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Lectures

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LECT 1

CONGENITAL HEART MALFORMATIONS AND EXTRACARDIAC ABNOMALITIES

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Congenital heart diseases (CHDs) have a complex and heterogeneous etiology, with a predominant genetic component (15%). Four hundred genes have been implicated in CHDs [1]. 70% of CHDs occur as isolated malformation, while 30% of subjects with CHDs have associated extracardiac abnormalities [2]. Syndrome related CHDs may be linked to chromosomal abnormalities or genetic mutations.

Every year CHDs affect approximately 0.8% of live births. In 40-50% of cases the diagnosis is made within the first week of life, in 60% of cases within the first month of life. The identification of a malformative syndrome can be prenatal or postnatal. The family and pathological history of the infant's parents allows the identification of any risk factors for the development of malformations. It is also important to note that, if performed between 18 and 22 weeks of gestation, the fetal echocardiography is an excellent prenatal screening for major CHD [3, 4]. The examination of nuchal translucency and the latest and most innovative non-invasive prenatal screening tests allow the early identification of chromosomal abnormalities in the fetus. On the other hand, if the presence of congenital abnormalities is not identified during the fetal period, the diagnosis is postnatal: through the objective examination of the newborn it is possible to identify the congenital abnormalities specific of each chromosomal syndrome, whereas a cardiological survey by electrocardiogram and echocardiography can highlight any CHD.

In Europe, in 2017, the prevalence of newborns with CHDs was 69.31 cases per 10,000 live births, while the prevalence of newborns with chromosomal syndrome was 16.80 per 10,000 live births.

CHDs play a key role in the clinical situation of the newborn suffering from chromosomal syndrome: not only are they recorded in almost all cases, but they often represent the congenital defect that most affects the prognosis and life expectancy of the newborn.

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LECT 2

WHEN TO SUSPECT A CONGENITAL HEART DISEASE *IN UTERO*

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INTRODUCTION

Congenital heart diseases (CHDs) are the most common type of congenital malformations and they occur in 1% of newborn infants. The estimated incidence for moderate to severe forms of CHDs is 6 per 1,000 live births, associated with high perinatal morbidity and mortality.

Therefore, an accurate prenatal diagnosis is essential to plan an adequate obstetric follow-up and to refer the pregnant woman to a tertiary care when necessary.

Around 20-24 weeks of pregnancy, the assessment of the fetal anatomy has been standardized to cover both the fetal heart and the fetal anatomy. According to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines, the screening procedure includes the four-chamber view, ventricular outflow tract view, three-vessel view, and three-vessel and trachea views. Any abnormal finding from such baseline screening is a formal indication for a fetal echocardiogram. In these cases the clinical suspicion is confirmed in about 40-50%.

In addition, a fetal echocardiogram is indicated in cases of higher maternal or fetal risk or in presence of family history of CHD. Therefore, most of the cases of CHDs are still unknown at the time of birth. Literature data reported that only 15% to 30% of infants with CHDs are identified prenatally [1, 2].

MATERNAL AND FAMILIAL RISK FACTORS

Gestational diabetes and pregestational diabetes mellitus are the most prevalent conditions associated to CHD. Pregestational diabetes entails a risk 2-3 times higher for malformations and it is now known that higher glycosylated hemoglobin level leads to a higher risk for congenital defects. In relation to CHD, there is a higher risk for structural malformation due to an altered embryogenesis potentially evident in early tests, and for septal hypertrophy and hypertrophic cardiomyopathy due to hyperinsulinism which can be evidenced in the third trimester.

Other maternal conditions that increase the risk for heart disease include autoimmune diseases with positive anti-Ro and anti-La antibodies, such as Sjögren syndrome and systemic lupus erythematosus. According to some authors the fetal echocardiography is indicated in case of autoimmune disease with a prior affected fetus and it may be considered in women affected by autoimmune disease without a prior affected fetus. In presence of pathologies with positive anti-Ro/anti-La antibodies, the risk for a complete atrioventricular block is 1-2% and, if a prior child has been affected, such risk increases to 15-20%.

About congenital infection, parvovirus is associated with heart failure secondary to severe anemia and myocarditis and a first-trimester varicella and rubella infection may lead to structural heart defect.

The intrauterine exposure to chemical agents, alcohol and drugs must be investigated. Commonly used drugs, such as angiotensin-converting enzyme inhibitor, lithium, isotretinoin, selective serotonin reuptake inhibitor, and some anticonvulsant agents, such as phenobarbital and valproic acid, are associated with CHD.

In the last decade, some authors reported that abnormal levels of specific second trimester maternal serum biomarkers are associated with an increased risk of heart defects. Particularly, cases with critical CHD are more frequently related to higher levels of alpha-fetoprotein (AFP) (multiple of the median [MoM] ≥ the 95th percentile) and/or lower levels of human chorionic gonadotrophin (hCG) and/or unconjugated estriol (MoM ≤ the 5th percentile). These results suggest that the serum biomarkers can improve the CHD detection in low risk pregnancies, but more evidences are necessary to establish this correlation.

Limited data support the indication of fetal echocardiography for pregnant obese women. However, some authors have reported a correlation between obesity and cono-truncal defects, right ventricular outflow tract defects and hypoplastic left heart syndrome.

A fetal echocardiogram may also be indicated in cases of family history of CHD. The risks are higher when one of the parents has CHD and even more if the mother is the carrier (10-15%) compared to the father (2%). Literature data reported also that the risk of recurrence after having an affected child is 2-5%, but varies broadly depending on the type of heart disease and the risk is higher in the case of more than one affected child.

In the last years, a correlation between CHD and pregnancies conceived with *in-vitro* fertilization/intracytoplasmic sperm injection has emerged. However, this finding deserves further investigation due to the heterogeneity of both assisted reproductive technology procedures and cardiac defects [3, 4].

FETAL RISK FACTORS

Positive screening at the ultrasound of the 11-13 weeks and molecular diagnosis of a Mendelian pathology are indications for fetal echocardiography. Some ultrasound markers in the first trimester, such as increased nuchal translucency thickness, reverse flow in the ductus venosus and/or tricuspid regurgitation, have also shown a correlation with CHD. Moreover, trisomy 21 is strongly associated with the atrioventricular canal defect, monosomy of the X chromosome correlates with coarctation of the aorta, and microdeletion 22q11.2 or DiGeorge syndrome is associated with cono-truncal anomalies.

Extracardiac anomalies, such as omphalocele, diaphragmatic hernia and fetal hydrops, also increase the risk for CHD.

Fetal arrhythmias (persistent abnormal rhythm and not episodic forms of bradycardia, tachycardia, or extrasystole) are also indication for echocardiography.

About twin pregnancies, literature data reported that in monochorionic twin pregnancies an accurate fetal screening is necessary, given the high risk of congenital defects which increases even more in monochorionic twin pregnancies complicated with

twin-to-twin transfusion syndrome (TTTS). In fact, in the TTTS, the "recipient" twin has a 10% chance of having right ventricular outflow tract anomalies [3-5].

CONCLUSION

Fetal echocardiography is the ultrasound evaluation of the fetal cardiovascular system that requires unique skills and knowledge to be performed.

An early detection of fetal CHD allows to address the pregnancy to a tertiary level of care and to decrease neonatal morbidity and mortality rate.

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LECT 3

DIAGNOSIS AND MANAGEMENT OF FETAL AND NEONATAL CARDIAC ARRHYTHMIAS

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Fetal heart rhythm irregularity is diagnosed in 1-3% of pregnancies during routine obstetrical ultrasound [1]. The majority of fetal arrhythmias (FA) are benign and/or transient but in some cases may result in low cardiac output, fetal hydrops and fetal demise. Fetal echocardiography remains the dominant modality to analize FA with M-mode and pulsed Doppler ultrasound.

PREMATURE ATRIAL CONTRACTIONS

Premature atrial contractions (PACs) are the common type of FA (62% of cases) and tipically occur in the 2nd and 3rd trimester. In the majority of cases they resolve spontaneously before birth and do not require therapy. Despite this, multiple PACs can increase the risk of sustained supraventricular tachycardia (SVT) in presence of atrioventricular (AV) conduction through accessory pathways (AP). A rare form of PACs is the blocked atrial bigeminism (BAB) in which a sinus beat is followed by a premature beat not conducted to the ventricles. BAB often produces a low fetal heart rate (HR) (70-90 bpm) and is frequently misdiagnosed as second-degree AV block. The distinction should be correctly identified to avoid management mistakes [2].

TACHYARRHYTHMIAS

Supraventricular tachycardia

SVT accounts for 90% of tachyarrhythmias. SVT can be intermittent or persistent. The mechanism predominantly associated is AV reentry (AVR) related to presence of AP. Typical features of fetal SVT include regular tachycardia with HR of 180-300 bpm, 1:1 AV conduction and, in intermittent SVT, the sudden onset and termination of tachycardia. In neonates, typical electrocardiogram (ECG) showed narrow QRS complex followed by a retrograde P wave. Adenosine is the first-choice drug for acute termination of SVT. Antiarrhytmic prophylaxis is recommended during the 1st year of life. Flecainide, in monotherapy or associated to β-blockers, is effective in 95% of case [3].

Atrial flutter

Atrial flutter (AFL) is sustained by a macro-reentrant circuit within the atrium. Typically, atrial rate ranges between 300-500 bpm with an AV conduction 2:1 and HR of 150-250 bpm. It can cause fetal heart failure and hydrops. Maternal digoxin, sotalol and flecainide are the therapeutic options. Postnatal ECG is characterized by a typical "saw-tooth pattern". After birth AFL is usually treated with DC cardioversion. Recurrences are uncommon and long-term therapy is rarely required.

Permanent junctional reciprocating tachycardia

Permanent junctional reciprocating tachycardia (PJRT) is a rare form of incessant AVR tachycardia caused by slow retrograde conduction through decremental AP. Typical features are HR about 200 bpm and long RP interval with inverted P waves in inferior leads. Pharmacologic therapy is always necessary.

Ectopic atrial tachycardia

One ectopic atrial focus can lead to an incessant irregular tachycardia with HR 150-250 bpm. Not responsive to adenosine or DC shock, ectopic atrial tachycardia (EAT) can induce ventricular disfunction if not controlled ("tachycardiomiopathy").

Junctional ectopic tachycardia

Congenital junctional ectopic tachycardia (JET) is a rare form of incessant tachycardia sustained by a single ectopic focus near His bundle. It usually shows AV dissociation with an atrial slower than ventricular rate and is associated with high morbidity and mortality in neonates [4].

VENTRICULAR ARRHYTMIAS

Premature ventricular contractions (PVCs) are relatively uncommon compared with PACs having a long-term good prognosis. Ventricular tachycardia (VT) is defined by wide QRS complex with an HR > 120 bpm and AV dissociation: it can be idiopathic or associated with myocarditis, cardiac tumors, CHD, cardiomyopathy and channelopathies (i.e. LQTS).

BRADYARRHYTHMIAS

Fetal bradycardia is defined as a sustained fetal HR below 110 bpm over at least 10 min [5]. The main causes are fetal hypoxia, LQTS, BAB and complete AV block. This latter is often associated with maternal anti-Ro/SSA and anti-La/SSB autoantibodies and typically appears between 18 and 24 weeks. Maternal high-dose dexamethasone should be initiated at time of diagnosis and continued during the pregnancy, salbutamol can be associated at fetal HR below 50 bpm. It represents a neonatal emergency requiring often pacemaker implantation.

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LECT 4

WHEN THE DUCTUS OF BOTALLO REVEALS ITSELF TO BE A FRIEND: HOW TO GUARANTEE ITS PATENCY

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Congenital heart defects with ductus-dependent circulation are that in which the patency of the ductus arteriosus (DA) is mandatory for maintaining systemic perfusion. Ductal closure may cause significant decrease in systemic circulation (ductus-dependent systemic blood flow, like critical aortic stenosis, severe coarctation of the aorta, interruption of aortic arch, and hypoplastic left heart syndrome), or significant decrease in pulmonary circulation (ductus-dependent pulmonary blood flow like pulmonary atresia with or without ventricular septal defect, critical pulmonary stenosis, tricuspid atresia, severe tetralogy of Fallot, severe Ebstein's anomaly).

The PGE1 infusion since mid 1970s is beneficial in opening the ductus and raising the systemic arterial oxygen saturation in neonatal patients with duct-dependent congenital heart defects [1].

Surgical placement of a systemic-to-pulmonary shunt has been firstly performed in 1944, becoming a therapeutic possibility.

As an alternative to systemic-to-pulmonary shunts or surgical reconstruction of the aortic arch, ductal stenting in neonates with duct-dependent pulmonary or systemic circulation may maintain duct patency for several months [2].

The results of ductal stenting have improved significantly over the years thanks to a better patient selection, technical improvements, and new devices [3].

Ductal stenting in case of duct-dependent pulmonary circulation may be performed in patients who have more than one source of pulmonary blood flow (requiring additional pulmonary blood flow for a short period of time), and in infants with only the arterial duct as pulmonary blood flow. The ductal stenting should not be performed if there is an obvious proximal pulmonary artery (PA) stenosis in the vicinity of the ductal insertion [4].

Ductal stenting in neonates with duct-dependent systemic circulation is mostly used for palliation of hypoplastic left heart syndrome (HLHS) but may also be performed in other complex lesions. In HLHS the ductal stenting is part of a "hybrid procedure" that refers to a strategy that combines surgical placement of bilateral PA bands with ductal stenting [1].

Ductal stenting is considered a safe procedure, with a procedure-related mortality rate of < 1% in favorable DA anatomy; however, occurrence of acute and delayed complications remains a point of concern. The complication rate for ductal stenting is currently between 9% and 13% [1, 5].

The minor complications are mostly associated with vessel injury and/or occlusion in a neonate's femoral artery. Usually, this complication is successfully managed with intravenous heparin therapy, with favorable evolution in a few hours. Major acute complications, like ductal spasm (resulting in sudden and severe hypoxemia), are rare (< 1%), but can occur during guidewire manipulation across the ductus; ductus perforation or dissection may be related to wire or catheter positioning and can be treated by coronary stent implantation. Stent malposition or embolization is less frequently nowadays [4, 5]. A severe complication is acute stent thrombosis, which may occur just after stent expansion or within the hours following the procedure.

A recent meta-analysis showed lower mortality rates and a shorter hospital stay for patients who received palliation via ductal stenting as opposed to systemic-pulmonary surgical shunt, although there was no difference in PA growth or hazard of unplanned reinterventions [6].

Last but not least, ductal stenting may be considered more rarely, in patients with supra-systemic PA hypertension with a small patent DA with a significant improvement in functional status, as it is seen with the surgical Potts shunt.

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LECT 5

PATENT DUCTUS ARTERIOSUS: THE HIDDEN ENEMY. HOW CAN WE TREAT IT?

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The ductus arteriosus (DA) is a vascular structure that connects the aorta with the pulmonary artery allowing the passage, during fetal life, of the cardiac output into the aorta. At birth, it closes within 48-72 hours of life in 90% of full-term infants. The incidence of patent DA (PDA) is inversely proportional to gestational age. In preterm newborn, different factors contribute to delaying its closure, especially hypoxia and acidosis, a reduced response of the immature DA to the vasoconstrictive stimulus of oxygen and an increased sensitivity to prostaglandins (PGE2). Other associated risk factors are chorioamnionitis, sepsis, respiratory distress syndrome and a reduced platelet count.

After birth, failure to close the DA leads to an increased flow to the pulmonary circulation, with stealing to the systemic circulation. This ductal steal predisposes to the development of pulmonary congestion and respiratory worsening, with reduction in the systemic blood flow and consequent hypoperfusion in various districts, such as brain, kidney and bowel.

When PDA is associated with clinical and echocardiographic signs of pulmonary hyper-perfusion and systemic hypo-perfusion, it is defined as hemodynamically significant (hsPDA). Currently, there is no international consensus that allows to define whether or not PDA is hemodynamically significant, and a multi-organ evaluation should be considered.

Complications of an hsPDA are: bronchopulmonary dysplasia (BPD), prolonged mechanical ventilation, pulmonary hemorrhage, necrotizing enterocolitis (NEC), renal impairment, intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy and increased mortality. The available strategies of intervention vary from prophylactic treatment to early therapy and conservative approach.

The prophylactic treatment of PDA involves drug treatment within the first 24 hours after delivery, generally without echocardiographic evaluation and regardless of hemodynamic significance. However, it has been shown to have no benefit on mortality and long-term complications, otherwise increasing exposure to the risk of side effects even in infants who did not require treatment.

The early target approach has found greater success in recent years. The advantage is to expose only those infants with hsPDA to potential drug side effects.

Indomethacin was the first drug administered, but it has been progressively replaced by ibuprofen since, with the same efficacy, ibuprofen has been shown to have fewer side effects, particularly on the kidney and is associated with a reduced incidence of NEC. They both act reducing PGE2, which is essential for maintaining the patency of the DA.

Paracetamol is also emerging as an alternative due to its excellent pediatric safety profile with similar efficacy to ibuprofen and potentially fewer adverse effects. However, there are limited data on its use in preterm.

An improvement in long-term outcomes has not yet been demonstrated in terms of reducing the incidence of IVH, NEC and BPD. For this reason, and considering the high percentage of spontaneous closure of the PDA, a conservative approach was proposed. This approach involves water restriction, permissive hypercapnia and the maintenance of high positive end-expiratory pressure.

In case of failure or contraindications to medical therapy, an alternative is surgical ligation, which has high effectiveness, but is burdened by several complications, such as post-ligature syndrome, diaphragm paralysis and vocal cord paralysis. It would also seem to be associated with neurodevelopmental impairment and a higher incidence of BPD. Among new therapeutic options, percutaneous transcatheter closure is emerging, even in the lowest gestational ages.

CONCLUSION

Management of PDA in preterm newborn remains controversial.

Multi-organ evaluation is the key in detecting hsPDA, and the treatment should be individualized to each newborn considering the severity of symptoms, short- and long-term clinical outcomes.

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LECT 6

TRANSCATHETER CLOSURE OF PATENT DUCTUS ARTERIOSUS IN PREMATURE BABIES

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The ductus arteriosus is an essential in fetal life. It shunts placental oxygen-rich blood from the right heart to the systemic circulation bypassing non-functional fetal lungs. The large majority of patent ductus arteriosus (PDA) close postnatally, prior to few days of life. However, in up to 50% premature babies born less than 29 weeks of gestational age, it remains open [1]. In those with persistent patency, shunting becomes left-to-right, resulting in variable degrees of hemodynamic impact. A large variety of complications may occur because of PDA, including bronchopulmonary dysplasia, necrotizing enterocolitis, pulmonary hypertension, intraventricular hemorrhage, sepsis, pulmonary over-circulation, heart failure and infective endo- carditis. In infants born before 29 week of gestation, mortality risk increases 8-fold if PDA has been described [2]. Medical treatment is the first line therapy; however, when it fails, a mechanical closure must be considered. Options include surgical closure and transcatheter occlusion. Percutaneous closure of the PDA was first described over 20 years ago [3], but has been mostly considered in infants > 6 kg. The small and extremely low birth weight premature babies have been excluded in the past because of small size, lack of appropriate devices, and assumed higher risk. Recently, the technical advances have allowed the development of properly designed devices and delivery system to perform this procedure safely

and consistently [4]. Transcatheter closure of the PDA is nowadays feasible in very premature infants, when clinically indicated, with high procedural success and a low complication rate. However, there are some specific technical tips and tricks. They include: (a) an anterograde approach with avoidance of arterial cannulation; (b) specific anesthesiologic care with dedicated respirators; (c) minimization of fluoroscopy and contrast use; (d) intraprocedural transthoracic echocardiography to guide device implantation. Ideally, the avoidance of opening the chest and traumatic procedures have the major advantage of reducing complication rate and post procedural complications. A major cultural change in the neonatological approach to this clinical situation is the major step needed to provide this approach to a wider population. In fact, waiting longer days after failure of medical treatments may impair the potential advantages that PDA closure may provide.

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LECT 7

BRONCHODYSPLASIA AND PULMONARY HYPERTENSION

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INTRODUCTION

Bronchopulmonary dysplasia (BPD) is among the most common and severe complications of premature birth [1]. It is considered to be the result of an aberrant reparative response to both pre-natal and post-natal damage to the developing lungs. Infants who are born before 28 weeks of gestational age are those most at risk because they are born just when rudimentary bronchioles are developing in the early stages of alveolar development. Recent studies have shown that BPD is no longer to be considered only as a lung parenchymal disease but also as a pulmonary vascular disease with arrest of vascular growth, remodeling and rarefaction of the pulmonary vascularization. All this leads to increased pulmonary vascular resistance and pulmonary hypertension (PH) [2].

The association between BPD and PH (BPD-PH) significantly worsens the prognosis, since it leads to reduced somatic growth and neurological development, higher rates of tracheostomy, increased use of supplemental oxygen, feeding problems and frequent hospitalizations [3]. Mortality of infants with BPD-PH has been reported between 14% and 38% [4].

AIM OF THE STUDY

The aim of the present study is to evaluate the presence of predictive factors for the development of PH in premature patients with BPD. The ultimate goal is to identify that subgroup of premature babies with BPD who will develop PH to improve care during hospitalization in intensive care, carry out close clinical monitoring, intervene early with targeted medical and pharmacological therapy and perform adequate follow-up over time.

PATIENTS AND METHODS

86 patients admitted at birth to the Neonatal Intensive Care Unit of the Policlinico di Monserrato, University of Cagliari, with a gestational age of less than 30 weeks were selected between January 2015 and December 2020. Of these 86 preterm, 17 were excluded: 11 died prematurely before the 14th day of life and 6 were transferred to other centers for complications related to prematurity that could not be treated in our center.

RESULTS

69 premature babies were enrolled: 36 males and 33 females. 23 out of 69 (33%) did not develop BPD, while 46 out of 69 (67%) developed BPD. Of the 46 who developed BPD, 14 (30%) had PH as an associated complication: 6 males and 8 females. Of the 14 patients who developed PH, 12 (86%) had a severe form of BPD, 1 (7%) a moderate form and 1 (7%) a mild form. Oligohydramnios ($p = 0.0000224$), pPROM ($p = 0.00000$) and early PH (< 14th day of life) ($p = 0.00191$) were predictors of the development of BPD complicated by PH. There was no statistically significant difference

considering the days of invasive ventilation between the group with BPD and the group with BPD-PH (p = 0.07499). On the contrary, the difference in the days of oxygen dependence was statistically significant between the group with BPD and that with BPD complicated by PH (p = 0.0226). The Apgar scores at the first minute (p = 0.826) and at the fifth minute (p = 0.558) and the number of doses of surfactant (p = 0.3277) were not statistically significant.

CONCLUSIONS

PH complicates the course of extremely premature babies and is associated with BPD. Identifying the onset of early PH is important in predicting the possibility of developing BPD and BPD-PH at 36 weeks of post-menstrual age.

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LECT 8

COUNSELLING OF CONGENITAL HEART DISEASE

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Congenital heart malformations occur with a frequency of about 9 in 1,000 live births and about 1/3 of cases require invasive treatment in the first year of life [1].

Advances in prenatal screening have led to a significant increase in heart disease diagnosed *in utero*, allowing for greater postnatal survival especially for duct-dependent forms [2]. The task of the pediatric and fetal cardiologist is not only to make a correct diagnosis, but also to explain, effectively to parents, the nature of the heart abnormality, the short- and long-term consequences and the need for intervention.

Counselling therefore becomes a crucial moment whose objectives are basically 4: to provide an accurate diagnosis of the malformation, to provide a clear and reliable picture of the prognosis, to outline the management and therapeutic options available, to help parents and to choose the type of management that is the most suitable for them [3].

From a timing point of view, it must be performed as soon as possible with respect to the diagnostic suspicion, in order to reduce the stress resulting from waiting and allow for the possible termination of pregnancy. If there are technical limitations to the examination represented, for example, by fetal position, early gestational age or maternal habitus, they must be exposed to the couple, emphasizing the fact that they could affect the accuracy of the prognosis. Moreover, the counseling must take place in a different room than the one where the ultrasound examination was performed, in a silent place and without interruptions, with the parents seated opposite in order to promote a two-way dialogue and not a simple monologue. For this reason, the counselor must estimate, from time to time, what information has been received taking into account that in the first meeting the emotional impact of the parents (resulting from the diagnosis) will compromise the effectiveness of the communication itself. Diagrams, anatomical drawings, models and videos can be used to explain the heart defect, which can be useful as a reminder when parents have left the physician's office. The counselor must also inform the couple about the dubious usefulness of acquiring information from the internet and websites and be prepared to answer questions deriving from these often inappropriate and never scientifically validated sources. It is important not only to talk about the short- and long-term cardiac aspects, but also about the neurological implications. In fact, there is increasing evidence of how some surgical techniques, prolonged and repeated interventions can negatively impact the acquisition of motor skills or the intelligence quotient (IQ).

Among the factors that influence counselling, the gestational age at diagnosis plays a central role: on the one hand, due to the possible evolution of congenital heart disease (a valve stenosis can subsequently determine the growth failure of a ventricular chamber with consequent impossibility of biventricular surgical correction), on the other hand, for the possibility of terminating the

pregnancy if the diagnosis is made no later than the 22nd week of gestational age. The counselors must present this option regardless of their religious beliefs, they must refrain from imposing their personal vision and limit themselves to providing, in the most detached way as possible, all the information necessary to allow the parental couple to take the most appropriate decision for them. From this point of view, it is a must, precisely because it can help in choosing, to exclude or confirm the presence of extracardiac anomalies or real syndromes.

Prenatal diagnosis determines effects on both the couple and the fetus. In fact, a series of emotional states follow one another: manifest or hidden anger, sense of guilt, pain, denial and doubt. High levels of maternal stress and, consequently, of cortisol can negatively impact first fetal and then neonatal outcomes, causing alterations on somatic growth, on neuro-evolutionary development and on cardiovascular conditions [4].

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LECT 9

THE CARE OF THE RELATIONSHIPS BETWEEN SOCIAL-HEALTH WORKERS AND PARENTS FOLLOWING THE COMMUNICATION OF A PERINATAL DIAGNOSIS OF CONGENITAL MALFORMATION

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The experience of pregnancy is becoming increasingly different thanks to the opportunities offered by neonatal screening, which allows you to become aware of fetal abnormalities. It is therefore important to know what impact the communication of a diagnosis has on the parental couple and the role of the social-health workers involved in the relationship with them.

The awareness of the emotions that the couple can experience is a necessary starting point for the professional figures to interact effectively. Although the risk of a congenital deficit affects 3% of pregnancies, few parents are aware of this possibility. They approach ultrasound scans in an optimistic way, imagining that they are seeing the baby, identifying his/her somatic features, not thinking about the possibility of receiving inauspicious news.

Some studies report that knowing about such possibility reduces the emotional impact in the event of a bad outcome, compared to couples who approach screening without adequate information. Therefore, it is good to provide knowledge of the possible outcomes before the exam is carried out, in order to establish trust in the relationship reducing the emotional impact. The knowledge of a perinatal diagnosis, from a psychological point of view, implies the loss of the idealized child and project: they are replaced by the real child, which differs from the one imagined, because of his/her anomalies. Parents experience a sense of ineffectiveness for having conceived an "imperfect" child. If the anomaly involves postnatal operation and the prospect of an impact throughout the child's life, parents are faced with a difficult choice with a limited decision time. The couple feels the need to acquire more information and to manage the pain, considering the already presence of an emotional bond with the child. The feeling of uncertainty plays a predominant role, and this has also been found in cases where the initial diagnosis has been disconfirmed by subsequent examinations.

In cases of false positives, a state of alert remains that can negatively affect the mother-child attachment relationship even after delivery, being dismissive and poorly emotionally involved in understanding the needs of the newborn.

In cases of voluntary termination of pregnancy, the feelings typically present are often conflicting: a strong sense of guilt and the presence of constant doubt alternate with feelings of relief. The conflict is determined by the dissonance between love for

their child and the sense of inability to raise him/her. It is important that social-health workers are aware of the emotional impact that the choice has on the couple, in order to have an appropriate approach to their emotional response. The absence of judgment and a safe space for expressing emotions are fundamental.

In the event that the couple decides to continue the pregnancy, a first period of mourning is possible in which to process the "death" of the idealized child; it is necessary for the couple to be able to create an emotional and affective space for the real child and take steps towards conscious and appropriate parenting for their child.

The professional figures must be of support to the parents in facing the challenges they will have to face, and they must support them in the chosen coping strategies. They must also adequately inform not only about medical treatments, but also about problematic and non-problematic areas of life, reducing the impact of the social stereotyped concept of disability.

With adequate emotional support, parents are able, over time, to elaborate a new narrative of their experience and to regain their sense of effectiveness by improving the quality of their life and that of their child.

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LECT 10

OBSTETRICAL MANAGEMENT OF FETUS WITH HEART DEFECTS

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Among congenital malformations, heart defects, occurring in 1% of newborn infants, are the most common type of anomaly, and these are associated with a high perinatal and long-term morbidity and mortality. The rate of detection of congenital heart diseases (CHDs), even in developed countries, ranges between 30% and 60% [1-3]. Intrauterine detection depends on several factors, one of the most important among them is sonographers' expertise in the assessment of the fetal heart, since the vast majority of CHDs relate to abnormal morphogenesis during early intrauterine development and can only be diagnosed accurately by fetal echocardiography. Early detection of congenital heart defects *in utero* not only permits a better understanding of the progression of these malformations but also allows to provide better parental counselling, an adequate obstetric follow-up followed by a planned delivery and, in case of a complex CHD, it permits to refer the pregnant woman to a tertiary care facility capable of providing neonatal diagnosis and management, which has shown to reduce associated perinatal morbidity and mortality [4]. The fetal heart is assessed by means of a routine, detailed fetal ultrasound around week 20-24.

At present, this test has been standardized by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and consists in a screening procedure including the four chambers view, ventricular outflow tract view, and three-vessel views. A fetal echocardiogram is indicated in patients at a higher risk for CHD compared to the general population. Among maternal indications, some of the most prevalent conditions are diabetes mellitus, autoimmune diseases with positive anti-Ro and anti-La antibodies, such as Sjögren syndrome and systemic lupus erythematosus.

In terms of infections, varicella and rubella may lead to structural heart defects, whereas parvovirus B19 is associated with heart failure secondary to severe anemia and myocarditis.

CHD may also be the result of embryonic exposure to a wide range of chemicals such as lithium, isotretinoin, misoprostol, and some anticonvulsant agents, such as phenobarbital and valproic acid. A positive family history is also a known risk factor for CHD. The risks are also higher when one of the parents has CHD, and the risk of recurrence is higher if the mother is the carrier (10-15%) compared to the father (2%). Moreover, some ultrasound markers in the first trimester, such as nuchal translucency thickness, and ductus venosus

and tricuspid valve Doppler ultrasound, used to screen for chromosomal anomalies, have also demonstrated their usefulness as CHD markers. If a CHD is suspected in the prenatal period, an attempt should be made to establish its characteristics and determine if it is isolated or associated with other conditions, either other malformations and/or genetic disorders. In this case, the steps to follow include a detailed fetal echocardiogram, a detailed morphological ultrasound, and a genetic assessment [5]. Once the diagnostic evaluation is completed, the usual obstetric follow-up of maternal health should be provided together with a specialized follow-up of fetal health in order to try and reach a term pregnancy, given that newborn infants born at 37 to 38 weeks have increased risk of worse outcomes compared with those born at later term (39-40 weeks) [6]. Perinatal management should be tailored to the specific needs of the mother and fetus, and should include decisions regarding location, timing, and mode of delivery that in general minimize the risk of early or operative delivery. The type of delivery should be based on the obstetrician's judgment. The mode of delivery seems not to have any effect on the Apgar score, metabolic acidosis, presurgical and postsurgical morbidity including the risk of hemodynamic instability or survival to surgery or discharge. In general, CHD is not a contraindication for a vaginal delivery after spontaneous-onset labor, which is probably best for mother and baby in most cases. Iatrogenic late-term and early-term delivery should be discouraged. Cardiotocography should be considered as a method of surveillance in labor for fetuses with heart malformations, and the interpretation of the tracing is based on the same classification systems proposed for normal fetuses. A newborn with a CHD should be delivered by a trained neonatal team at a Neonatology Unit capable of providing cardiovascular assessment and management aiming to minimize perinatal morbidity and mortality for both infant and mother, optimize infant status before surgical intervention, if needed, and improve short-term and long-term outcomes [6].

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LECT 11

GENETICS OF CONGENITAL HEART DISEASE

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Congenital heart diseases (CHDs), including malformation of the heart and cardiovascular system present at birth, are mostly of genetic origin and among the most common congenital abnormalities in live births, with an incidence of 1%. Despite progress in clinical care, CHDs are still a significant cause of birth defect-related mortality [1].

To date, different genetic abnormalities are known to cause CHD, e.g. chromosomal aneuploidies, single nucleotide variants and copy number variations (CNVs) in one of a multitude of different genes. These variations can be either *de novo* or inherited [2]. Recent data report that 8-12% of patients are carriers of an aneuploidy or a chromosomal abnormality, 3-5% have a single gene defect and 3-25% have a CNV. Different testing methodologies depending on the type of the suspected genetic abnormality are available for genetic screening. Moreover, the approaches are different in fetus, infants, or adults.

In the case of a clinical suspicion of CHD, fetal genetic testing is conducted employing chorionic villus sampling or amniocentesis to obtain placental/fetal DNA. Recently, non-invasive prenatal testing is also employed to obtain cell-free fetal DNA from maternal blood to screen for aneuploidies and common duplications or deletions. In newborn infants, first-level genetic tests include karyotype analysis, FISH, and chromosome microarray

analysis. The genetic approach is similar in adults but the outcome is different, particularly in terms of genetic counseling and patient treatment.

Second level CHD genetic tests range from single-gene analysis to large multi-gene panels and whole exome/genome sequencing (WES/WGS). Recent decreases in sequencing cost currently allow for clinical application of WES. This approach is an efficient and cost-effective tool in assessing patients with a suspect of a complex monogenic disorder. Due to our limited knowledge of the significance of non-coding variants, WGS sequencing is still limited in use, although this is an area of active investigation.

At present, the diagnostic yield in genetic CHD testing is 5% to more than 35%, and higher in syndromic CHDs [3, 4]. This wide range is due to variability in study design, differences in cohort size and patient classification. Other reasons include unknown genes involved in CHDs and non-routine use of second generations technologies.

In our laboratory we conduct phenotype-driven WES analysis in CHDs. This is done employing virtual gene panels as an alternative to traditional gene panel testing, so as to provide for the best diagnostic yield. Virtual panels include in addition that for congenital structural heart diseases, ciliopathies, rasopathies and other syndromic and non-syndromic heart diseases.

Genetic counseling is extremely important when a genetic analysis is performed, especially in the case of WES in the presence of negative results or variants of unknown significance. Even when a genetic cause of CHD is identified, this information today rarely changes patient treatment but influences clinical management as well as prognosis, and, hence, the outcome of CHD. Moreover, the result allows for better assessment of recurrence risk for family members [5].

We expect that genetic testing in rare diseases, including CHDs, will move towards WES as a first testing strategy. Genomic-scale testing allows for "real-time" up-to-date diagnosis with emerging scientific discoveries. This will require that genetic professionals, well versed in the complexity of genetic disorders in both clinical and laboratory settings, operate in close collaboration for precise diagnosis and best clinical management of the affected patients.

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