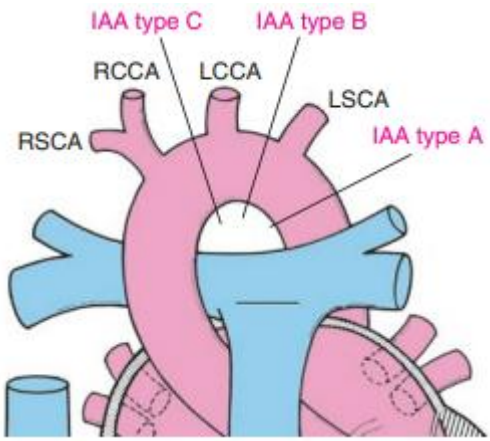

Figure 17 - Classification of IAA (17)

IAA is a rare cardiac malformation that occurs in 1% of CHD and is often associated with other abnormalities such as posterior malalignment VSD, bicuspid aortic valve, PDA and syndromes like DiGeorge or PHACE. (33,40)

Conversely to coarctation of the aorta, where ventricular size disproportion is evident, here the LV size is conserved, especially on IAA type B and when the VSD is large. Furthermore, the longitudinal view doesn't give evidence of the

normal arch's curvature. The VSD is confirmed by the color Doppler in four and five-chamber views. (20)

IAA has systemic ductal dependence since during fetal circulation the ductus arteriosus guarantees the only blood supply to the distal extremities. After its closure, a systemic malperfusion occurs and manifests with differential cyanosis and blood pressure among the upper and lower extremities, which lead to acidosis and multi-organ failure, along with tachypnea and poor feeding manifestation.

For this reason, prostaglandin E1 infusion is necessary as a bridge to surgical treatment, with the objective of forming an unobstructed continuity between the ascending and descending aorta and repairing associated defects, such as VSD. (41) The arch's reconstruction follows the techniques previously described for CoA with possibility of performing and end-to-end or end-to-side anastomosis with patch augmentation and PDA ligation and division. In cases of significant outflow tract obstruction, a staged Yasui procedure is preferred. Firstly, a Norwood operation is performed, and the aorta and pulmonary artery are reconstructed. A shunt between the two vessels is created through an end-to-side Damus-Kaye-Stansel (DKS) anastomosis. Subsequently the Rastelli procedure involves patch closure of VSD and baffling the left ventricle into the neo-aorta through the VSD. The pulmonary blood flow is guaranteed by a right ventricular-pulmonary artery valved conduit.

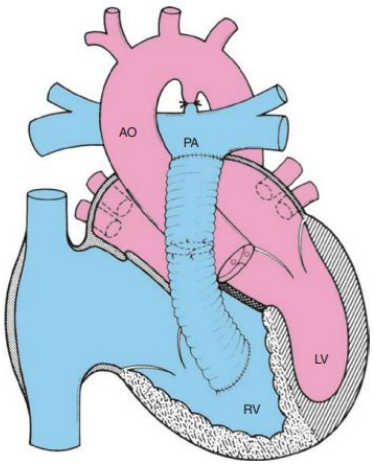

Figure 18 - Rastelli procedure outcome (18)

6.6. Atrioventricular canal defect (AVSD)

Atrioventricular canal, or atrioventricular septal defect (AVSD), defines different degrees of malformations of the atrioventricular (AV) septum and atrioventricular valve. Partial AVSD presents primum ASD with partitioned AV valves and a cleft in the anterior mitral valve leaflet. The transitional AVSD is characterized by a large primum ASD, small inlet VSD and two sperate AV valve orifices and leaflets. On the other hand, severe forms present as complete AVSD with a common AV valve orifice, primum ASD and inlet VSD. Intermediate AVSD instead, presents as a form of complete AVSD with both ASD and VSD, a common AV valve orifice but with two separate AV valves. (17)

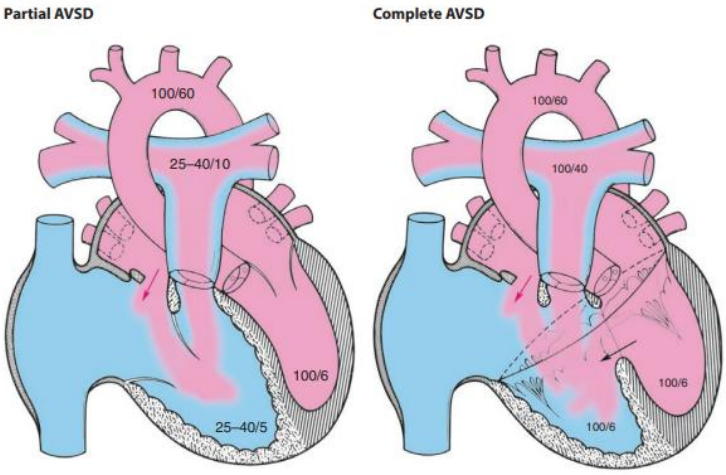

Figure 19 - partial AVSD and complete ASD (17)

AVSD is frequently associated with further anomalies such as TOF, DORV, CoA and PDA and it is estimated that in over 40% of patients with Down syndrome affected by CHD, 45-50% of cases present AVSD. Furthermore, this malformation is characteristic for 85% of right isomerism and 40% of left isomerism. (17)

Diagnosis is well documented by characteristic ultrasound findings: in diastole, the common valve is open and the chamber communication resulting from the large atrial and ventricular septal defects is evident in the center of the heart.

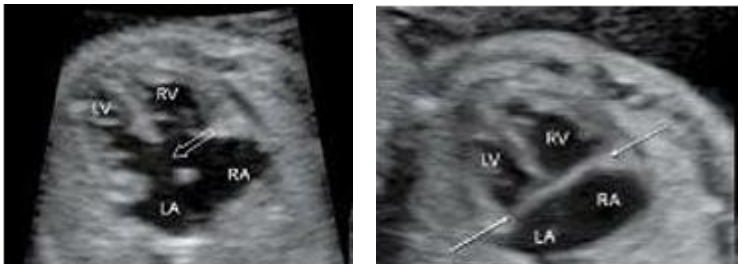

Figure 20 - Four-chamber views in diastole and systole of AVSD heart (20)

Contrarily, in systole, the valve is closed, and it appears as a linear line. In partial forms instead, just the linear AV valve and the ASD are seen. (20)

After birth, newborns may present symptoms of congestive heart failure due to the atrial left to right shunt that leads to a right heart volume overload with consequent pulmonary over circulation. In complete AVSD, the shunt is worsened by the VSD, causing severe pulmonary hypertension and early Eisenmenger reaction. Furthermore, severe AV valve regurgitation can rapidly aggravate the left to right shunt and early operation is requested.

Regarding surgery, it is indicated for all patients, with time priority to complete AVSD newborns and patients with Down syndrome, while partial AVSD can be repaired during childhood and after early infancy. Different surgical techniques are available, starting from a single patch repair technique, which consists of the division of the common valve and the closure of both atrial and ventricular communications with a single patch and reconstruction of the left and right AV valves, to the two patches technique, in which ASD and VSD are closed using two separate patches. (33)

6.7. Double outlet right ventricle (DORV)

DORV represents less than 1% of all CHDs, occurring in 0,5-1 per 10,000 live-born neonates. These malformations refer to a heterogeneous group of cardiac malformations in which the aorta and the pulmonary artery origin primarily from the morphologic right ventricle, with an aortic valve to mitral valve discontinuity. Traditional classification accords to the position of the VSD: subaortic VSD (50% of cases) where a muscular structure separates the mitral valve from the aortic one;

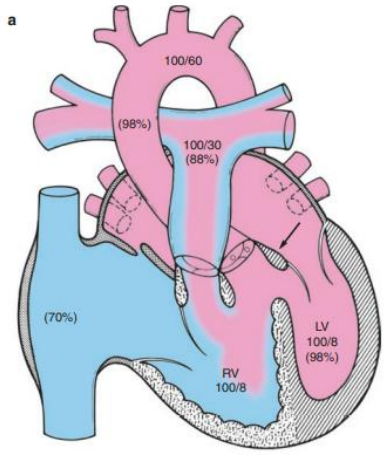

Figure 21 - DORV with subaortic VSD (17)

subpulmonary VSD (30%) in which the mitral and pulmonary valve are separated from a muscular structure; doubly committed VSD (below both great arteries); non-committed VSD (remote VSD from the great arteries). Furthermore, the location of the great arteries can be normal, aside or anterior posterior. (20,33)

Prenatal diagnosis of DORV is led by evidence of both great arteries originating from the right ventricle at the fetal echocardiography. In this circumstance further attention should be given to the pulmonary outflow tract, to examine possible combination with pulmonary stenosis, and to the presence and size of a thymus for possible deletion 22q11.2 syndrome.

The clinic differs based on the morphological presentation of the malformation. A DORV VSD-type presents a subaortic, doubly committed or non-committed VSD with no obstruction to the right ventricle outflow. Instead, if obstruction is present, it will manifest with a cyanotic clinic, and it is referred to as DORV TOF-type. Furthermore, if the subpulmonary VSD is associated to right and left ventricle obstruction, its manifestation is similar to TGA malformation. (17,20)

Regarding DORV treatment, surgery is indicated for all patients starting from 7-8 months of life or from 8-10 kg, and palliation through pulmonary artery banding or shut placement is necessary as bridge to surgery. In specific for DORV VSD-type, an intraventricular tunnel repair is performed, which connects the aorta to the left ventricle. In concern with DORV TOF-type instead, the operation consists in repairing the intraventricular tunnel, performing a right ventricle myectomy (as a solution to the RVOT) and finally in the Rastelli procedure, described above. Finally, if both ventricle outflows are obstructed, biventricular repair such as Rastelli or Nidaidoh procedures are performed, with the Nidaidoh technique allowing closure of the VSD and translocation of the great vessels.(33)

II. AIM OF THE THESIS

7. Rationale of the study

The diagnosis of a fetal cardiac abnormality is a disquieting experience for parents which relates with stress and a broad spectrum of variable emotional responses to the trauma. Adequate perinatal counseling providing clear and consistent information about the anomaly, the prognosis and possible treatments, as well as the limitations of ultrasound diagnostic, can reduce stress and uncertainty in expectant parents. Furthermore, the progress in ultrasound diagnosis and the updated cardiac screening guidelines permit early detection, which allows parents a suitable time frame to decide for continuation or termination of pregnancy.

8. Purpose of the study

This experimental study has the aim of evaluating the effects of multidisciplinary prenatal counseling in the diagnosis of fetal CHD and on the parental choice of termination of pregnancy (TOP).

III. MATERIALS AND METHODS

9. Study design

In 2023, the Obstetrics and Gynecology Division of Padua introduced an integrated clinic for newly diagnosed fetal congenital heart disease (CHD). The study consists of a single-center and retrospective analysis to investigate the effects of multidisciplinary counseling for congenital heart malformations on termination of pregnancy rates. Data was collected by reviewing patient medical records, gynecological and cardiological clinic notes, termination of pregnancy operative reports and birth reports. The information was organized into a dedicated database.

10. Study population

The gynecological and fetal cardiological visits are second level investigations addressed to women who have been detected with fetal factors or patient/familial disease or environment exposures that are associated with high risk of congenital heart disease (CHD) (specific indications from ISUOG guidelines are reported under the chapter ‘Cardiac examination’ and at the source (19)). For the purposes of this study, women that received prenatal diagnosis of CHD after the time limit established by national government for termination of pregnancy were rolled out, since TOP was not an option. Similarly, mothers with syndromic fetus, for which the choice of TOP could not have been solely due to the present CHD, were not taken into consideration.

11. Data collection

The multidisciplinary team involves an obstetrician specialized in maternal-fetal medicine, a pediatric cardiologist and a pediatric cardiothoracic surgeon. In the joint clinic session, the obstetrician first assesses the mother’s previous investigations such as blood test, excluding the development of anemia, gestational diabetes and infections, previous ultrasound sonographies and genetic tests, both non-invasive (Bi-test, cell-free fetal DNA, expanded carrier screening) and invasive ones (amniocentesis, chorionic villus sampling).

Secondly, the echocardiography, standardized as transabdominal, is performed and the heart is studied in its structure and function. Standard views and imaging plans include abdominal situs; four-chamber view, RV and LV outflow tract, 3VV, 3VT, biCaval view, long-axis view of the aortic arch, long-axis view of the ductal arch

and short axis views. Furthermore, other cardiac biometrics are investigated reporting:

- Heart rate and rhythm.
- RV and LV length in diastole.
- RV and LV volumes.
- Transverse atrial dimensions.
- Thickness of the ventricular free walls and interventricular septum in diastole.
- Cardiothoracic ratio.
- Tricuspid and mitral annulus in early diastole.
- Aortic and pulmonary annulus measured at end-diastole/early systole open or closed.
- Main pulmonary artery diameter proximal to bifurcation and branch diameters in systole.
- Ascending aorta, aortic isthmus and transverse aortic arch.

Finally, the cardiothoracic surgeon is called, and the multidisciplinary counseling is performed in a dedicated room, with an extensive time slot. Expectant parents are talked through the ultrasound appearance of the fetus heart and informed about the limitations of the diagnostic techniques currently available to physicians. To allow a better comprehension of the anatomical complexity, visual supports such as drawings and 3D-printed anatomical reconstructions are used. Thus, enabling a hands-on approach and improving overall understanding of the disease. Subsequently, expected progression in utero and after birth clinics are clarified as well as short and long-term prognosis and quality of life expectancies. Explanation includes also possible fetal intervention and postnatal treatment options. The presence of a pediatric cardiothoracic surgeon allows the parents to have a schematic and realistic view of postnatal care which the newborn will undergo. Furthermore, appropriately timed counseling before birth allows the parents to prepare and organize for the newborn's upcoming hospitalization, rather than being overwhelmed by it if the counseling should take place after birth.

Along with the discussion of physiological pregnancy's progression and the therapeutic options, termination of pregnancy is also discussed, according to the current Italian legislation, in neutral terms and without personal bias.

During the counseling, clear and simple language is used, repeatedly verifying parents' comprehension and perception of the diagnosis through repetition and replying to their questions.

To identify the effects of a multidisciplinary approach to CHD diagnosis and termination of pregnancy rates, the registry of fetal echocardiography was reviewed, confronting the data from 2022, when the multidisciplinary clinic was yet to be open, and 2023-2024, after it was introduced. For this study, an analysis of the echocardiography and number of CHDs detected was conducted and the prevalence of TOP was investigated for each specific diagnosis group.

Fetal echocardiography was classified as follows:

- Abnormal: any anatomical abnormality detected
    1. Major CHDs requiring postnatal surgical intervention in the first 6 months of life:
        - TGA.
        - TOF.
        - DORV.
        - HLHS.
        - Aortic severe abnormalities (Coarctation, severe hypoplasia).
        - AVSD.
        - Complex CHD (combination of major CHD).
    2. Minor CHD
        - VSD.
        - Other minor findings.

12. Study variables and Statistical Analysis

The independent variable is represented by the multidisciplinary clinic of which we want to investigate the effects. This categorical variable is divided into two major groups, the intervention one including the expectant parents who visited the integrated clinic in 2023 and 2024, and the control group with parents that didn't have access to the multidisciplinary clinic in 2022. Therefore, 2022 represents year 1, 2023 year 2 and 2024 year 3.

On the other hand, the outcome of the integrated clinic is measured in continuation or termination of pregnancy, and it defines the dichotomic, categorial dependent variable. In specific, value 0 is assigned to continuation of pregnancy and value 1 termination.

Furthermore, the study involves CHDs' severity as a covariate, with the aim of investigating its role in the process of decision-making among continuation or termination of pregnancy.

Since the study presents a small population, Fisher's exact test was used to evaluate the association among two categorial variables, such as multidisciplinary and non-multidisciplinary group with continuation or termination of pregnancy, and results were considered statistically significant for $p<0.05$.

To further investigate the influence of the main confounder, being CHD severity, on the termination of pregnancy trend, a Mantel-Haenszel test was performed. Data was stratified in major and minor CHDs and specific analysis was conducted to study the relationship between multidisciplinary counseling and termination of pregnancy rate. Statistical relevance was considered for $p<0.05$.

IV. RESULTS

13. Descriptive statistics

The results have been analyzed coherently with the aim of the study which is to evaluate the effects of introducing multidisciplinary prenatal counseling for congenital heart malformations. For this reason, parameters of evaluation have been divided into the year before the establishment of the multidisciplinary clinic (2022) and the years that represent the ongoing counseling method (2023-2024).

	2022	**2023**	**2024**
FE PERFORMED	595	668	683
PATIENTS	576	626	574
PATHOLOGICAL FE	84	92	100

Table 2 - Total data collected divided for each year

In 2022 a total of 595 fetal echocardiography were conducted in 576 patients and performance progressively increased in the following years, counting 668 total fetal echocardiography on 626 patients in 2023 and 683 investigations on 574 patients in 2024. The surplus in FE carried out compared to the number of patients is due to control echocardiography conducted during the pregnancy duration, personalized for each patient. Specifically, after the first diagnosis received in Padua's tertiary care center, expecting mothers from another town of residence, whose newborn wouldn't require immediate life support after birth, were referred to their local hospitals.

	2022			**2023**			**2024**		
	n	TOP	% TOP	*n*	TOP	% TOP	*n*	TOP	% TOP
Aortic Severe Abnormalities	4	0	0	7	2	28.57	11	0	0
AVSD	3	2	66.7	3	0	0	4	0	0
DORV	6	2	33.3	1	0	0	2	1	50.0
HLHS	6	3	50.0	9	4	44.4	7	5	71.4
TGA	9	1	11.1	12	1	8.3	8	3	37.5
TOF	15	1	6.7	10	1	10	6	1	16.7
Heterotaxy	0	0	0	5	3	60	3	0	0

Complex CHD	9	3	33.3	10	3	30	21	4	19.0
Minor CHD	32	3	9.4	35	0	0	38	0	0
Total major CHD	52	12	23.1	57	14	24.5	62	14	22.6
Total pathological FE	84	15	17.9	92	14	15.2	100	14	14.0

Table 3 - Incidence of pathological FE and TOP rate specified for each CHD category

In 2022, 52 major CHD were diagnosed with the highest incidence represented by TOF (15 cases), followed by complex CHD (9) and TGA (9). Among 84 expectant mothers with pathological fetal echocardiography, TOP was performed in 15 cases, (17.9%). In the following years, total FE increased and with it the number of total pathological findings: 92 in 2023 and 100 in 2024. In 2023 among the 57 major CHDs the three most frequent malformations were TGA (12); TOF (10); complex CHD (10) while in 2024, 62 major CHD were counted, with complex CHD (21), aortic severe abnormalities (11) and TGA (8) representing the highest incidence. Regarding TOP decision, overall percentages were lower both in 2023 (15.2%) and 2024 (14.0%) compared to 2022.

14. Association between variables

Investigating the relationship between CHD severity and TOP rate, resulted in a significantly higher rate of TOP for major CHDs: 40/171 (23.4%) for major CHDs and 3/105 (2.86%) for minor CHDs; $p<0.001$. (*Table 4)*

	No TOP	**TOP**
Major CHDs	131/171 (76.6%)	40/171 (23.4%)
Minor CHDs	102/105 (97.1)	3/105 (2.86%)

Table 4 - Association between CHD severity and TOP decision.

Specifically, the TOP rate was investigated over the three years registers and separately for major and minor CHD. After the introduction of the multidisciplinary clinic, a significant reduction in termination of pregnancy is evident only in the latter group, while major CHDs' TOP rate decrease is not relevant. *(Table 5)*

	2022	2023	2024	*p*-value
Major CHD	12/52 (23.1%)	14/57 (24.6%)	14/62 (22.6%)	0.97
Minor CHD	3/32 (9.4%)	0/35 (0%)	0/38 (0%)	0.03

Table 5 - TOP rate over the three registered years in relation to the severity of CHD

To support the study of TOP's trend over time, it has been investigated in relation to the multidisciplinary counselling. These tables highlight how receiving integrated counselling has led more expectant parents with diagnosis of minor CHD to decide for continuation of pregnancy over termination, with a significant reduction in TOP rate ($p<0.03$). *(Table 6)*

	No prenatal counseling	Prenatal counseling	*p*-value
Major CHDs	12/52 (23.1%)	28/119 (23.5%)	0.95
Minor CHDs	3/32 (9.38%)	0/73 (0%)	0.005

Table 6 - TOP rate in relation to introduction of multidisciplinary clinic

Furthermore, analyzing the outcomes of the multidisciplinary clinic specifically for each CHD category, a significant decreasing TOP trend was registered only within AVSD cases and minor CHDs, respectively presenting *p*-value of 0.02 and 0.03. *(Table 7)*

	No prenatal counseling	Prenatal counseling	*p*-value
AVSD	2/3 (66.7%)	0/7 (0%)	0.02
Minor CHDs	3/32 (9.4%)	0/73 (0%)	0.008

Table 7 - TOP rate for specific CHD category in relation to the introduction of the multidisciplinary clinic

Among the category of complex congenital heart disease, an additional analysis was led, to investigate the relationship between uni or biventricular heart malforations and the decision to terminate pregnancy. The analysis revealed a significant effect ($p<0.001$) of the anatomical structure of the malformed heart and TOP rate. In particular, univentricular abnormalities are more frequently associated with interruption of pregnancy, compared to biventriculare ones.

This data is reasonable since univentricular hearts present worse prognosis and more complicated treatments. *(Table 8)*

	Univentricular heart	**Biventricular heart**
TOP	17/35 (48.6%)	23/136 (16.9%)
No TOP	18/35 (51.4%)	113/136 (83.1%)

Table 8 - Association between univentricular or biventricular heart CHD and TOP decision

Finally, examinating the overall trend of TOP in the three years register, no significant reduction in the number of terminations of pregnancy is present among the total population (*p*-value 0,8). *(Table 9)*

	2022	**2023**	**2024**
TOP	15/84 (17.9%)	14/92 (15.2%)	14/100 (14.0%)
No TOP	69/84 (82.1%)	78/92 (84.8%)	86/100 (86.0%)

Table 9 - Total TOP rate over the three registered years

V. DISCUSSION

The results show an increase in the number of fetal echocardiography performed since the opening of the multidisciplinary clinic and with it a rise in pathological findings. As supported by literature findings, progress in clinical management and easier access to prenatal diagnosis, lead to a substantial increase in ante natal diagnosis rate. (42)

Specifically, an increase in aortic severe abnormalities diagnosis's incidence is registered over the years: 4 (2022); 7 (2023); 11 (2024). It is outstanding that among all cases (22 in total) TOP was performed in just 9.1% of them, meaning 2 cases and representing the major CHD with the least numbers of TOP.

Atrioventricular canal defects (AVSD) are confirmed to be a rare malformation counting 3.6% (2022); 3.3% (2023) and 6.4% (2024) of all pathological FE carried out in this three years register. Comparing TOP performance over the years, there is statistical evidence that TOP was conducted in less cases after the introduction of the multidisciplinary clinic 66.7% (2022) vs. 0% (2023-2024) (*p*-value 0.02).

A different trend is registered for double outlet right ventricle (DORV) malformations. Overall, less diagnosis of DORV were made, 6 (2022) vs. 1 (2023) and 2 (2024) and no linear decrease in TOP performance is visible. In 2022, 33.3% of expectant parents decided to terminate pregnancy, while the following year the only DORV case was brought to term birth. In 2024 one out of two pregnancies, affected by DORV fetal malformation, was interrupted (+16.7% compared to 2022).

Regarding hypoplastic left heart syndrome (HLHS), the untreated post-natal survival rate is low, occurring in less than 30.0% after the first week and surgical treatment is complex, consisting of three consecutive operations. These reasons may suggest why TOP is preferred in a high percentage of cases 50% (2022); 44.4% (2023); 71.4% (2024), with overall increase of 6.3% after the introduction of the multidisciplinary clinic, compared to the previous year. Therefore, parents that are well informed about post-natal prognosis and palliative surgical treatment, may be mostly decided to interrupt the pregnancy, conscious of the severity of the disease.

A similar trend is measured for transposition of the great arteries (TGA), a malformation with a high recurrence in all three groups. During the first year of the multidisciplinary clinic a minimal decrease in TOP performance was registered,

compared to the previous one, 8.3% (2023) vs. 11.1% (2022). On the other hand, 2024 counted 3 terminations of pregnancy among 8 diagnoses, resulting in TOP being performed in 37.5% of cases.

Regarding Tetralogy of Fallot (TOF), less cases were diagnosed over the three years. Nevertheless, only one termination of pregnancy was performed each year and, considering 2023 and 2024 together, TOP was conducted in 12.5% of cases, resulting in almost double the rate of 2022 (1,87 times 2022). A possible limitation of this analysis is that during the data collection no distinction was made among the severity of the pulmonary stenosis, and it is not referred to which degree of severity interruption was chosen.

Concerning heterotaxy, the first cases were registered in 2023 meaning that no comparison with the years before the start of the multidisciplinary clinic are available. Nonetheless, confronting 2023 and 2024 data, a decrease in TOP performance is evident, 3 (60.0%) cases in the first year and zero in the second one.

A constant trend is recorded in the total number of diagnoses for complex CHDs in the year before and the first year after the beginning of the multidisciplinary clinic, 9 (2022) vs 10 (2023). In 2024 instead, 21 fetal abnormalities were classified as complex CHD, overcoming the sum of the cases of the two previous years. The proportion of TOP cases hovered around 30%, specifically 33,3% (2022) and 30% (2023), while a positive decrease was registered for 2024 (19.0%).

With regards to minor CHDs, an increasing trend was observed in the number of cases over the three-year timeframe: 32 (2022), 35 (2023) and 38 (2024). The results show a statistically relevant positive effect of the introduction of the multidisciplinary clinic on the TOP performance, starting from 9.4% in 2022 and reaching 0% in the following years (*p*-value 0.03). This trend highlights how an integrated approach can lead to a reduction in pregnancy interruption in those cases where post-natal prognosis is favorable.

Concerning the association among variables, analyzing the three years TOP trend in relation to CHDs' grade of severity first and to accessibility to multidisciplinary counselling secondly, a decrease in termination of pregnancy choice is registered among expectant parents with diagnosis of minor congenital heart malformation. Coherently with literature findings, CHD's severity is reported to be an influencing

factor in the parental decision regarding continuing or terminating pregnancy. Furthermore, this study supports that high anomaly complexity, such as univentricular malformations, appears to be a strong predictor for termination of pregnancy, a plausible finding because of common parental concerns about surgical risks. (43) Among all major CHDs categories, AVSD is the only group where a significant reduction in TOP rate was reported.

Despite the overall TOP rate not significantly decreased in the three-year period time study, prenatal integrated counseling could still be appreciated by expectant parents. Positive evidence is found in a recently published article about the impact of interdisciplinary counseling for decision-making in cases of fetus diagnosis of congenital heart malformation. (44)

15. Limits of the analysis

Several challenges were identified when defining the study's design. An important limitation to these findings is the single-center nature of the investigation, related to a small sample size. Therefore, the study set presents a low statistical power and might not be representative of the population. Furthermore, various key variables were considered potential confounders in the relationship between integrated counseling and the decision to terminate pregnancy. These included: socioeconomic status, which covers parental income and education level; parental health literacy, that influences the comprehension of medical information; psychosocial factors, meaning social support and parental coping mechanisms; and parents' personal, religious or spiritual values.

VI. CONCLUSION

A multidisciplinary approach to prenatal counseling for CHD can have a variable influence in the reduction of parent's choice of TOP. In this study it is observed that expectant parents who receive a diagnosis of minor CHD are positively influenced to continue pregnancy, as to suggest that a multidisciplinary approach may lead to a major understanding of the favorable post-natal prognosis and possible conservatory or surgical treatment. On the other hand, in our data set, life threatening malformations, such as HLHS or TOF in severe forms, present a growth over time in the TOP rate, possibly advising how a wider comprehension of the severity of post-natal care and palliative treatment options bring more frequently to decide for pregnancy termination. Thus, having different outcomes, parents' access to an integrated clinic allows them to take a wider informed decision.

Furthermore, because of the possibility to selectively terminate pregnancy, it should be considered that CHD prevalence at birth can be influenced by interruption rate, and that the impact varies internationally, since reasons for termination can vary, including local abortion laws, socio-cultural environment, disease prognosis, as well as family background and personal resources (emotional, cognitive, economic). These variables are confounder that can't be directly measured and represent a major challenge in clinical and social research. Further investigation could be done with the aim of operationalizing these variables, to measure their effect on the outcome. Therefore, questionnaires derived from validated measurements scales could be submitted to expectant parents, investigating aspects of socioeconomic status and family functioning. These surveys can highlight specific family needs and provide valuable insight, which could help implement the multidisciplinary clinic's design. Tailoring healthcare services to meet the specific needs of expectant parents may lead to a substantial reduction in psychological distress and its consequences, on the mother and on the fetus.

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