Chapter 2. Fetal diagnosis

In the last few decades, the fetal diagnosis of congenital heart defects has made remarkable progresses, allowing the recognition of virtually almost all heart malformations between the 16th and 18th week of pregnancy, with a sensibility over 96% and a specificity close to 100% (1, 2).

The potential impact of fetal diagnosis in congenital heart defects includes:

- knowledge of the natural history of the congenital heart defects "in utero"
- potential fetal medical or interventional cardiology therapeutic interventions in the case of diagnosed heart failure, arrhythmias, or malformations with poor neonatal prognosis
- safer management of the pregnancy itself
- organization of the peri-natal period in or close to institutions with facilities available for the immediate management in the case of life-threatening heart malformations
- parental counseling

The current expansion worldwide of fetal diagnosis of congenital heart defects (3-30) has been based on several elements: availability of equipment, specific level of expertise, local development of structures and infra-structures, all factors over time variable among institutions, as services and policies evolve, and therefore affecting rate and impact of the fetal screening. The incidence of fetal diagnosis had an influence on the trends and

outcomes of congenital heart defects, while several additional factors must be included in the evaluation of the outcomes: pregnancy management and delivery planning, associated non-cardiac co-morbidities, long-term neurodevelopmental consequences, resources utilization and costs/benefits issues.

Various studies have taken in consideration all various points listed above, and the unavoidable relationships among them, being their correlation very strict, even if it is impossible to quantify the sensitivity/specificity of the fetal screening or the subsequent outcomes (31-42).

The matter becomes much more delicate when considering all potential ethical and social implications of fetal diagnosis of heart malformations, particularly regarding parents counselling and decision-making, frequently dealing with the dichotomy between interruption of pregnancy versus full treatment.

Another important consideration when dealing with ethical issues following fetal diagnosis, becomes the distinguishing between complex and simple heart malformations.

Complex congenital heart defects

The largest group of complex congenital heart defects includes all malformations with "functionally" single ventricle, regardless their individual morphologic characteristics.

The outcomes achieved in single ventricle have recently remarkably improved (43-47), however the definition of "intractable" congenital heart defect remains unfortunately attached to the diagnosis of single ventricle, due to the questionable late outcomes

(37,48). “Intractable” (48) or “uncorrectable” (37) has been used to define a cardiac malformation not suitable to bi-ventricular repair, but only to multi-staged complex palliations aiming to achieve the Fontan circulation, or eventually a heart transplant. Alternatively, avoidance of any treatment and compassionate care remains the only available option in these children (37,48).

Reports with evident discrepancies appeared in the literature about the various outcomes obtained with heart transplantation after different surgical stages for single ventricle (49-52).

After fetal diagnosis of single ventricle (4,8,11,13,18,19,32,34,35,37,38,41,47,53), the decision-making process has been oriented to pregnancy termination or compassionate care in percentages variable from 8% of cases (32), through 16% (18,19), 30% (11,13), 33% (8), up to 47% (41), due to various among the following reasons: frequent association of genetic abnormalities and/or severe non-cardiac defects (41), reduced early and late survival, poor quality of life, child suffering (4,13), stress for the entire family, including siblings (4,37).

Generally, after fetal diagnosis of complex congenital heart defect, a comprehensive multi-specialties pre-natal screening, including chromosomes assessment, complete intra-and extra-cardiac evaluation, should be performed to provide the family with an appropriate explanation of the expected future (11,13,14,18,19,32,34,37,42,47,53,54). The

parents and their families have all the right to receive the information indispensable to prepare and support them (37).

Following pre-natal diagnosis of congenital heart defect, parents and family face a dramatic psychological crisis because of their state of shock, contradictory information available on potential early and late outcomes, limited availability of time for decisions and for autonomous choices (4,47,53). Furthermore, not all the parents are willing to perform autonomous choices due to family or other cultural and societal pressures (4).

The process of parents counseling, already complicated by the often-difficult communications between healthcare providers and families, can present additional obstacles due to education, cultural, religious and social backgrounds, individual cognitive and emotional processes (5,6,37,39,47,53). Cross-cultural patient care is a challenging issue for the caregivers: dealing with families totally refusing medical treatments because of their educational and/or religious backgrounds requires an open mind to insist on proposing a medical plan (6,39,47,53).

Nowadays many families can become aware of the best outcomes accomplished in the top hospitals, while the same excellence not necessarily can be achieved by the services locally available to them. In such situations, it can be quite uncomfortable for a doctor to inform the prospective parents that the local results for complex congenital heart defects may be less satisfactory than the gold standards reported on internet, and this can also skew subsequent discussions (47,53).

Well recognized is the knowledge about how influent are the modalities of communications transmitted by the physicians during the counselling process, as well as the perceiving mode of the parents. While it is not surprising that optimistic surgeons are capable of attracting the parents' approval for the proposed surgical approach, more unexpected can be the negative reaction not infrequently shown by families after the advice received by physicians (14,15,35-37,42,47,53).

The belief of the involved caregivers can range between extreme optimism on the potential long-term outcomes versus advice to seriously take into consideration the possibility of pregnancy interruption, with obvious influence on the decisions of the parents (7,33,35,38,40,47,53).

Fully focused attention should be given to the sensitivity of each specific case, particularly considering that, within each couple of parents and family, there are various degrees of capability to accept and support for long-term a poor quality of life.

In general, the suggestions made by the doctors try to maximize the possibility of achieving the best available outcomes, without always providing complete details about the chances of negative outcomes; furthermore, their knowledge on expected outcomes are inevitably biased by their previous clinical experiences. (7,47,53).

The risk of misunderstandings in the transmission of information is particularly high when the available evidence is limited, or when the available treatments available are reported with significantly variable outcomes (7). Finally, because of the variability of

the available pre-natal screening in complex congenital heart defects and the large contrast in the reported results, it can be extremely challenging for the physicians to maintain a scientific and objective perspective untainted by their personal feelings and opinions (47,53).

Often doctors are asked the following question: "What if it were your child?" (10). At the first joint meeting of the "European Association Congenital Heart Surgeons" and the "Congenital Heart Surgeons Society" of North America, the "Audience Response Survey" tried answering the above question interrogating a group of more than 70 experienced professionals in congenital heart surgery. Their answers are reported in ***Table 1*** (31,53).

Table 1 Results of the "Audience Response Survey"

Options	Patient	Family member
Norwood	73%	26%
Heart transplant	0%	1%
Compassionate care	6%	5%
Pregnancy interruption	21%	68%

The expert congenital cardiac surgeons participating to the survey provided completely different answers among the available options after pre-natal diagnosis of hypoplastic left heart syndrome in a patient versus a hypothetical close member of their family (31,53).

In all families and health care professionals involved, the fetal diagnosis of complex congenital cardiac malformation is always followed by important consequences (53). The counselling with the parents and the entire decision-making process become very challenging due to the large variability of heart defects with different clinical presentations, potential associations of genetic abnormalities, presence of other intra- or extra-cardiac malformations, and the reported poor early and late outcomes. Evidence resulting from observations on the treatments used nowadays should provide adequate knowledge to facilitate the parents counselling after pre-natal diagnosis of complex congenital heart defects.

Simple congenital heart defects

The ethical considerations can become even more controversial in the presence of fetal diagnosis of simple cardiac malformations, even if this could be unexpected.

After the introduction in the clinical practice of fetal diagnosis for congenital heart defects, interruption of pregnancy has become not only available, but strongly supported on these grounds in many Western countries (1,2). As a result, in some of these countries the number of neonates born with simple congenital heart disease has declined significantly despite remarkable progresses in the treatment options and outcomes, as reported on the database of the European Congenital Heart Surgery Association (https://echsacongenitaldb.org) and of the North America STS Congenital Heart surgery database (www.sts.org/registries-research-center/sts-national-

database/sts-congenital-heart-surgery-database). This was the consequence of policies applied and reported, with certainly debatable decision-making processes, after fetal diagnosis of simple congenital heart defects (27).

The report of a discrepancy between pre- and post-natal diagnosis of congenital heart defects is relatively rare, but, when this happens, the treatment immediately after birth as well as the long-term management can be effectively and positively modified, like in reported cases with fetal diagnosis of hypoplastic left heart syndrome, modified in aortic coarctation at the post-natal investigations (55). Therefore, the caregivers involved should maintain extreme caution during their pre-natal counselling to the parents, when related with the treatment based on the diagnosis obtained with fetal echocardiogram, particularly when interruption of pregnancy is among consideration (55).

The reported study (27) reflects the clinical experience collected in a country with a level of socio-economic and health organization among the most advanced in the world, with a particular social demographic quite different even from many other high-income countries. The data presented may result in significant questions to be accepted or indeed understood in other health care systems with completely different levels of socio-economic status, and among other cultures, religions, educations, and ethnicities (5,6,37,39,53).

Unfortunately, interruption of pregnancy has been offered for fetal diagnosis of simple congenital heart defects, treatable like isolated aortic coarctation, atrioventricular septal defect, tetralogy of Fallot, double outlet right ventricle, truncus arteriosus, transposition of the great arteries, and aortic arch interruption (27), all malformations with recognized low STAT risk stratification (56) and excellent outcomes, with overall hospital mortality reported lower than 5% (57).

When the decision-making must take into consideration scientific as well as ethical aspects, different perspectives can substantially complicate the process.

As the natural history of some of the congenital heart defects may result in spontaneous abortion, before the availability of the information on fetal diagnosis, families and caregivers must choose between medical management and abortion. The availability of termination of pregnancy largely influences the perspectives and subsequently the approach by physicians in these situations (58).

In a genuinely ambivalent society praising this option, in a near future many doctors will suppress patients even with very simple congenital heart defects instead than offering them treatment, and the medical profession will have to deal with the very debatable opinion that “some life is not worthy to be lived” (58).

To become a doctor is not privilege: it is a commitment, with patients, families and community, requiring every possible effort to help the diseased people, and to push the boundaries of knowledge, with a work ethic far beyond that of research alone (59).

Interruption of pregnancy eliminates the fetus with a malformation, instead of curing the underlying malformation. Therefore, interruption of pregnancy doesn't address the defect, and doesn't care the affected individuals (59). Our responsibility is to contribute to the development of a science without cultural stagnation, to encourage advanced research, and to involve not only patients and families, but health organizations, and society at large (59).

Fetal diagnosis of congenital heart defects results in an ethical dilemma for both parents and physicians. The right to decide should be left to the parents, while the caregivers must support them with nondirective counselling, providing the complete and correct information required for a meaningful parental decision (53,60).

When involved individuals with congenital heart defects have been asked about a choice for their own life, the preference was always for some life, even if short and characterized by poor quality, rather than no life at all (39,46).

Full information about a fetal diagnosis of congenital heart defect, particularly in the case of simple defects, must be provided with all available data on the early and late outcomes achievable with the currently available treatments (56,57)., keeping in mind that the way the family is perceiving the information received is definitively influenced by the modality used by the counsellor to transmit the information (53,60).

Special considerations

After the general considerations on the ethical and social consequences of fetal diagnosis of complex and simple congenital heart defects, specific points to consider for each fetal diagnosis are the following:

- Non-cardiac issues
- Cardiac issues
- Survival
- Morbidity
- Neurological development
- Pregnancy management and delivery planning

Non-cardiac issues

An important point to consider is that in fetuses with congenital heart defects, particularly in the more complex cardiac malformations, the association of chromosomal disorders has always been reported with an elevated incidence (18,19,61-82), as well as reduced fetal body weight and growth (83,84), associated non-cardiac malformations (19,85-88), and the presence of situs inversus or heterotaxy (89).

Cardiac issues

The incidence of complex congenital heart defects has been observed as higher in the fetal pre-natal cardiac screening than in the post-natal diagnosis (61,83,99-104).

The pre-natal cardiac screening can also be useful to detect fetal arrhythmias (95). Of course, the pre-natal diagnosis of complex congenital heart defect has opened the possibility of investigating potential fetal interventions (105).

Among the various findings provided by fetal echocardiography, the most important information is relative to morphology, size, shape, and function of the ventricular chambers, despite the known difficulties in evaluating the ventricular performance based only on fetal screening (8,106-109).

The data collected on the morphology and functioning of the right atrio-ventricular valve are also relevant in the presence of hypoplastic left heart (8,99,109), as well as the fetal evidence of endocardial fibroelastosis is accompanied by negative prognostic implications (19,109).

In the specific cases of fetal diagnosis of hypoplastic left heart syndrome, the presence of restrictive inter-atrial communication, and the type and direction of the flow through the inter-atrial communication itself (8,18,107,110), as well as the responsiveness of the fetal pulmonary vasculature to maternal hyperoxygenation (110), are indispensable for a prognostic evaluation and for the organization of the immediate post-natal treatment.

Type and direction of flow through the patent ductus arteriosus (111), and particularly the presence of obstructed or retrograde flow through the aortic arch, are essential findings to predict the expected post-natal pathophysiology (8,108).

Another potentially associated cardiac malformation, the presence of ventriculo-coronary arteries connections, has been demonstrated in fetal echocardiographic screening (105).

Survival

The most important parameter to evaluate the impact of the fetal diagnosis on the outcomes is evidently early and late survival, and this issue has been addressed by many studies (8,83,104,110,113-125). When considering the survival, discrepancies have been demonstrated between the observations made for relatively simple congenital heart defect, such as aortic coarctation, where the fetal diagnosis contributed to substantially improve the outcomes, including survival (116,120,123-125), while for more complex defect, such as transposition of the great arteries, disagreements have been reported on the impact of the fetal diagnosis, from reporting improved pre-operative as well as post-operative survival (113,120,123-125), to reporting only improved pre-operative condition but without any improvement of the post-operative outcomes (114). When dealing with the most complex congenital heart defects, because of the presence of multi-factorial elements influencing the outcomes, there is a more striking discrepancy among the impact of fetal diagnosis on survival (8,83,112,115,117-126).

Contrary to the past, when clinical studies failed to show an improved overall survival with fetal diagnosis of hypoplastic left heart syndrome (127,128), more recently, with remarkable improvement of the perioperative management, a dichotomy became evident with divisive reports proving improved survival with fetal diagnosis (8,118-126) against

the studies showing no difference in survival between cases with and without fetal and diagnosis (83,104,114,115,117).

Despite these discrepancies regarding survival, almost all reports confirmed the evidence of improved pre-operative conditions achieved thanks to fetal diagnosis and the subsequent timely transfer to tertiary referral hospital for intensive care management. Prompt referral after fetal diagnosis has been proven to reduce incidence and severity of pre-operative metabolic acidosis and subsequent need for bicarbonate administration, to minimize the requirements for pre-operative inotropic support, to reduce occurrence and degree of ventricular dysfunction and right atrio-ventricular valve regurgitation, and to almost abolish the complication of end-organs dysfunction (8,83,114,115,117-125).

In the case of identification of restrictive inter-atrial communication, the fetal diagnosis allows to perform early intervention (126).

A point to take in serious consideration is that despite in most of the reported studies the pre-operative conditions were significantly better with fetal versus without fetal diagnosis, in about half of the reported studies this pre-operative improvement was not associated with increased hospital survival.

The impact of fetal diagnosis has not yet been evaluated on the outcomes of the hybrid approach for hypoplastic left heart syndrome, with bilateral pulmonary artery banding and stenting of patent ductus arteriosus, option increasingly considered in recent years in patients considered with high-risk for the conventional surgical treatment (129-137).

Morbidity

Even regarding the post-operative morbidity, differences were reported between the two groups with fetal and post-natal diagnosis, exactly as for the survival (8,83,114,117,119), with only a few reports demonstrating a reduced post-operative morbidity in the group with fetal diagnosis (8,83,119). The arguments in favor of decreased morbidity were better clinical conditions before surgery, particularly because of the controlled metabolic acidosis (8,119), reduced duration of mechanical ventilation (83), and reduced requirement for emergency operation (83), and better post-operative ventricular function (8,119).

As for the observations on survival, other studies didn't observe any reduced morbidity in the group of patients with fetal diagnosis (114,117).

Neurological development

Numerous studies investigated early and late neurocognitive development in children with complex congenital heart defects, but very few of them were focused on the impact of fetal diagnosis (115,118,138-143). Despite in fetuses with hypoplastic left heart syndrome, a significant decrease in head growth and chronic diffuse white matter injury of variable severity have been reported (138,141), the fetal diagnosis has been associated with decreased incidence of adverse peri-operative neurologic events (115,140-143), as well as reduce occurrence, and lesser severity of neurocognitive deficits (139,140-143). It is common knowledge that neonates with complex congenital heart defects present an increased incidence of central nervous system abnormalities, due to inadequate development, fetal low oxygen delivery because of low oxygen content and/or

reduced systemic perfusion, post-natal cyanosis, and exposure to general anesthesia and cardio-pulmonary bypass; nevertheless it appears that fetal diagnosis, accompanied by a substantial reduction of the peri-operative multi-organ injuries, can remarkably improve the long-term neurologic outcomes (115,118,139-143).

Pregnancy management and delivery planning

Commonly acknowledged is the positive impact of fetal diagnosis of complex congenital heart defect in the management of pregnancy and particularly in the appropriate planning of delivery (8,100,111,144-151).

Following fetal echocardiographic diagnosis of complex congenital heart defect, a maternal-fetal care program can be organized, with meticulous pregnancy follow-up and mode of elective delivery, either cesarean or vaginal with induced or spontaneous labor, timely established and planned and in a tertiary referral hospital.

With such an organization the appropriate multi-disciplinary management of the neonate can be planned from the delivery room directly to the interventional or operating room, following echocardiographic confirmation of the fetal diagnosis shortly after birth, and immediate transfer to the neonatal intensive care unit for prompt administration of prostaglandins, maintenance of normal acid-base status, tracheal intubation with mechanical ventilation to provide and maintain adequate balance between systemic and the pulmonary circulation (8,111,144-151).

Delivery planning is also an important component of the counseling, because fetal cardiologists and maternal fetal medicine specialists collaborate working as caregivers for the mother and fetus with heart defect. Delivery at a tertiary care hospital with access to intensive pediatric cardiac care is recommended for all ductal-dependent malformations and all heart defects expected to require neonatal intervention. Parental counseling should be provided in close cooperation with the obstetrical team to give consistent information to the parents and optimal care for the fetus.

Delivery of neonates with congenital heart defects at later gestation has been shown to be associated with improved survival (152). High morbidity and mortality have been reported in neonates with congenital heart defects born before 36 weeks of pregnancy, particularly in the presence of extracardiac and/or genetic abnormalities (153). Even the delivery at an early term neonate (37–38 weeks of gestation) is associated with worse morbidity (complications, hospital length of stay) and mortality after neonatal cardiac surgery than a neonate delivered after 39 weeks of gestation, and based on these observations a delivery after 39 weeks is typically recommended (154,155).

Prenatal diagnosis of congenital heart defect has been reported associated with a threefold risk of developing intrauterine growth restriction (156), and therefore, monitoring fetal growth is essential. Parents should be counseled that intrauterine growth restriction is associated with increased morbidity after neonatal cardiac surgery

(157), as well as lower weight (<2.5 kg) is associated with higher mortality after neonatal cardiac surgery (158).

Resources utilization and cost/benefits issues

In this era of money-driven medicine, the efforts toward cost containing have also affected a potential impact on fetal diagnosis of congenital heart defects (159,160).

The costs of training cardiac ultrasound technicians and make them capable to independently perform fetal diagnosis of congenital heart defects have been compared with the costs of organizing emergency transports to specialized tertiary centers of neonates after post-natal diagnosis. The results showed a substantial saving, considering the costs of training the cardiac ultrasound technicians plus the planning of elective transfer for delivery to a tertiary referral center in the case of fetal diagnosis of complex congenital heart defect, versus emergency transportation and care after postnatal diagnosis of similar heart malformations (159). The saving was directly correlated with the detection rate, with considerable increase for each day of exposure to specific training of the cardiac ultrasound technicians (159).

Conclusions

One of the major achievements of pediatric medicine in the last 50 years is the tremendously increased understanding of the pathogenetic causal mechanisms of congenital heart defects as well as their treatment, and any resultant sequelae. For infants with congenital heart defects, the progress of the surgical treatments has allowed

a huge increase in the proportion of these children reaching adult life with a decent quality of life and social integration. Therefore, we should refuse that global widespread of fetal diagnosis, justifying pregnancy interruption, may cancel all those gains. Furthermore, the resulting decrease in the post-natal population undergoing treatment will have a remarkably deleterious effect on the experience and expertise of all individuals involved in the care of these patients, which might conceivably produce a reduction in outcome quality which cannot be positively considered.

With all respect for the parental choices and the obligations to follow the national laws, however the resulting feeling is the necessity to observe that our society is genuinely ambivalent.

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