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Lectures

Selected Lectures of the 3rd Course of Perinatal and Pediatric Cardiology

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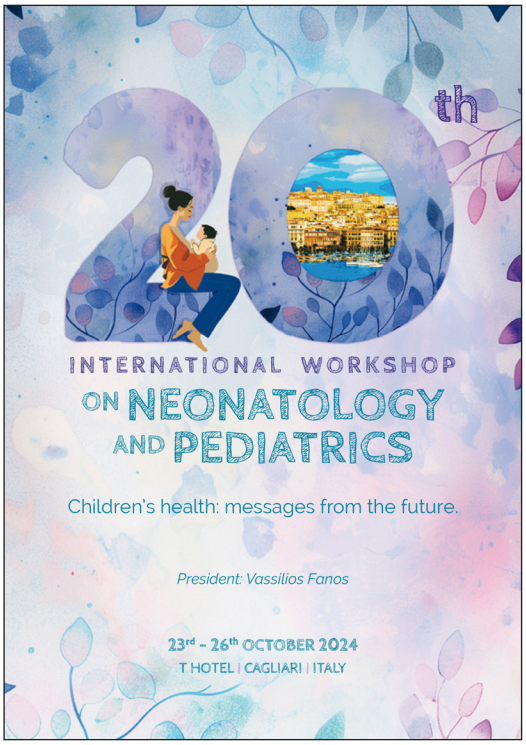

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LECT 1

PRENATAL DIAGNOSIS OF CONGENITAL HEART DISEASES: HOW AND WHERE TO GIVE BIRTH?

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Congenital heart disease (CHD) is the major malformation in the fetus and newborn; approximately, 1% of the world's newborns are born with a structural abnormality of the heart and great vessels.

The classification of CHD encompasses a broad spectrum of defects with varying degrees of severity and sequelae. Advances in prenatal diagnosis and management of the newborn in the Intensive Care Unit (ICU) have resulted in increased survival, especially of newborns with critical CHD; the latter is defined as such when the heart disease requires urgent treatment in the first 24 hours of life to prevent death of the newborn.

At birth, the transition from parallel to series circulation that occurs following shunt closure represents a crucial moment of possible hemodynamic instability for the cardiopathic infant. The detection rate of heart disease *in utero* remains low and highly variable between 40-80% [1]; for some CHD, prenatal diagnosis improves short- and long-term outcomes. The fetal echocardiogram helps (by closely monitoring the progression of heart disease *in utero*) to predict the degree of instability and to plan the level of care (LOC) in the Delivery Room first and in the ICU later; defining the timing, location, and mode of delivery. Many CHDs tend, by a yet unknown pathophysiological mechanism, to progress *in utero* into forms that later prove critical at birth. In particular, 83% of fetuses with dextro-transposition of the great arteries and 64% of those with hypoplastic left heart develop progressive obliteration of the interatrial septum requiring emergency neonatal interventions, with a high incidence of mortality. Hemodynamic instability at birth depends on the type of heart defect, how the circulation is affected by the change in systemic and pulmonary vascular resistances in the transition period, and the patency of the Botallo's duct and foramen ovale. Most infants with CHD can be delivered locally without the need for specialized care in the perinatal period (given that they have better prognosis and longer survival than those diagnosed postnatally), while for some it is critical to schedule delivery at Level III Centers with Neonatal Cardiac Surgery Departments. Recently, the American Heart Association statement on fetal cardiology has drafted a protocol for risk stratification in the Delivery Room by referring to fetal ultrasound criteria [2, 3]. Thus, 4 levels of postnatal care were identified, based on expected hemodynamic compromise, and with the main therapeutic strategies to be implemented:

- low-risk (LOC1) CHDs, represented by left-to-right shunts, mild mitral valve abnormalities, and benign arrhythmias;
- low-risk (LOC2) CHDs, with severe systemic or pulmonary obstruction that are generally stable in the Delivery Room and destabilize following Botallo's duct closure;
- finally, high-risk (LOC3 and LOC4) CHDs, which require immediate stabilization after birth, with percutaneous or surgical cardiac interventions, such as balloon atrial septostomy, atrial septoplasty, cardioversion of uncontrollable arrhythmias, or extracorporeal membrane oxygenation in case of obstructed abnormal pulmonary venous return.

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LECT 2

CARDIOVASCULAR HEALTH AND EXERCISE IN CHILDREN WITH CONGENITAL HEART DISEASES

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Epidemiological studies indicate that cardiovascular conditions are the leading cause of disqualification from competitive sports, accounting for 60-80% of cases. It is well established that most patients with congenital heart defects (CHD) lead a more sedentary and less active lifestyle compared to their peers without cardiac conditions. Encouraging daily participation in appropriate physical activities for these individuals, who are at risk for exercise intolerance and obesity, is a critical role for pediatricians.

The American Heart Association emphasizes the importance of maintaining physically active lifestyles for the health and well-being of children and adults with CHD. Regular physical exercise in children with CHD has been shown to improve physical fitness, reduce the incidence of obesity, and have significant positive effects on psychosocial well-being and academic performance.

CRITERIA

The criteria for evaluating sports eligibility in patients with CHD, whether post-surgical or managed conservatively, can be categorized into general and specific criteria.

General criteria

- Type of CHD: simple/complex;
- type of correction: anatomical/palliative;
- arrhythmias: rare/frequent;
- risk of sudden death: equal to/higher than the general population.

Specific criteria

- New York Heart Association (NYHA) classification (I-IV);
- residual anatomical defects;
- biventricular function;
- exercise tolerance;
- arrhythmias.

STRUCTURED APPROACH

When assessing patients with CHD, a structured approach (in 6 Steps) is essential. This methodology allows for a personalized evaluation, considering that the same lesion may present with varying degrees of severity. Patients should be evaluated using 5 fundamental parameters (see Step 2).

Step 1

Medical history and physical examination.

Step 2

Evaluation of 5 fundamental parameters:

1. assessment of ventricular function;
2. evaluation of pulmonary pressures;
3. examination of the aorta;
4. identification of any arrhythmias;
5. measurement of oxygen saturation at rest and after exercise.

Step 3

Exercise recommendations: type of exercise.

Step 4

Cardiopulmonary exercise testing.

Step 5

Exercise recommendations: intensity of exercise.

Step 6

Follow-up.

CONCLUSIONS

- According to the World Health Organization, physical inactivity increases mortality from all causes, doubles the risk of death from cardiovascular diseases and diabetes, and significantly raises the risk of colon cancer, hypertension, osteoporosis, and depression.
- Literature data indicates that 60-85% of the global population does not engage in sufficient physical activity.
- The most concerning data pertains to children: over two-thirds do not engage in adequate physical activity.
- While a fully functional cardiovascular system is required for competitive sports, engaging in healthy recreational activities is possible even for those with heart conditions.
- All children, including those with CHD, can significantly improve their exercise capacity when guided toward appropriate activities.

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LECT 3

HEART AND MIND: THE HIDDEN LINK

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Congenital heart diseases (CHD) are the most common congenital anomalies, with an incidence of 5 to

8 per 1,000 live births. Over the years, improvements in diagnosis and management have led to enhanced survival rates, with mortality rates around 5-10% in patients under 5 years of age. The increased life expectancy has shifted researchers' focus towards other aspects, particularly neurocognitive development. These children exhibit an increased incidence of developmental delays or neurodevelopmental alterations [1]. Moreover, many CHDs are associated with genetic syndromes like Down syndrome and 22q11.2 deletion syndrome (DiGeorge syndrome), which include both heart defects and neurocognitive developmental delays. The most common issues include delays in motor development, visuo-spatial and social functioning problems, attention deficit, hyperactivity, and autism spectrum disorders.

The causes of these disorders are varied and interconnected, including not only the direct complications of the cardiac anomaly but also genetic, environmental, and treatment-related factors. Understanding these complex mechanisms is crucial for developing appropriate strategies for high-risk patients. Three primary hypotheses explain the association between heart disease and cognitive delays: first, the heart defect restricts the flow of nutrients to the brain during fetal development; second, complications from corrective surgery can cause brain damage; third, a genetic mutation is responsible for both the heart defect and the neurodevelopmental delay, such as mutations in the *RBFOX2* or *ADNP* genes [2, 3].

Long-term management of children with CHD requires a multidisciplinary and longitudinal approach. To enhance the future outcomes for these children, it is essential to implement early intervention programs that address developmental delays, provide personalized educational support, and offer psychological support for families.

Future research will play a critical role in deepening our understanding of CHDs and their neurological effects. Longitudinal studies that follow children with CHD over time are crucial for assessing the long-term impact of various intervention strategies. Genomic research could identify genetic markers that predict risks or outcomes, helping to personalize treatment plans. Moreover, developing safer surgical techniques and perioperative care protocols that minimize neurological risks is paramount.

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LECT 4

INTERCURRENT PATHOLOGIES, CONGENITAL HEART DISEASES AND CLINICAL MANAGEMENT: WHAT ELSE?

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Congenital heart defects represent one of the most common congenital defects in the neonatal period, with a significant contribution in terms of neonatal morbidity and mortality. The incidence is estimated to be 8 births affected by heart disease per 1,000 live births; if, on the one hand, medical and surgical therapeutic progress has significantly improved the survival and quality of life of these patients, on the other hand their management has become extremely complex, requiring a multidisciplinary approach aimed at guaranteeing adequate growth and appropriate management of the disease by the child and his/her caregivers.

It is indisputable that a hemodynamically relevant heart disease impacts the growth of a newborn and a child, with a multifactorial etiology in growth delay: poor growth due to water restriction, difficulty in feeding due to hemodynamic alterations and reduced tissue oxygenation act in synergy with an increased incidence of infectious diseases of the gastrointestinal and respiratory tract, especially in heart disease with hyperinflux. The infant who must approach palliative surgery or definitive correction of the heart defect requires a nutritional intake to ensure growth for the surgical timing, but it is important to plan for these patients an adequate prophylaxis of infectious pathologies, which can complicate the pre-operative phase, as is done for example for respiratory syncytial virus infections. The management of patients

undergoing palliative interventions is extremely complex: for example, patients with univentricular heart present growth retardation in the phases preceding the Fontan operation and an increased incidence of gastrointestinal infections in the clinical and therapeutic course. Recent studies have also highlighted how the intestinal microbiome has a decisive role in the evolution of congenital heart disease and in the genesis of heart failure, highlighting a clear discord between intestinal bacteria in healthy newborns and in the group of newborns suffering from heart disease: in the latter, in fact, there is a constant reduced growth and a smaller head circumference, with a prevalence of pathogenic microbial flora and a poor representation of the physiological microbiome.

Even if it cannot be classified as an intercurrent pathology, it is necessary to remember an emerging pathology in pediatric age and in children with heart disease: obesity, which is defined as the "epidemic" of the century; it is estimated that a quarter of children with heart disease are at risk of becoming overweight or obese.

Therefore, there are two fundamental objectives for the management of heart disease children with intercurrent pathologies: a correct nutritional regime and prevention and prophylaxis of infectious diseases. Starting with the simplest rules: wash our hands and cover the sneeze!

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LECT 5

ARTERIAL HYPERTENSION IN THE CHILD

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High blood pressure has been recognised mostly as just an adult health issue for a long time. However, it is now being increasingly acknowledged as a significant issue also among children and adolescents. In fact, the hypertension detected in adulthood may manifest since childhood as random raises in blood pressure or abnormal blood pressure response to physical or psychological triggers. Like other kinds of chronic diseases, hypertension tends to develop a few decades prior to the occurrence of its clinical signs and symptoms. Since blood pressure levels are usually retained throughout life, children and adolescents with higher blood pressure values are more likely to become hypertensive adults. It is the so-called "tracking" of blood pressure [1].

Extensive normative data on blood pressure in children have long been available both in the United States (since 1987) and Europe (since 2009) and periodically updated. There is also significant variance between that outlined by the European Society of Hypertension, the European Society of Cardiology in 2022 [2], and the last 2017 statement released by the American Academy of Pediatrics [3] regarding the blood pressure cut-offs to identify young hypertensive subjects. Not only this is true, but the American Academy of Pediatrics have also ruled out obese children in the new normative data. This is undoubtedly concerning.

Paediatric blood pressure nomograms are based on percentiles for an age range between 5 and 13 years. Blood pressure values under the 90th percentile are considered normal. Children with blood pressure over the 95th percentile are hypertensive. At least three distinct blood pressure checks are needed before making diagnosis of hypertension. Confirmation by means of 24-hour ambulatory blood pressure monitoring is sometimes needed.

After the age of 13, adolescent patients are considered hypertensive on the basis of adult cut-offs, rather than using paediatric centiles. This is with a view to matching the adult classification of hypertension. As such, according to the American Academy of Pediatrics, those individuals with a blood pressure > 130 and/or 80 mmHg suffer from high blood pressure. Conversely, with regard to the European Society of Cardiology, it is 120 and/or 80 mmHg the cut-off to consider adolescents as hypertensive.

On the contrary, both the American Academy of Pediatrics and the European Society of Cardiology agree that drug therapy should be reserved just for non-responders to measures like weight loss, salt intake reduction, and increase in aerobic exercise.

As hypertension is one of the most harmful risk factors for stroke and myocardial infarction, there is

no doubt that one of the most important challenges for clinician is the early prevention of high blood pressure onset in order to defer the occurrence of major adverse cardiovascular events in adulthood.

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LECT 6

CONGENITAL HEART DISEASE: HOW TO MANAGE THE TRANSITION FROM CHILDHOOD TO ADULTHOOD

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Thanks to the advancements made in recent years in cardiac surgery and interventional cardiology, the number of patients with congenital heart disease who reach adulthood is steadily increasing, and they have specific healthcare needs. One of the most delicate phases in these patients' lives is the transition from childhood to adulthood. During this phase, they face a series of changes that involve their entire family unit, as well as clinical peculiarities related to their congenital heart disease. For this reason, the need was felt to create a cultural, healthcare, and research bridge between the world of the child growing into an adolescent and that of the young adult. This bridge is represented by the "Transition Clinic" project, which consists of three main stages, each involving the implementation of targeted interventions.

1. Understanding one's own clinical condition. Through collaboration among various professionals of the multidisciplinary team, a folder has been created and is handed over by the dedicated nursing staff to the young patient and their family at the time of enrollment in the study, following the completion of the baseline questionnaire battery and the signing of the informed consent for participation in the study. Additionally, the necessary surgical, interventional, and pharmacological treatments are discussed in detail, depending on the specific heart disease.
2. Education and support. The second stage focuses on the psychological aspect of adolescents with congenital heart disease, aiming to support the delicate transition from childhood to adulthood through the activation of a psychological support and peer counseling service.
3. Involvement and collaboration. The third stage is dedicated to improving communication among the various professionals of the multidisciplinary team involved in the clinical-care pathway, as well as among patients, parents, and healthcare providers.

This model was designed to optimize the quality of life of young patients with congenital heart disease, encouraging positive life expectations and realistic prospects regarding future professional productivity. Understanding the needs of patients is essential to address the diversity and complexity of adolescents with congenital heart disease.

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LECT 7

SPORTS CERTIFICATION: DIFFERENCES BETWEEN ITALY AND OTHER COUNTRIES

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The international guidelines of 2020 [1] divide athletes into: those affected by pathologies and healthy subjects; under 35 years of age and over 35 years of age. They consider acute cardiovascular events, such as sudden cardiac death and myocardial infarction or stroke, less frequent in the population that practices sports. They suggest increasing the rehabilitation prescription of physical activity used as therapy [1].

In most countries outside Italy, one can approach sport more easily and freely, as it happens in Anglo-Saxon countries, where certification takes place online, on an anamnestic basis, without contact between the athlete and the doctor, with few targeted tests and without a predetermined procedure.

The rest of the European countries adopt the French model. This provides for the issuing of a medical certificate of non-contraindication, valid for all ages and sports activities. The same certificate is defined as invalid in Italy.

In the United States, there is a double vision: on one hand there is extreme liberality even for high levels (such as boxing), while on the other hand sport is used as a preventive and rehabilitative therapy for most pathologies, both in the surgical and medical areas.

On the contrary, in the Russian Federation, the methods and times in the management of ice hockey athletes are meticulously specified.

And what about Italy? The regulatory framework is legislated in various ways, sometimes in a Latin-like complex way.

The first rule is from 1982, then 1993, then 2013 and corrected by a revision after 3 months, with a distinction in: competitive, non-competitive and recreational sports activities.

The Italian philosophy starts from the fact that life is sacred and that, for this reason, the protection of health is a priority. It gives rise to a series of preventive checks (sometimes in antithesis to international guidelines – see echocardiogram and watt test). The Italian paradox is that it hyper-regulates access to sports practice but is scarcely present in the prescriptive field.

What about the exasperated request for competitive certificates, even for age groups where, in my opinion, the aspect is mainly recreational? Think of the cases of roller skating, handball, artistic or rhythmic gymnastics, where, by indication of the specific federations, activity is obligatorily considered competitive from the age of 8 years. 8 years? What will happen to the sporting spirit? And to the joints, muscles, and heart?

In conclusion: the world picture certainly sees us as pioneers in the regulation and attention towards sports practices, and this is right especially when compared to the excessive superficiality that many other countries show. But we will have to use sport more as a real therapy and bring closer an ever-increasing number not only of athletes but also of patients.

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LECT 8

METABOLOMICS AND PEDIATRIC CARDIOLOGY

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Pediatric cardiology has evolved significantly with progresses in molecular biology and genetics. Nevertheless, traditional diagnostic tools and therapeutic strategies often fail to capture the complexity and the heterogeneity of pediatric heart diseases, with congenital heart disease (CHD) being the most common congenital anomaly, affecting nearly 1% of live births worldwide. In this context, metabolomics, the large-scale study of small molecules (metabolites), within cells, tissues or organisms, could be a powerful tool in understanding the metabolic underpinnings of cardiovascular disease in this population. Indeed, this "omics" science provides a system-levels view of metabolic changes, offering new insight into disease mechanism, potential biomarkers for early diagnosis, and targets for therapeutic intervention [1].

Concerning biomarker discovery, some studies were able to identify the metabolic fingerprint of amniotic fluid of mothers who will give birth to newborns affected by CHD. The application of metabolomics to investigate congenital heart defects led to some very interesting results. Children and newborns

with CHD often exhibit disrupted mitochondrial function, leading to impaired energy production contributing to their vulnerability to heart failure. Moreover, oxidative stress could be a critical factor in the pathogenesis of CHD. Metabolomic profiling has identified increased levels of oxidative stress markers in children with CHD, correlating with disease severity and poor clinical outcomes [2]. Other studies focused on the outcomes of pediatric cardiac surgery and possible complications of these procedures, and showed that newborns who died after surgery had a precise metabolomic profile before surgery.

Everybody has a heart but not all the hearts are the same, especially in case of cardiovascular diseases in newborns and children. Metabolomics, providing an individual metabolic footprint for each and every individual, could pave the way of personalized medicine in this field that can improve outcomes for these little patients [3]. Despite the challenges that remain, the future of metabolomics in pediatric cardiology is promising, with the potential to transform the field and enhance the care of children with heart disease. In fact, metabolomic markers can be used to stratify patients according to their risk of developing complications, such as heart failure or arrhythmias, or even neurological complications, allowing for more targeted surveillance and early intervention.

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