The Fetus as a Cardiac Patient: Assessment and Therapy of Cardiovascular Pathology before Birth

Guest Editors: Anita J. Moon-Grady, Shinjiro Hirose, Greg Kesby, Samuel MenaHem, and Wayne Tworetzky
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Editorial

The Fetus as a Cardiac Patient: Assessment and Therapy of Cardiovascular Pathology before Birth

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The past few decades have seen major advances in evaluation and treatment of fetal cardiovascular diseases. Largely due to advances in imaging, recognition of structural pathology in the developing human heart can now be performed as early as the 12th week of pregnancy and can be seen to develop and progress through gestation. Because of the observation that serious structural congenital heart disease may progress from seemingly minor disease if untreated, several centers are now intervening before birth to address such abnormalities and attempt to prevent the further development of structural disease. Furthermore, detailed assessment of cardiac rhythm, function, and myocardial mechanics is now also possible as early as the first trimester. Transplacental treatment for fetal rhythm abnormalities has dramatically changed the outcomes for affected pregnancies in the past decade. More recently, several centers have begun to incorporate routine fetal cardiovascular assessment in the evaluation of diseases such as congenital cystic adenomatoid malformation of the lung, twin-twin transfusion syndrome, and congenital diaphragmatic hernia where structural disease may impose significant comorbidity postnataally, and hemodynamic derangements and functional pathology secondary to the primary process may impact the fetus in utero. Recognition of potentially treatable fetal cardiac disease may alter the prognosis for these patients in the perinatal period as in utero treatment to address the primary abnormality has been shown to improve the hemodynamic derangements observed. Finally, prenatal recognition of fetal cardiac disease in general may be changing the natural history and incidence of disease in the postnatal population.

Regardless of training and background, any healthcare professional involved in the diagnosis and management of diseases of the fetus and newborn now needs to be cognizant of the potential contribution of prenatal cardiac assessment and treatment in the congenitally malformed or unwell fetus. In this special issue on the fetus as a cardiac patient, we have invited a few papers addressing issues unique to this patient group.

The first paper of this special issue addresses ethical issues relating to fetal diagnosis of a major abnormality with special emphasis on cardiac malformations. Presented are discussions of the ethical concept of beneficence and the principle of patient autonomy in the context of counseling expectant mothers and the complex ethical situation which arises in the consideration of the fetus as a patient.

The second paper presents a comprehensive review of cardiac findings in twin-to-twin transfusion syndrome (TTTS), a condition which is a severe complication of mono-chorionic twin pregnancy. TTTS is characterized clinically on ultrasound by polyhydramnios in the “recipient” twin and oligohydramnios in the “donor” with varying degrees of cardiac dysfunction in the recipient. The pathophysiology of the syndrome itself and of the development of cardiomyopathic changes remains incompletely understood. The review discusses what is known with respect to the cardiac findings at presentation, natural history, and response to treatment.
and discusses current approaches to a comprehensive cardiac evaluation of affected fetuses. The third paper describes a large series of fetuses presenting with findings consistent with cardiomyopathy or myocarditis and represents a large natural history study of these entities, underlining the particularly high perinatal loss rate with diagnosis of dilated cardiomyopathy or myocarditis, as opposed to many of the hypertrophic myopathies.

The issue concludes with two thought-provoking review articles regarding the intrauterine environment and the complex interaction the developing fetal brain and circulatory system have with each other and the placental circulation. In the first of these, the authors present a discussion of intrauterine hypoxia, its various causes, and mechanisms whereby disease in the fetus may result. The final paper presents a comprehensive review of the current understanding of pathologic findings in the developing brain of the fetus and infant with congenital heart disease. Methods for detection, potential etiologies, and implications for neurodevelopmental outcome are discussed. Intriguing speculation regarding the possibility of altering the natural history of developmental brain abnormalities via in utero intervention will leave the reader eagerly anticipating future developments in the rapidly advancing field of fetal cardiovascular assessment and treatment.

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Review Article

Ethical Issues in Fetal Management: A Cardiac Perspective

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The ethical issues behind the management of a fetus with a serious abnormality and the decisions made in relation to the outcome of the pregnancy are complex. This reflective paper deals with the ethical principles of managing a pregnancy with a congenital anomaly, with particular emphasis on the fetus with a serious cardiac abnormality. One major ethical concern is whether the fetus is or is not independent being to whom obligations of beneficence are owed. We review the debate on this matter, and suggest that it is ethically more appropriate for physicians who are involved in management of fetal abnormality not to adopt and insist on their own position on this matter. Rather, the appropriate course is to respect the pregnant woman’s own view of her fetus and how it should be regarded. This is an application of the principle of respect for autonomy. Within this framework, we discuss the difficulties in counselling a pregnant woman or expectant couple in this situation, and recommend three key steps in ethically sound counselling.

1. Introduction

Prenatal diagnostic ultrasound is widely performed especially in the western world. Parents attending a scan expect to be told that their baby is normal. They want to be reassured regarding the size and well-being of the infant, and may wish to know its sex [1]. When a possible anomaly is identified, it comes as a shock to the parents, who were not expecting such an outcome. If the anomaly is subsequently confirmed, there may be an assumption that as the parents sought screening in the first place; they intended to proceed to an abortion [2]. However, this is not always the case, given their expectations at the outset. Counseling the parents in such situations is complex and requires much sensitivity. This paper reviews the ethical issues involved and makes recommendations for practice.

2. Basic Ethical Principles

Chervenak et al. have very eloquently described the basic ethical principles in the management of pregnancies complicated by fetal anomalies [3]. The first ethical concept is that of beneficence. Health related interests of the patient obligate the physician to seek clinical benefits over clinical harms for the patient. The second basic ethical principle is respect for the patient’s autonomy. This principle means that the patient’s perspective on health-related and other interests is paramount. The physician needs to respect the patient’s own set of values, beliefs and decision-making capacity. The physician’s role is to provide adequate information and a recommended management plan, or range of possible plans, for the condition in question. It is vital that the information is provided in a manner that allows the patient to understand it, so as to be able to reach an informed and voluntary decision. We will discuss the physician’s ethical obligations in relation to informed consent in more detail below. However, it is important to note that the expectant parents’ great state of distress, grief or shock may make it very difficult for them to take in, understand and assimilate what is provided [4], even with very careful presentation of information.

The crucial ethical question in pregnancies complicated by fetal anomalies, according to Chervenak et al. [3], is whether the fetus counts independently as a patient to whom the obligations of beneficence are also owed (in addition
to the pregnant woman). If the fetus is also a patient, then the ethical situation becomes much more complex. What is best for the pregnant woman may differ from what is best for the fetus (for example, where there are physical risks to the woman in continuing the pregnancy). In addition, the woman may make decisions which are contrary to the best interests of the fetus (for example to terminate a viable pregnancy). Difficult choices may have to be made and are based on where ethical priorities lie.

There are two possible approaches to dealing with the question of whether the fetus should be regarded as a patient. The first approach is that the physician comes to his or her own moral decision about whether the fetus should be regarded as a patient. This approach would require the physician to have a clear and sound moral or philosophical basis on which to make this decision. The second approach is that the physician adopts no view and leaves it up to the pregnant woman (and her partner, if involved) to decide how they wish to regard their fetus. This approach need not involve any moral or philosophical reasoning by the physician about the fetus; simply giving primacy to the pregnant woman's autonomy in relation to decisions relating to her fetus.

Chervenak et al. [3] suggest a variation of the first approach. They concede, as many others do [1, 5], that the fetus cannot meaningfully possess values and beliefs, and is therefore not a person to whom obligations can be owed. However, they maintain that the obligations of beneficence to the fetus arise from the fact that obligations are owed to the infant which that fetus will become after birth. This makes the fetus a patient, regardless of whether it is a person. More specifically, Chervenak et al. argue that the fetus becomes a patient only after viability; the pre-viable fetus does not have the status of a patient, and should only be treated as a patient if the pregnant woman wants to regard it as such. Once a fetus is viable (a state related to the biological stage of development aided by the availability of medical technology) it is possible for the fetus to survive independently outside the womb. Hence, according to Chervenak et al., there are beneficence obligations to the viable fetus, whenever it is presented to the physician and there exist medical interventions (whether diagnostic or therapeutic) that could produce a greater balance of clinical good over clinical harm for it in the future that is, when it becomes an infant, a child or an adult. There is extensive data to support the possibility of clinical benefit in cases of cardiac anomalies [6–8].

If this argument is accepted, it means that the physician may end up having an obligation to seek to change or override pregnant woman's wishes, for the sake of the fetus. If the physician believes the fetus is a patient, owed the same obligations as any other patient, then his or her obligation is directed to the best interests of the fetus. If the pregnant woman's decisions are contrary to the best interests of the child that the fetus will become, then the physician has an obligation to protect those interests, just as for any child put at risk by parental decisions about medical treatment. The logic of Chervenak and his co-authors' position implies that if attempts at persuasion do not work, the physician may have to seek legal avenues to override the woman's decision, a course of action that could lead to court-enforced fetal surgery [9], immediate delivery of the fetus and, in theory, court-ordered continuation of pregnancy (although it should be noted that in situations where the local laws permit abortion, they do not generally allow for a third party to prevent a woman having an abortion).

However, we caution against this approach, where the physician adopts an independent moral stance on the fetus, and seeks to act accordingly. Whilst the arguments of Chervenak et al. [3] are well reasoned, there are also well-reasoned arguments to the opposite effect, namely that the fetus should not at any stage of gestation be regarded as a patient to whom the physician has direct obligations, unless the pregnant woman chooses to do so. The obligation to the fetus, as Chervenak et al. acknowledge, is based on the well-being of the child it will become. However, whether or not the fetus becomes a child depends on the woman continuing with her pregnancy. It could be argued that if she decides to terminate her pregnancy, at any stage and for whatever reason, there is no longer any obligation to the fetus, since there will not be any child. This conclusion is contrary to the view of Chervenak et al., yet draws on the same reasoning they do.

The well-known difference in views about the status of the fetus and the morality of abortion, across different cultures and religions also introduces a note of caution. A physician working in the multi-cultural setting of today's increasingly globalised world is likely to encounter patients with quite varied views. In addition, laws relating to abortion vary considerably between jurisdictions. We suggest, then, that the second approach suggested above is preferable, namely for the physician to leave it to the pregnant woman (and partner) to decide if the fetus is to be regarded as a patient or not (providing that local laws permit abortion).

Adopting that view does not mean that the physician should not have a personal position on the status of the fetus, only that he or she should not attempt to impose it on his or her patients. If the wishes of the pregnant woman in regards to termination of her pregnancy or intra-uterine therapy for her fetus are significantly at odds with the physician's moral views, the physician should exercise the right to conscientious objection, and hand over the care of the patient to another doctor [10]. This obligation to refer is a standardly accepted caveat on the right to conscientious objection [11]. The Australian Medical Association Code of Ethics [12], for example, states the following:

When a personal moral judgement or religious belief alone prevents you from recommending some form of therapy, inform your patient so that they may seek care elsewhere, and recognise your right to refuse to carry out services which you consider to be professionally unethical, against your moral convictions, imposed on you for either administrative reasons or for financial gain or which you consider are not in the best interest of the patient.

This position is an attempt to negotiate between competing moral values: the woman's autonomy and the physician's integrity. The physician is not forced to do something he or she believes morally wrong, but the woman is also able to exercise her own choice.
3. Ethical Responsibility of Cardiologists When a Serious Fetal Cardiac Anomaly Is Found

Physicians working in obstetrics and gynaecology are presumably aware of the need to work through these issues of the status of the fetus, and to develop their position on abortion, as these issues form a major aspect of their practice. Paediatric cardiologists, on the other hand, have had little cause to consider such issues when working in their discipline, and may never need to do so. However, since it is now possible to detect fetal cardiac anomalies prenatally, cardiologists are coming face to face with these issues. There is usually (in most jurisdictions) an option to terminate an affected pregnancy and increasingly intrauterine interventions may be possible. Cardiologists must consider how they will counsel women in these situations, how directive they will be about which option should be chosen, and what they will do if the woman's choice is not the one that optimizes life and health for the fetus.

Here, we set out the key steps in the counseling process from an ethical perspective, and make recommendations about ethically appropriate practice. These steps may take place over more than one consultation, and may need to be re-visited on each occasion, due to the emotional nature of the situation and the complexity of the information to be conveyed.

3.1. Step 1. Give Accurate Information about the Diagnosis and Prognosis of the Cardiac Abnormality. The first stage is providing accurate information about the diagnosis and prognosis in a manner and at a timing that the expectant parents are able to understand. Fetal cardiac anomalies like any congenital anomaly necessitate that physicians provide the parent adequate information. For any counselling to be credible the diagnosis must be accurate. This is even more relevant in the case of antenatally diagnosed cardiac anomalies. The general screening detection rates for congenital heart disease (CHD) vary between 14%–45% [13]. A standard 4 chamber view can detect 40%–50% of major CHD [14], while a 4 chamber view and outflow tract detects 70%–80% of major CHD [15]. In dedicated fetal cardiac centres the diagnostic accuracy is close to 100% [4, 16].

Fetal cardiac malformations are compounded by the fact that other malformations may be present, as is the possibility of chromosomal abnormalities. The most accurate information possible should be given to the expectant parents, along with a clear explanation of what is still uncertain, unclear or subject to change as the pregnancy progresses. The physician should keep in mind the possibility of evolving lesions [10] (e.g., a developing left and right hypoplastic heart syndrome) and inform the parents accordingly. For such condition, there is inadequate or incomplete data as far as their outcome and natural history, and this also must be conveyed to the parents.

Shinebourne argues that most CHD are treatable with a resultant reasonable quality of life [5]. Even in serious cardiac conditions, one is not always able to clearly define the possible outcomes. Few cardiac conditions are not amenable to at least palliative surgery, if not complete repair. In most cases the neurological development is normal or close to normal [17]. When dealing with fetal anomalies detected on ultrasound, the questions and concerns raised by parents relate to the quality of life issues starting from infancy right up to adulthood [18]. Generally the details of the abnormality, while important, are not the paramount issue for the parents [19]. Complications of the abnormality and the results of surgery or any intervention also figure in the considerations. There is the need to describe possible poor outcomes, especially if they are severe even though unlikely to happen. This information allows the parents to decide how to proceed with knowledge of the worst case scenario [10].

The physician needs to ensure the expectant parents understand the information about the nature of abnormality, the implications for the life of the future child, the possibility of intervention, and the risk for each intervention prenatally or postnataally. Parents also need to know the figures for local practice, for short, medium and long term outcomes, especially with respect to quality of life issues. The physician must be ready to discuss all of these issues with parents, providing the best available information, but also indicating the limits and uncertainties in this information and at a time when the parents are able to take in the information.

3.2. Step 2. Identify Options. The next stage is to identify and present the options available. In brief, there are three main options: to continue with the pregnancy, to terminate the pregnancy (if legally permitted), or to consider prenatal intervention (if it is possible for the condition and available). If the decision is to continue with the pregnancy, there will perhaps be further decisions to make as to where the infant is to be delivered, the need for in utero transfer, and the mode of delivery [19]. There will also need to be an anticipatory management plan for the infant after birth. Parents will generally accept what is recommended to them on these matters, but still require them to be explicitly stated. If the decision is to terminate, there may be a need to shift hospitals (from example from a Catholic hospital), or change the obstetrician if termination is not personally acceptable to him or her. The parents should be made aware of these implications, not in an attempt to change their mind, but to inform and prepare them for the process.

Local laws and practices play an important role in the decision making. For example in some places it may be legal to terminate a pregnancy for maternal psychosocial reasons [17]; in other places, fetal indications may be specified in the law. There may or may not be restrictions on termination related to the stage of gestation. Broadly speaking, obstetricians are able to carry out a termination before 12 weeks [20], but the risk of legal complications increases after 12 weeks and especially after 20 weeks (which is about the stage at which antenatal diagnoses of cardiac anomalies are more commonly made.) In our state of Victoria, in Australia, the law has recently changed to allow termination for any reason up until 24 weeks, and after that there is the need for two doctors to agree that it is reasonable. Physicians must develop an accurate understanding of their local laws and seek legal clarification if necessary.
During the counselling, assuming a “neutral” tone on the part of the clinician—not overly pessimistic or optimistic—is vital [2] but may be extremely difficult to achieve. The ultimate aim is to allow the expectant parents to form their own assessment of the impact the condition would have on their future child. As Shinebourne [5] notes: “It is the mother’s perception of the fetal cardiac anomaly and not the cardiologist’s that should determine outcome (continuation or termination)”. It is open to question, though, how achievable this is in a setting of acute emotional distress where the mother is in a state of shock and grieving the loss of a sought-after normal infant [4]. The ethical obligation is to do one’s best to achieve this aim.

3.3. Step 3. Discuss Options. The next stage is discussing the options with parents which is the most ethically contentious stage. There are different views even about which matters are ethically appropriate to raise and discuss, let alone about the degree to which it is appropriate to recommend or favour a particular option, rather than being as neutral as possible. Most professionals advocate non-directive [4, 5, 21] counselling if possible. It is important to realize that the impact of counseling is affected by the physician’s approach, speech, tone, and so forth [5]. In many counseling sessions, selective information is provided, whether deliberately and inadvertently, though some feel obligated to provide all the information available. There is also the question as to who is the best person to do the counseling. Cardiologists, genetic counsellors or obstetricians have counseled independently or together [4].

Making a decision may not be easy for the parents. They have to come to terms with the abnormality and grieve the loss of a normal infant, as well as grapple with the questions of what they think about abortion, disability, their personal capacity to care for such an infant/child and their ideas about parenthood and family life. They may wish to talk through the options. They may want their cardiologist’s opinion about what they should do. Simply giving such an opinion may not be the best option as the personal circumstances of the clinician differ from that of the parents. It is preferable to discuss how one might decide, what factors one would take into account, in order to model to the expectant parents a way of thinking about the issue, rather than simply give them an answer.

The reasons for considering termination may be very variable, complicated and as Shaffer et al. [22] acknowledge, may not necessarily be “rational” in the strictest sense. This can make the discussion of options difficult, especially for those not specifically trained for these situations. The reasons for which women decide to terminate affected pregnancies are not well documented or understood, though the few studies done in the area indicate it is the nature of condition rather than the stage of gestation that carries most weight [23]. A common understanding of physicians is that most terminations for fetal cardiac anomaly are done to minimize distress and grief to the parents of having a child with reduced physical activity who may die young. This allows mother time for other important aspects of her life, care of the other children and to prevent hardship to others [5]. There may be also be other social reasons, or a medical condition of the pregnant woman.

Note that in these discussions, the pregnant woman (and partner) is not necessarily thinking of the the fetus as a baby, or being with independent rights. Ethically speaking, a pregnant woman's decision need not be based on what is best for the future child; she may legitimately considers her own and others’ interests [5]. For example, there is the perception that an anomaly may have a traumatic or deleterious effect on the parents and the other children, as well as the future child [24]. Here, it is important to note the differences between expectant parents’ decisions regarding termination of pregnancy and actual parents’ decisions regarding the treatment of the newborn infant. The actual parents’ role is to decide on behalf of the infant, on the basis of what is in best interests of the infant [11]. Once delivered, the priority is on maintaining the life and health of the infant, aiming for the best outcomes. If the parent's wishes are significantly contrary to the infant's well-being they can be legally overridden. In contrast, decisions regarding the termination of the pregnancy are not ethically required to be about the best interests of the future child. If the local laws permit termination of the pregnancy, prospective parents may decide for their own reasons. This may include what they perceive would be in best interests of the future child, but will not necessarily do so.

Specialist prenatal genetic counsellors may be particularly helpful for the expectant parents in talking through these sorts of issues, though such counselors may not have the detailed cardiac knowledge to answer the relevant questions. What parents need most from the paediatric cardiologist is the best available understanding of what their child’s life would be like, what sort of interventions would be needed and the risks of these to the child in the local setting.

4. Intrauterine Intervention: Ethical Issues

If intrauterine interventions are available the further important issue is the pregnant woman's autonomy versus the potential beneficence to the fetus and future child, where the pregnancy is going to continue and the fetus can reasonably be regarded as a patient. In this situation, the pregnant woman is in the ethical role of parent making decisions for the health of her future child—but she is also making decisions about herself and her own health. There is a conflict between American College of Obstetricians and Gynecologists and the American Academy of Pediatrics [25] regarding the issue of fetal interventions. The latter accords less weight to maternal decision making and more tolerant of overriding maternal refusal of intervention which may be suggested for fetal benefit. An intervention to the fetus may pose risks to pregnant woman which she may not be willing to take. One example is prescribing medication to the mother for treating fetal arrhythmias. Another example is surgical intervention for critical aortic or pulmonary stenosis [26–28] which has been employed to improve fetal outcomes, though it may lead to premature labour and may require a
surgical incision in pregnant woman to facilitate needling of the ventricles.

One important question to answer is whether the potential benefit to the fetus warrants the risks to the pregnant woman. Another important question is about the risks to the fetus: are they sufficiently outweighed by potential gains that it is reasonable to expect overall benefit to the fetus? One may argue that it is reasonable to offer and recommend fetal therapy if there is a probability of saving the life of the fetus or to prevent serious or irreversible disease to fetus or child and yet carries a low mortality/morbidity risk to the fetus/child and low morbidity to mother [27]. But when the results of such an intervention are questionable and not without risks to the mother, it is not so straightforward. We suggest that in these situations, respect for the woman’s autonomy and her assessment of her own and her future child’s health-related interests be given priority.

Arguably, such innovations as in utero fetal surgery need to be conducted and evaluated as research [29], preferably conducted in centres of excellence. In such cases, the women need be considered as research participants. Genuine voluntariness and informed consent is a standard prerequisite for any such research.

5. Multiple Pregnancies with One Fetus with a Serious Cardiac Anomaly: Ethical Issues

We have discussed this issue in detail in a separate paper [30]. To summarise, dealing with the management of a twin pregnancy where one fetus has a serious anomaly is one of the most challenging and confronting issues a clinician faces. The management depends on the wishes, values and preferences of the mother/parents once provided with detailed and accurate information about the condition of the twins. The risk to the unaffected fetus depends on chorionicity and becomes much more problematic in monochorionic pregnancies. Selective termination of an affected twin with a serious congenital heart disease is possible in some circumstances. Clinicians need to provide detailed probability of the risks of selective termination to pregnant woman and the risks to the normal fetus, including the onset of premature labour, cerebral hypoxia and death to the unaffected twin. It is also important for expectant parents to understand that fetal death of the normal twin, especially in monochorionic twin pregnancies, may occur even if the twin pregnancy is continued, in circumstances where the affected twin becomes unwell or dies.

6. Conclusions

The basic ethical principles of respect for autonomy and beneficence play the major role in grounding physicians’ ethical responsibilities in pregnancies where there may be a fetal cardiac anomaly. The physician’s main ethical obligation is to provide adequate and correct information, in a way that takes account of the extremely distressing circumstances, so as to allow for informed decision making. The ethical principle of autonomy creates a responsibility for the physician to help the pregnant woman make informed decisions based on her values and aspirations. A decision to terminate is partly a medical matter, relating to the procedure and its risks, and partly a personal moral decision bound by legal, cultural and religious constraints. Clinicians can advise regarding the former, but it is not within their realm to advise regarding the latter. The decision whether to continue or terminate in fetal cardiac anomalies is complicated by the fact that in the present era there are very few cardiac conditions which are not amenable to repair and with a reasonable future quality of life. Parents have to deal with shades of grey. There is the additional issue of increasing fetal interventions which may be helpful for the fetus/infant/child but may put the mother at risk and who in turn may opt out of any such intervention. A twin pregnancy with one affected twin further compounds the ethical considerations further. In all situations, the overriding imperative is to provide accurate information about the diagnosis and outcome, identify and discuss possible options and their potential consequences for the fetus and the pregnant woman.

References


The Fetal Heart in Twin-to-Twin Transfusion Syndrome

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Twin-to-twin transfusion syndrome is a severe complication occurring in 10% of monochorionic twin pregnancies. The disease is usually explained as due to an intrauterine imbalance in intertwin blood exchange, which leads to a volume depleted-donor twin and an overfilled recipient twin. The recipient has signs of cardiac dysfunction, which can be measured using echocardiography or blood and amniotic fluid derived biomarkers. Whereas cardiac dysfunction typically progresses in pregnancies treated with amniodrainage, it usually disappears within a few weeks after fetoscopic laser coagulation of the connecting intertwin anastomoses. Nevertheless, recipients remain at an increased risk of pulmonary stenosis. In this paper, we summarize the cardiac alterations in twin-to-twin transfusion syndrome, describe the changes seen after fetal therapy, list the newly proposed staging systems based on fetal cardiac function, and make recommendations about the use of fetal echocardiography in the evaluation and followup of pregnancies complicated by twin-to-twin transfusion syndrome.

1. Introduction

Monochorionic diamniotic twin pregnancies carry a 9%–15% risk of developing twin-to-twin transfusion syndrome (TTTS) [1, 2]. The pathophysiology of this disease is not fully understood, but the presence of vascular anastomoses connecting both fetal circulations at the level of the placenta is mandatory for its development. In carefully performed vascular injection studies, anastomoses have been documented in up to 95% of monochorionic placentas [3, 4], yet most of these pregnancies remain uncomplicated as the intertwin blood exchange is in balance. In a small subgroup however, the distribution of unidirectional arterial to venous anastomoses is imbalanced and an insufficient number of compensating bidirectional venovenous or arterio-arterial anastomoses is present, leading to a net shift of blood from one twin to the other [5, 6]. The pathophysiology and therapy of twin-to-twin transfusion syndrome have recently been covered in an extensive review [7]. In brief, our current concept is that a net intertwin transfusion takes place over placental anastomoses, leading to volume shifts for which the fetuses cannot compensate. Additionally, plasma exchange and hormonal factors may play an important role in the disease. This ultimately results in a volume depleted donor twin, who will show signs of oligouria and oligohydramnios and a volume overloaded recipient twin who will present with polyuria and polyhydramnios. The diagnosis of TTTS is based on strict sonographic criteria reflecting severe intertwin fluid discordance. The criteria for TTTS are met when the deepest vertical amniotic fluid pocket is 2 cm or less in the donors amniotic sac. In Europe, gestational age-dependent criteria are used to define the polyhydramnios in the recipient twin (a deepest amniotic fluid pocket of more than 8 cm prior to 20 weeks and more than 10 cm after 20 weeks), whereas in the United States the 8 cm cutoff is used throughout gestation. The disease is currently staged based on the “Quintero system” which takes in account the filling of the bladder in the donor (stage I if the bladder is seen on ultrasonound, stage II if not), the presence of arterial or venous Doppler flow abnormalities (stage III), the presence of fetal hydrops (stage IV) and intrauterine fetal demise (stage V) [8]. When left untreated, TTTS has a mortality
and morbidity of up to 90%, mainly due to preterm rupture of the membranes and miscarriage or severe preterm birth as a result of the massive polyhydramnios [9]. However, intrauterine demise of one or both fetuses due to severe cardiac failure can also occur [10]. Treatment of severe midtrimester TTTS has shifted over the last 10 years from (repetitive) amniodrainage to fetoscopy laser coagulation of the connecting placental vessels. The latter therapy interrupts the intertwin transfusion and has been shown to improve neonatal survival and to decrease infant morbidity when compared to amniodrainage in a randomized trial [11, 12].

Although different research groups have focused on this disease and the number of publications on TTTS has risen exponentially over the last years, we still do not understand the exact nature of the disease [7]. Consequently, the currently used staging system does not describe the natural evolution of the disease, nor does it predict individual fetal survival after laser surgery adequately. Other insufficiently answered clinical questions are the prediction of the disease [13–16] and the optimal therapy for early (stage I) disease (expectant management, amniodrainage, laser) [17].

In an attempt to address the above questions, and with the advent of more sophisticated imaging tools in fetal cardiology [18], fetal medicine specialists and cardiologists have turned to comprehensive examination of the recipients heart. Indeed, one could expect volume shifts towards the recipient [20–22] due to an increased myocardial strain and strain rate, although diastolic function has not been widely studied in TTTS [23].

In TTTS, diastolic function is even more compromised than systolic function. As a consequence of the thickened, dysfunctional myocardium, monophasic ventricular filling patterns such as those seen in restrictive cardiomyopathy occur in about 20–30% of cases, again with a predominance on the right side [21, 28]. Moreover, we often observe a shortening of the ventricular filling time [29], a prolongation of the isovolumetric relaxation time [30] and an increase in the Tei-index (which is a geometry independent indicator of both systolic and diastolic function based on the assessment of the isovolumetric relaxation and the isovolumetric contraction time [31, 32]). On average, the Tei-index is 40% higher than normal [23, 30, 33] and values above the upper limit of normal are observed in about 50% of cases [24, 28, 30]. Interpretation of the Tei-index in the fetal setting nevertheless deserves particular caution as fetal blood pressure is often unknown and prolongation of the isovolumetric contraction time can be a reflection of hypertension rather than of systolic dysfunction. Therefore, separate analysis of the isovolumetric contraction and relaxation time is justified, yet only technically possible at the level of the left ventricle due to the implantation of the pulmonary and tricuspid valve precluding simultaneous recording of the pulmonary and tricuspid flow.

Tricuspid regurgitation occurs in about 30–50% of recipients [21, 28, 34] but is severe in only half of these [10, 21–23]. Mitral regurgitation on the other hand is much less frequent (6–14% of cases) [21, 28], yet usually severe (9%) [21]. The presence of valvar regurgitation allows to estimate fetal blood pressure using the Bernoulli equation and studies have shown that recipient fetuses display marked hypertension with systolic pressures over 2-fold the normal value for gestational age [35]. Further down the vascular tree, Doppler assessment of the ductus venosus and the umbilical venous flow allows to estimate the right atrial pressure curve. Reversed flow in the ductus venosus and umbilical vein pulsations have been integrated in the Quintero staging system and their presence upstages the disease to stage III. In most series from tertiary referral centers, abnormal ductus venosus dopplers are seen in about 1 in 3 recipients [21, 23, 28, 34] and a pulsatile umbilical vein in 1 in 10 [21, 22, 28].

A summary of the fetal echo findings in a prospective series of 78 consecutive cases seen in our unit is presented in Table 1 (unpublished data). It is important to note that in Quintero stage I, already 45% of cases show signs of ventricular dysfunction in terms of an increased Tei index and that 35% of cases have a fused right ventricular inflow pattern suggestive of diastolic dysfunction. The occurrence of these so-called early findings remains relatively stable over stage I to III, similar to what has been published earlier [24].

Nevertheless, other findings such as the left ventricular Tei-index and mitral and tricuspid regurgitation increase with Quintero stage [21] suggesting that the Quintero staging system, at least to some degree, reflects progressive fetal cardiovascular compromise.

Our group has shown that changes in cardiac function are already present well before the actual development of TTTS. As such, about 30% of fetuses with moderate amniotic

2. Echocardiographic Findings in TTTS

2.1. Recipient Fetuses. Up to 70% of recipient fetuses of TTTS show some echocardiographic sign of cardiac compromise at the time of diagnosis [19], either at the anatomical or at the functional level. As such, in about half the cases, the heart is enlarged [20–22] due to an increased myocardial thickness [23] rather than to ventricular dilatation [10, 24]. In terms of systolic function, shortening fraction is considerably decreased in 30% of the recipients [10, 21, 22], and this predominantly at the level of the right ventricle [10]. Accordingly, speckle-tracking-derived measurements of strain and strain rate, although difficult to perform, show decreased strain in the right ventricle of recipient fetuses of TTTS [25]. In contrast to the lower contractility and to earlier reports that did not show differences in cardiac output between donors and recipients [22, 26], two recent series in relatively large cohorts of recipient fetuses have shown a moderate increase in cardiac output when corrections were made for fetal weight [23, 27]. This finding clearly fits in with the volume overload theory.

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Our group has shown that changes in cardiac function are already present well before the actual development of TTTS. As such, about 30% of fetuses with moderate amniotic
fluid discordance not fulfilling the criteria of TTTS but ultimately progressing to the syndrome show an increased myocardial performance index [36]. Along the same line, 40% of monochorionic twins that ultimately will develop TTTS have already abnormal findings in the ductus venosus flow [1, 13] or discordant nuchal translucency measurements reflective of altered hemodynamics in the first trimester of pregnancy [14, 15, 37]. Unfortunately, these findings are not very specific, nor very sensitive. They cannot therefore be used for early prediction of the disease, nor should they be used to “upstage” (often benign) fluid discordance to TTTS.

Once a TTTS is fully installed, echocardiographic findings tend to progress over time, with worsening ventricular hypertrophy and systolic dysfunction, which can ultimately lead to fetal hydrops and intrauterine fetal demise [38]. Moreover, as growth of fetal cardiac structures is dependent on the blood flow through them, persistent ventricular dysfunction can lead to secondary anatomic changes. Consequently, in a consecutive series of 150 recipient fetuses, 16% had a smaller than expected right ventricular outflow tract at the time of initial presentation [21]. In up to 4%, extreme right ventricular dysfunction can result in functional pulmonary atresia (Figure 1) with retrograde perfusion of the pulmonary trunk through the ductus arteriosus [10, 34] and more rarely even in complete right heart flow reversal [39].

2.2. Donor Fetuses. In contrast to recipient fetuses, donors seem to have a normal cardiac function, yet some 5%–10% present with abnormal Doppler waveforms in the ductus venosus, and 3% with tricuspid regurgitation or umbilical vein pulsations [34, 40], findings which are generally explained by the presence of severe placental insufficiency. The latter is also supported by an increased occurrence of abnormal diastolic flow in the umbilical artery in the donor fetus.

Furthermore, although not significant in most studies, the donor twin has a trend towards a lower Tei-index than in the normal population which is suggestive of hypotension [27, 40]. Finally, there have been speculations about an increased incidence of aortic coarctation in donors due to a lower venous return from the placenta and hence a decreased loading of the left ventricular outflow tract [41].

3. Biomarkers of Altered Fetal Hemodynamics in TTTS

Different vasoactive peptides have been investigated in TTTS, mainly in an attempt to further explain the underlying pathophysiological mechanisms.

The renin angiotensin aldosterone system has been found to be upregulated in the donor kidney [42]. Transfer of these hormones towards the recipient through the placental anastomoses partly explains the hypertension (angiotensin II) and the hypervolemia (aldosterone) seen in this fetus. Additional upregulation of atrial natriuretic factor (ANF) has been observed in recipients when compared to donor fetuses [43]. Plasma levels of ANF are correlated with the amount of amniotic fluid yet not with the severity of cardiac dysfunction [43] and are therefore thought to mediate the recipients polyuria.

Increased endothelin-1 [44], brain or b-type natriuretic peptide (BNP) [28, 44, 45] and cardiac troponin T [28] levels have been observed in the plasma and/or the amniotic fluid of recipient fetuses, similar to observations in adults with chronic heart failure. Endothelin-1 can certainly play a role in the development of the severe hypertension [35, 44], stimulates the myocardial remodeling [46] and could decrease cardiac function. The presence of both BNP and cardiac troponin T [28] suggests that the myocardium is not only stretched by the volume load but also that it undergoes structural damage/remodeling.

4. New Staging Systems in TTTS

In an attempt to provide a more pathophysiologic classification of TTTS [47], different groups have suggested to use new staging systems that are mainly based on the severity of cardiac dysfunction in the recipient fetus. The most extensive system has been elaborated by the Children’s Hospital Of Philadelphia (CHOP) [21] and requires the evaluation of 12

### Table 1: Occurrence of cardiac function alterations in 78 consecutive recipient fetuses assessed at the University Hospitals Leuven, Belgium.

<table>
<thead>
<tr>
<th></th>
<th>Stage I (n = 11)</th>
<th>Stage II (n = 19)</th>
<th>Stage III (n = 42)</th>
<th>Stage IV (n = 6)</th>
<th>Overall (n = 78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversed a-wave ductus</td>
<td>0</td>
<td>0</td>
<td>62</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>venosus (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Umbilical vein pulsation</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>67</td>
<td>32</td>
</tr>
<tr>
<td>Fusion of RV inflow (%)</td>
<td>9</td>
<td>21</td>
<td>38</td>
<td>67</td>
<td>31</td>
</tr>
<tr>
<td>Tricuspid regurgitation (%)</td>
<td>45</td>
<td>47</td>
<td>48</td>
<td>83</td>
<td>49</td>
</tr>
<tr>
<td>RV-MPI &gt; percentile 97.5 (%)</td>
<td>9</td>
<td>21</td>
<td>29</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td>Mitral regurgitation (%)</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>LV-MPI &gt; percentile 97.5 (%)</td>
<td>25</td>
<td>42</td>
<td>38</td>
<td>83</td>
<td>41</td>
</tr>
</tbody>
</table>

RV: right ventricle, LV: left ventricle, and MPI: myocardial performance index.
variables which, in experienced hands, takes 30–45 minutes per fetus and is therefore not feasible in routine clinical practice (Table 2). Also, different parameters of cardiac function are correlated. For example, we have shown that the ejection fraction correlates with the myocardial performance index [33] and others demonstrated that abnormal flow in the ductus venosus correlates with tricuspid regurgitation [34]. Finally, Rychik et al. [21] showed that the right ventricular Tei-index was strongly correlated with their full 12 parameter score, suggesting that the creation of an easier staging system, still encompassing the full extent of the disease should be feasible.

Going further into this, Stirnemann et al. [23] used cluster analysis and partitioning algorithms to determine that a staging system including only the assessment of the left and right ventricular myocardial performance index allows to stratify cases as well as a system with additional inclusion of shortening fractions, ductus venosus pulsatility index and cardiac output. A comparison of the anatomic and functional parameters in the different proposed “cardiac” staging systems is presented in Table 2.

At present, we do not feel that these new staging systems should replace the Quintero system, which is an easy and widely accepted method for patient stratification that has proven some usefulness in terms of predicting fetal outcome after laser therapy [11, 49]. Nevertheless, cardiac staging systems may play an important role in the further understanding of the pathophysiology of the disease and are useful in research settings.

5. Effect of Prenatal Therapy

Amniodrainage usually does not cure TTTS but is rather a palliative and repetitive intervention aimed at relieving the polyhydramnios. As such, it does not improve fetal cardiac function and fetuses undergoing repetitive amniodrainage show progressive cardiac disease and hydrops and are at risk for intrauterine demise [10, 50].

On the other hand, closure of the vascular anastomoses at the level of the placenta and functional separation of both fetuses by fetoscopic laser leads to a rapid improvement in cardiac function in the recipient fetus. Already in the first 48 hours after therapy, cardiac size, precordial venous Dopplers, valvular regurgitation, and ventricular inflow patterns normalize in about half of the cases and the Tei-index improves with approximately 40% [19, 20, 40, 51]. Survival is worse in fetuses lacking this functional improvement immediately after surgery [19]. In the longer term, further amelioration in cardiac function continues and approximately 6 weeks after therapy most cases have regained normal cardiac function [40]. The normalization of cardiac dysfunction is very similar to, but slightly faster than, what is seen in neonates delivered at the time of TTTS.
Table 2: Comparison of the cardiac parameters assessed in the different proposed staging systems.

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<tbody>
<tr>
<td></td>
<td>“CHOP-score”</td>
<td>“Cardiovascular profile score”</td>
<td>“Cincinnati staging”</td>
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<tr>
<td>Cardiothoracic ratio</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Ventricular wall thickness</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Shortening fraction</td>
<td>x</td>
<td>x</td>
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<td></td>
<td></td>
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<tr>
<td>Tei-index right ventricle</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Tei-index left ventricle</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td>AV regurgitation</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AV inflow</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Outflow tract size</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ductus venosus</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
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<tr>
<td>Umbilical vein</td>
<td>x</td>
<td></td>
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<td></td>
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<tr>
<td>Hydrops</td>
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<td></td>
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<tr>
<td>Umbilical artery donor</td>
<td>x</td>
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</table>

AV: ventricular valve.

[52]. Interestingly, even severe cardiac dysfunction such as functional pulmonary atresia and hydrops resolve in almost all cases [51, 53], which argues against the use of selective reduction in these fetuses.

In contrast to recipients, about 1 in 4 donor fetuses has a temporary worsening in cardiac function with increased cardiac size [20], tricuspid regurgitation, ductus venosus alterations, and subcutaneous oedema [34, 40, 54] after fetoscopic laser therapy. These findings however disappear by 2–4 weeks after the surgery [40, 54] and are probably explained by the sudden arrest of the transfusion imbalance and temporary relative volume overload in the former donor fetus.

Different groups have investigated whether fetal demise after laser therapy (which occurs in about 18% of recipient fetuses [49]) can be predicted by preoperative fetal cardiac function. In a retrospective series, Shah and colleagues showed that recipient cardiovascular profile score can predict outcome to a certain extent [48]. In line with this finding, we have shown that recipient fetuses with a normal Tei-index and low amniotic fluid cardiac troponin T levels have an improved survival compared to those with alterations in either of these 2 parameters. However, cardiac function alone does not predict outcome [28], as confirmed in a larger multicenter series including more than 200 TTTS cases [55]. This is explained by the fact that fetal demise after laser is multifactorial and also depends on other factors such as placental sharing or incomplete laser separation. For clinical practice, it means that for now, fetal therapy cannot be tailored to the individual situation based on fetal cardiac function assessment.

6. Long Term Cardiac Outcome after TTTS

Followup until the age of 10 year has shown that both donors and recipients of nonlasered TTTS have normal cardiac function in the longer term [56]. Recipient twins nevertheless maintain a slightly reduced early diastolic ventricular filling as compared to donors (diastolic dysfunction). Donors on the other hand seem to have higher arterial wall stiffness than recipients, suggestive of intrauterine vascular programming [57]. Fetoscopic laser therapy can alter this prenatal vascular programming. As such, fetuses that underwent laser have normal wall stiffness and normal cardiac function at the age of 2 year [58, 59]. However, the increased occurrence of right ventricular outflow tract obstruction observed at the time of TTTS (16%) [21] does not disappear completely and recipient fetuses remain at a 3-fold increased risk (5%–8%) of pulmonary stenosis at the time of birth when compared to uncomplicated monochorionic twins [22, 59].

7. Clinical Recommendations

In clinical practice, the main question remains whether (functional) fetal echocardiography should be used in the evaluation and follow-up of pregnancies complicated with TTTS and if the answer is yes, when echocardiography should be performed. From the above listed data, we feel that the only clinically useful echocardiographic finding in TTTS pregnancies booked for fetoscopic laser therapy is the presence of persistent pulmonary artery stenosis after therapy which would impact on the place of delivery and on postnatal management. As a result, we would recommend a thorough (structural) cardiac evaluation 8–10 weeks after the fetoscopic surgery, when cardiac dysfunction has completely resolved, to assess pulmonary artery development and to plan the site of delivery.

In TTTS pregnancies managed expectantly or undergoing (repetitive) amniodrainage, the evidence is less clear, yet we feel they should undergo intensive cardiac follow-up with at least assessment of ductus venosus and umbilical vein flow.
and evaluation for the presence of hydrops to time eventual delivery or to switch therapy to laser before intrauterine fetal demise occurs. Additionally, these fetuses should undergo evaluation for pulmonary artery stenosis before birth.

As all recipient fetuses of TTTS, both managed conservatively or with laser, are at increased risk of pulmonary artery stenosis, we are convinced that an early postnatal screening echocardiogram is indicated. Moreover, because all monochorionic twins are at increased risk for structural cardiac abnormalities compared to singletons or dichorionic twins [22], all should benefit from midtrimester structural echocardiographic assessment.

8. Conclusions and Future Perspectives

In summary, cardiac dysfunction is a common finding in recipient fetuses and different new “cardiac” staging systems have been proposed. Although they may bring new pathophysiologic insights, their clinical value remains limited as they do not predict the occurrence nor the outcome of the disease. However, further evaluation is necessary in stage I disease, where equipoise is still present about the optimal treatment strategy [17]. Additionally, the impact of the decreased cardiac function on cerebral perfusion and long-term neurologic development requires further investigation. Fetoscopic laser coagulation of the vascular anastomoses interrupts the intertwin transfusion and has been shown to lead to fast normalization of cardiac function. Nevertheless, recipients remain at increased risk of pulmonary artery stenosis. Further work should be directed at detecting prenatally which twins will have clinically important lesions at the time of birth.

Acknowledgments

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References


Clinical Study

Features and Outcomes In Utero and after Birth of Fetuses with Myocardial Disease

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1. Introduction

Myocardial disease (MD) is a group of diseases with very variable forms, etiology, entity, and natural history that are mostly diagnosed in adolescence and adulthood [1]. It was reported to occur in about 2–7% in the series of neonates and infants [2, 3]. Fetal echocardiography allows now an early recognition of MD, based upon the pattern of dilated and hypocontractile ventricles or of a various degree and localization of parietal hypertrophy. The frequency of MD in fetal life is difficult to establish—we can consider the figures given in some fetal series: in our experience it was found in 1–1.7% of two series of pregnancies at risk for CHD studied by fetal echocardiography, while its prevalence was 6.7%, 7.5%, and 8.9% of cases with CHD [4–7].

Echocardiographic features and outcomes in utero of cases with MD have been described in some studies [8–10], however the data are very variable, being often included also cases with some specific conditions like twin-to-twin transfusion syndrome or cases associated with anemia. In the era of fetal echocardiography, the referral for familial MD is quite frequent and the counseling in these cases is difficult. Therefore we feel it is of interest to have more data regarding this pathology.

2. Objectives of the Study

The aim of this paper is to analyse retrospectively our experience regarding the characteristics and outcome of cases with myocardial disease, detected at fetal echocardiography.

3. Material and Methods

Between 1990 and 2005, 91 fetuses (1.5%), out of around 6000 cases, referred for fetal echocardiography in 2 centers presented with a pattern of dilated or hypertrophic cardiomyopathy (DCM, HCM), at 17–38 weeks’ gestation, median 28. The fetuses were referred often for a finding of abnormal cardiac features or of a fetal hydrops at obstetric
scan: some came for a family history of HCM or for maternal diabetes; and, also, the fetuses with extracardiac anomalies were sent for an evaluation of the cardiac state. Cases with twin-twin transfusion syndrome or anemia, as well as those associated with specific congenital heart lesions were excluded from this study. Infections, extracardiac anomalies (ECAs) and maternal disease were always checked.

3.1. Methodology. Two-dimensional echocardiography with M-mode and pulsed/continuous wave and Color Doppler were performed using the echocardiographic machines: Acuson Sequoia, Imagegate, Siemens, Erlangen, Germany, and Vivid 7, General Electrics, Healthcare, Italy, with transducers 5 and 3.5 MHz according to the fetal age.

Measurements of the right and left ventricles were done in 2D in 4-chamber view in diastole (at the level of the mitral and tricuspid valve annulus) and in M-mode in a horizontal 4-chambers view, measuring the thickness of the right ventricular anterior wall, of the interventricular septum and of the left ventricular posterior wall. Shortening fraction of the left ventricle was calculated on the basis of the M-mode measurements in systole and diastole (normal values 28–42%).

Pulsed and Color Doppler examinations were always performed, and, specifically, pulsed Doppler waveforms were analysed at the level of the atriocentrical and semilunar valves and at the level of the inferior vena cava, ductus venosus, and umbilical artery.

We used as a criterion for the diagnosis of DCM the ventricular enlargement above the 97.5% according to the normal standards for gestational age [11–13] without thickening of the walls and with reduced contractility (shortening fraction <28%).

The term of the “noncompaction” of the left ventricular myocardium was used in cases that showed dilated ventricle with reduced function and numerous prominent trabeculations with deep myocardial recesses [14–16]. HCM was diagnosed on the basis of an increased parietal thickness above 97.5% of normal standards for gestational age [17, 18]. In all cases, congenital heart anomaly was excluded.

Fetal hydrops was defined by the presence of serous effusion in at least two compartments: of a mild degree, when in 2 compartments (ascites+ hydropericardium or hydrothorax), of a moderate degree when in 3 compartments (ascites, hydrothorax, and hydropericardium), and severe, with associated skull edema.

After the diagnosis was made, all cases were screened for possible infections (parvovirus, Coxsackie, cytomegalovirus, and toxoplasmosis), fetal anemia, and diabetes. The fetal rhythm was always evaluated.

3.2. Postnatal Assessment. In the cases born alive echocardiography was performed after birth, usually within the first day and repeated subsequently according to the clinical necessity (median follow-up: 6 years; range: 2–14). Methodology of the examination was performed according to the standard criteria, and M-mode measurements were used for functional assessment, as exposed for the fetal examination, comparing the data with normal standard values for the infants’ weight and body surface area [19]. All infants underwent a complete check-up of laboratory tests, to exclude underlying conditions as metabolic disorders, infections, and so forth.

3.3. Analysis of the Data. The characteristics of the cases and their course in utero and after birth were analysed, according to the type: Group 1-DCM, Group 2-documented myocarditis, and Group 3-HCM.

3.4. Statistical Analysis. Gestational age at presentation in cases that died and those who survived was compared by means of Student’s test t for unpaired data, for single groups.

Influence of hydrops in Groups 1 and 2 and of extra cardiac anomalies in Group 3 on outcome was tested by Student’s test t for paired data, and the differences in outcomes in categories with and without hydrops in Groups 1 and 2 were compared by chi-square test.

4. Results

4.1. Features

Group 1 (see Table 1). Pattern of DCM with dilated left ventricle was found in 18 fetuses, associated in 5 (15.8%) with extracardiac anomalies. One fetus had a form with dilated right ventricle, associated with an abnormal tricuspid valve apparatus.

Three fetuses presented a pattern of noncompacted myocardium (2 siblings), and 8 fetuses had a highly echodense endomyocardium, suggesting endocardial fibroelastosis (3 with ECA), with calcifications in one case (Figure 1(a)) that were documented also at postnatal X-ray and at autopsy following the death in the 1st day of life. One fetus had a family history of cardiomyopathy, in a 3-year-old sibling affected with a mild form.

Thirteen cases (68.4%) showed at presentation fetal hydrops: 12 of a moderate-to-severe degree and 1 of a mild degree.

Cardiac Function at Echocardiography. All cases had reduced contractility—with fractional shortening ranging between 10 and 20%, median 16. An abnormal pattern of systolic and diastolic flows of the mitral and tricuspid valves (reduced E/A ratio and a small A-wave) and atrioventricular valves regurgitation were seen at Echo-Doppler. All fetuses showed mitral regurgitation of a mild-moderate degree, and the 13 cases with hydrops presented moderate-severe holosystolic tricuspid regurgitation, associated with anomalous flow of the inferior vena cava and ductus venosus (a reverse A-wave flow in systole) and the fluctuation of the umbilical venous flow in cases in preterminal condition.

Group 2 (see Table 1). Twelve fetuses with documented viral infection (5 with Cytomegalovirus and 7 with Coxsackie virus) presented dilation of both ventricles (see Figure 1(b)), with tricuspid and mitral regurgitation and fetal hydrops in
Table 1: Data of cases with DCM and myocarditis.

<table>
<thead>
<tr>
<th>Type of CMP</th>
<th>N.</th>
<th>W.g. at dg.</th>
<th>Assoc. ECAs</th>
<th>Hydrops</th>
<th>Arrh.</th>
<th>Ther. in utero</th>
<th>Outcome in utero-w.g.</th>
<th>Postnatal death</th>
<th>Total death of cases continuing preg.</th>
<th>Alive/age</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM LV Idiopathic</td>
<td>Tot. 18</td>
<td>18–35, (median 26)</td>
<td>13 (1 Fam., 3 NCM, 5 EFE)</td>
<td>9</td>
<td>1-SVT 1 ExS</td>
<td>3-dig. 3–4 d</td>
<td>1 TP 2 IUD (24, 30 w.g.) 2 lost, 8 delivered at 33–36 w.g.</td>
<td>4 died</td>
<td>5 alive at 3–10 yrs, improved after 3 months–1 yr</td>
<td></td>
</tr>
<tr>
<td>With ECA</td>
<td>5 (3 EFE)</td>
<td>3</td>
<td>2 renal, 1 CNS, 1 thor. cyst, 1 multiple malform.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCM RV</td>
<td>1</td>
<td>32</td>
<td>1</td>
<td>Dig. 14 d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCM total</td>
<td>19</td>
<td>18–34</td>
<td>5 ECAs</td>
<td>13 (68.4%) 1 SVT</td>
<td>4 dig.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>12</td>
<td>20–37 (median 23)</td>
<td>11 (91.7%) (5 severe, 5 moder., 1 mild)</td>
<td></td>
<td></td>
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</table>


11 cases (91.7%), of a severe degree in 5 cases, of a moderate degree in further 5 cases, and of a mild degree in one case.

All these cases presented abnormal systolic left ventricular or biventricular function and signs of regurgitation of both atrioventricular valves, associated in the cases with fetal hydrops to abnormal venous flows, as described for Group 1 (see Figure 2).

Group 3 (see Table 2). Sixty fetuses presented HCM of the left ventricle, with outflow tract obstruction in two; 10 also presented right ventricular hypertrophy; 26 (43.3%) had extracardiac anomalies (ECAs), 3 cases were affected by syndromes precised after birth (1 Thomas syndrome, 1 prune-belly, and 1 Noonan).

Seventeen fetuses (28.3%) had mothers with diabetes (pregestational in 12; gestational in 5); 17 fetuses were considered to be "idiopathic", however in one of them a metabolic disorder (cytochrome-oxidase deficiency) was found postnatally, while 5 remaining cases presented a family history of HCM.

Systolic function was normal or slightly increased (shortening fraction between 30 and 45%, median 36), some fetuses showed signs of abnormal diastolic flow through the mitral valve (higher E-A velocities) at Echo-Doppler and mild mitral regurgitation. The two cases with left ventricle obstruction had slightly increased Doppler velocity through the aorta (2 and 2.2 m/sec.). Heart failure in utero was infrequent and only mild (in 4/60 cases = 6.7%).

None of the fetuses with hypotrophy had features fitting for the diagnosis of restrictive cardiomyopathy—showing no particular enlargement of atria and no specific Doppler findings of mitral valve.

4.2. Outcome and Evolution: (See Tables 1 and 2 and Figure 3 with a Flow Chart)

4.2.1. DCM. Out of 19 cases with DCM, 1 opted for termination of pregnancy (TP), 2 were lost at follow-up, and total mortality was 11/16 cases that continued pregnancy and with a known follow-up (68.75%). Eleven out of 13 cases with fetal hydrops died (2 in utero). Two of the 3 cases with noncompacted myocardium died in utero. Surviving cases improved after 4 months–1 year.

4.2.2. Myocarditis. Out of 10 cases with moderate-to-severe hydrops, 1 opted for TP and only 2 survived. One fetus with
Figure 1: (a) Echocardiography of a fetus with endocardial fibroelastosis—a high echodensity of the left ventricular (LV) walls due to calcifications is evident. RV—right ventricle, A—aorta. (b) Fetus with myocarditis and fetal hydrops: both ventricles and atria are dilated and the arrows indicate the pericardial effusion. RV—right ventricle, LV—left ventricle.

Figure 2: Doppler findings in fetuses with DCM and fetal hydrops: (a) The tracing of the tricuspid valve (T) shows a reduced systolic A-wave, with respect to the diastolic E-wave; (b) holosystolic tricuspid regurgitation (ITr); (c) a reverse systolic flow of the inferior vena cava (small arrow); (d) a reverse systolic flow of ductus venosus (small arrow); (e) the fluctuation of the umbilical vein.

mild-initial hydrops that presented at 20 w.g. and another one who presented late at 37 w.g. without hydrops survived.

Total mortality was 7/11 cases that continued pregnancy (63.4%) Four cases that survived improved all after 3–12 months.

4.2.3. HCM

(a) Idiopathic Form. One out of 5 cases with familial history (in mother, grandfather, or siblings) was diagnosed after birth to have a metabolic disorder-cytochrome-oxidase deficiency (as said above) and died at 38 days. The remaining 4 infants are alive at 5–14 years and present mild-moderate forms, one needing recently, at 10 years, propranolol for a moderate left ventricular obstruction.

Out of the 12 cases with a negative family history, 1 case was lost at follow-up, 1 infant born premature for fetal distress at 28 w.g. died at 15 days and 2 other cases worsened: one with a biventricular obstruction, shown in
Table 2: Data of cases with HCM.

<table>
<thead>
<tr>
<th>Type</th>
<th>N.</th>
<th>W.g. at dg.</th>
<th>Assoc, ECAs/ other conditions</th>
<th>Heart failure</th>
<th>Ther. in utero</th>
<th>Outcome in utero—w.g.</th>
<th>Postnatal death</th>
<th>Total death of cases continuing preg.</th>
<th>Alive/age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Idiop.&quot;</td>
<td>17</td>
<td>—</td>
<td>5 familial history</td>
<td>—</td>
<td>—</td>
<td>1 lost 11 delivered at 31–38 w.g.</td>
<td>1–38 d (met.dis)</td>
<td>2/16 with known f-up = 125%</td>
<td>14 alive at 2–14 yrs; 3 worsened—1 Tx at 2 m; 1 operated at 3 yrs for LVOT-mitral tissue obstruction; 1 needing betablockers; 5 unchanged (mild-moderate); 6 improved at 3 m–1 yr.</td>
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<td></td>
</tr>
<tr>
<td>Secondary to ECA</td>
<td>26</td>
<td>Median 17–30</td>
<td>16 renal, 3 CNS, 7 (skeletal anom., arthrogryposis, Thomas s., Noonan s.)</td>
<td>3 (mild-moder.)</td>
<td>8 TP, 6 IUD at 23–30 w.g., 12 delivered at 28–37 w.g.</td>
<td>7 (1–35 d)</td>
<td>13/18 = 72.2%</td>
<td>5 alive, regressed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary to maternal diabetes</td>
<td>17</td>
<td>27–37</td>
<td>12 pregest., 5 gest.</td>
<td>(mild)</td>
<td>1 flutter Dig.*</td>
<td>17 delivered at 37–39 w.g.</td>
<td>2 (2 d, 4 m)</td>
<td>2/17 = 11.8%</td>
<td>15 alive, normalized at 3–6 m</td>
</tr>
<tr>
<td>HCM total</td>
<td>60</td>
<td>17–39</td>
<td>4 (6.7%)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Idiop.: idiopathic, n.: number, w.g.: weeks’ gestation, dg.: diagnosis, ECAs: extracardiac anomalies, anom.: anomalies, CNS: central nervous system, s.: syndrome, arrh.: arrhythmias, SVT: supraventricular tachycardia, ther.: therapy, dig.: digoxin, TP: termination of pregnancy, IUD: intrauterine death, d: day, m: month, yr: year, s.: syndrome, met.dis.: metabolic disease, prem.: premature, gest.: gestational, preg.: pregestational, moder.: moderate, f-up: follow-up, Tx: heart transplant, and LVOT: left ventricular outflow tract.

Figure 4, delivered at 32 w.g., required a heart transplant at 2 months and is alive at 4 years, while the second one, also with a biventricular obstruction since birth, treated with betablockers, developed a severe left ventricular obstruction due to an excessive mitral valve tissue at 3 years and needed a cardio surgical excision of this tissue together with a plasty of the mitral valve. Two cases remained stable and 6 improved at 3 months–1 year.

(b) HCM Secondary to ECA. Eight opted for TP, 6 had IUD (5 renal anomalies-Potter syndrome and 1 Prune Belly). Seven out of the 12 infants that are born alive died after birth and 5 are alive at 5–12 years and improved.

One case with CNS anomaly was operated for craniosenosis and is alive; equally, the infant with Noonan syndrome suffered initially from pleural effusions, stabilizing thereafter.

(c) HCM Secondary to the Maternal Diabetes. One fetus of a mother with pregestational diabetes presented at 29 w.g. with mild fetal hydrops and atrial flutter resolved by the maternal-fetal therapy, with digoxin was delivered at term showing only a mild LV dyskinesis after birth, regressed at 1 month.

Two infants with pregestational maternal diabetes died: one with a poor control of diabetes in pregnancy had a severe HCM and died immediately after birth, of cardiac arrest, while the second one, with a borderline thickness of the interventricular septum in the third trimester and immediately after birth, developed progressively a massive parietal hypertrophy, obstruction of the left ventricular outflow and died at 4 months of an untreated heart failure. All surviving cases with maternal diabetes progressively normalized after 3–6 months.

Total mortality in HCM (Group 3) was 17/51 (33.3%) of the cases continuing pregnancy with a known follow-up,
13/18 (72.2%) of those with severe ECA, and 2/17 (11.8%) of infants with maternal diabetes.

4.3. Statistical Analysis. There were no significant differences between the age at presentation in cases with DCM and myocarditis and relative outcome; cases with fetal hydrops presented poor outcome, but the differences between cases with and without hydrops did not reach statistical significativity.

In cases with HCM, a negative prognostic factor was apparently the presence of a severe ECA, not reaching statistical significativity with respect to the remaining categories.

5. Discussion

Our data confirm a variable spectrum of myocardial disease presenting in the fetal age with different etiology and the possibility of association with extracardiac anomalies both in hypertrophic and dilated forms. Hypertrophic form of cardiomyopathy was more frequent in our series, both in proportion versus the dilated form and with respect to the two previous reports [7, 10], and, particularly, we have found a relevant number of cases with secondary forms. Our figures may be partly due to the referral reasons, operating in the third level centers for prenatal diagnosis where there is a policy to perform the fetal echocardiography also in all cases with extracardiac anomalies.

The dilated form of cardiomyopathy, either isolated or associated to extracardiac anomalies or infections (myocarditis) was related to a higher perinatal loss than the hypertrophic form, considered on the whole. The outcomes of cases with dilated form of cardiomyopathy was clearly worse in presence of the fetal hydrops, despite the fact that its presence, as well as the earlier age at presentation, did not reach a statistical significativity. An equally high perinatal loss of 82% of cases with DCM was reported by other authors [7].

Interestingly, 15.8% of our cases with DCM presented also various extracardiac anomalies and some of these also showed specific features of endocardial fibroelastosis as well as the fetuses with isolated, idiopathic form.

Family history of DCM was not frequent in our series; it was present in only one of our cases, in a sibling, and of a mild entity. On the other side, the familial DCM may occur more frequently, with a possibility of recurrence in 20–55% [20–22]. Often, there might be underlying metabolic disorders, difficult to precise in the fetal life, as it was in the case of one of our infants; this fact shows how the term of an “idiopathic” form may be incorrect, until a complete evaluation after birth or later in life is done [22].

The problems of a variable timing of presentation of DCM were shown in a fetal-postnatal study on cases with a family history for a nonhypertrophic cardiomyopathy [23], indicating a high recurrence rate of DCM (8/26 = 30.7%), but only half of the cases presented already in utero, in the
third trimester (after normal findings at the mid-trimester), while the remaining cases worsened after birth.

This fact makes it very difficult or impossible to reassure the women referred for the fetal echocardiography for the family history, even in presence of normal fetal exams in the third trimester.

5.1. Infections. The infective processes were often put in relationship with the development of dilated cardiomyopathy or endocardial fibroelastosis, following to the finding of antibodies anti-Coxsackie or other viruses in affected patients [7, 9]. Other agents, such as Cytomegalovirus, Rubella virus, parvovirus, and adenovirus, may cause acute myocarditis, with a high perinatal loss. Our cases were all due to Cytomegalovirus and Coxsackie infection and the outcome was poor in those with hydrops, while a few others improved—one already during the fetal life.

A Recovery of the Left Ventricular Dysfunction. It, both in cases of idiopathic DCM and after myocarditis, is known to occur, with a variable frequency [24, 25]. Effectively, around one third of our surviving cases with DCM and with myocarditis improved at follow-up, after 3 months–1 year.

5.2. Association with Arrhythmias. Tachy- or bradyarrhythmias induce potentially the left ventricular impairment, but there may probably be cases with a major predisposition for the left ventricular impairment in some cases. In our experience (of more than 50 tachyarrhythmias) we have found only one fetus presenting with a specific pattern of DCM. Also the fetuses carrying antibodies anti-Ro, anti-La, passed through placenta from mothers affected with clinical latent immunological disease, may have a predisposition for the development of DCM [26, 27].

Noncompaction of the Left Ventricle. It is a particular form of myocardial disease due to a failure of a normal embryological process of myocardial compaction and the cases affected present a variable degree of functional impairment and therefore a variable outcome [14–16]. This condition may be familial, as it occurred in two of our cases—siblings.

Hypertrophic Form of Cardiomyopathy. It was more frequent in our series than the dilated form, as mentioned above. HCM is known to be transmitted in some families by autosomal dominant type, with a variable severity. Some of our familial index cases presented a rather mild form of the disease, which increases the difficulty of predicting a possible recurrence later in infancy or in adulthood.

In the fetal life it is difficult to exclude an underlying metabolic disease as glycogenosis or other inborn errors of metabolism found after birth as in one of our cases. Therefore it is imperative to perform a detailed postnatal checkup for metabolic of infective conditions.

We have found during the period of this study also a large number of cases with secondary forms of HCM, in presence of some extracardiac anomalies or of the maternal diabetes. Hypertrophy secondary to renal anomalies was described also in another experience [28], and it probably has a similar pathophysiological explanation in the action of angiotensin-renin system, as postnatally. Other extracardiac anomalies, as those of CNS, or multiple anomalies, do not have apparently a clear etiopathogenesis.

Also syndromes as Noonan’s can present as HCM, without other associated intracardiac lesions, and in our series we also had a fetus with another rare condition—Thomas’s syndrome, defined only after birth.

A more common form of a secondary HCM is the one related to the maternal pregestational diabetes [29], in which there is an accumulation of glucose, due to a poorly controlled carbohydrate metabolism. These forms are expected nowadays to be less frequent, with a better control of mothers affected. Our series includes, however, 2 earlier cases who died after birth with features of a marked HCM. Otherwise, these fetuses present usually only minor anomalies of the diastolic flow through the mitral valve due to an impaired...
compliance [30], but have generally a progressive regression of hypertrophy and normalization after birth, as occurred in all surviving infants of our series.

The evolutivity of HCM is variable, at times worsening, as occurred in two of our cases, one of which needed a heart transplant very early, at 2 months; otherwise some cases can improve or completely regress, mainly the secondary forms, when not related to severe extracardiac anomalies. Echocardiographic follow-up allows nowadays a better assessment of the natural history of affected cases.

6. Conclusions

Our data confirm a variable spectrum of myocardial disease in the fetal age, with a possible association of extracardiac anomalies in both forms and more severe prognosis in DCM and myocarditis and in HCM associated with severe extracardiac anomalies. We have to underline the delicacy of the prenatal counseling, in cases with familial history, due to an impossibility to exclude a further presentation of the disease later in infancy or adulthood, as well as a potential association with metabolic or syndromic disorders detectable only after birth.

As a policy, it is imperative to perform a complete evaluation of the extracardiac organs in utero and a thorough postnatal check-up aiming to exclude underlying conditions. The limits of the early detection of myocardial disease are obviously greater in fetuses examined in the second trimester, therefore it is recommendable to repeat the examination in the third trimester and after birth. The cases with family history should also be followed up echocardiographically even later, during infancy and adolescence.

References


Review Article

Causes and Mechanisms of Intrauterine Hypoxia and Its Impact on the Fetal Cardiovascular System: A Review

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Until today the role of oxygen in the development of the fetus remains controversially discussed. It is still believed that lack of oxygen in utero might be responsible for some of the known congenital cardiovascular malformations. Over the last two decades detailed research has given us new insights and a better understanding of embryogenesis and fetal growth. But most importantly it has repeatedly demonstrated that oxygen only plays a minor role in the early intrauterine development. After organogenesis has taken place hypoxia becomes more important during the second and third trimester of pregnancy when fetal growth occurs. This review will briefly address causes and mechanisms leading to intrauterine hypoxia and their impact on the fetal cardiovascular system.

1. Introduction

Embryogenesis, fetal growth, and survival of the perinatal period all depend on optimal maternal health and normal placental development. Maternal exposure to a persistently hypoxic environment may lead to critical injury to vital organs. Failure of the normal placental function may have profound acute and chronic effects on the developing fetus and lead to intrauterine growth restriction (IUGR), asphyxia, multiorgan failure, premature delivery, and perinatal demise. In the United States, IUGR and prematurity complicate about 12% of the deliveries and represent the leading cause of perinatal mortality and morbidity to this day, accounting for up to 75% of perinatal deaths. Long-term disabilities such as cerebral palsy, hearing loss, retinopathies, and chronic lung disease are associated with a substantial emotional burden for affected families and health care costs to the society [1].

In this paper, we will briefly address relevant aspects of the normal fetomaternal physiology and then focus our attention on the causes of chronic intrauterine hypoxia and how this affects the development and performance of the fetal heart.

2. Normal Pregnancy

The process of placentation is initiated once the blastocyst makes contact with the epithelium of the uterus. An initial trophoblastic shell is penetrated by columns of proliferating extravillous cytotrophoblast that form the anchoring villi and provide specialized invasive cells that transform the decidual and proximal portions of the decidual spiral arteries [2]. During the initial phase of implantation and uterine wall invasion, the main role of extravillous trophoblast is to form plugs that occlude capillaries in the endometrial gland stroma; this prevents maternal hemorrhage from disrupting the conceptus and maternal blood from entering the lacunar spaces of the trophoblastic shell. Embryogenesis thus takes place in a hypoxic environment for the first 10 weeks of pregnancy because oxygen tension within the placenta is much lower than in the surrounding endometrial glands [3–6]. The “plugging” mechanism protects the growing embryo and the primitive placental villi against oxidative damage; antioxidant enzymes such as mitochondrial superoxide dismutase are not expressed by the syncytiotrophoblast before 8 to 9 weeks of gestation [7, 8]. In the period of 11–13 weeks,
the trophoblastic plugs are breached by maternal blood that now enters the intervillus space. Uteroplacental blood flow increases exponentially from less than 50 mL/min in the nonpregnant state to approximately 350 mL/min by fullterm. The demands of this large rise in uteroplacental blood flow (to 20% of the total maternal cardiac output), require large adaptations in maternal physiology [9].

The maternal cardiac output increases by 20% to 25% during the first trimester. It reaches its peak at the beginning of the third trimester when it exceeds the prepregnancy output by 30% to 40%. This is primarily achieved by an increase in the circulating blood volume resulting in a rise in stroke volume of about 30%, by an increase in the resting heart rate of 10 to 20 beats/min and by lowering the systemic arterial blood pressure secondary to the effects of gestational hormones, circulating prostaglandins, the excessive release of human placental growth factors, and the low-resistance uteroplacental unit [10–13]. The increase of total blood volume is related to plasma expansion by 30 to 40 mL/kg body weight rather than an increase in total red blood cells and accounts for the relative anemia of pregnant women. The increased cardiac output together with the low blood viscosity lead to a rightward shift of the hemoglobin-oxygen dissociation curve [13–16]. The maternal gas exchange adapts in parallel with the hemodynamic changes. The increase in fetal-maternal oxygen demand is achieved by mild hyperventilation and anatomical changes that allow the mother to maintain her natural lung capacity despite the increase of the intra-abdominal volume.

Increased production of endothelial nitric oxide and other vasodilators in conjunction with attenuated adrenergic vasoconstriction is thought to be responsible for maintaining uterine artery flow [17–19]. By midgestation, the human uterine artery has doubled its diameter and the increased flow is accommodated by hyperplasia of all cell layers [20–22].

2.1. Embryonic Heart Development. The embryonic heart develops early post conception from its origins in the heart field to a completely looped 4-chamber organ by 8 weeks of gestation [23–28]. During this period the oxygen saturation never exceeds 20%, protecting the embryo from oxidative damage [6–8]. By the time the extravillous spaces of the trophoblast are starting to be filled with maternal blood, the newly-formed fetal heart is ready to meet the increasing oxygen and nutritional demands of the growing fetus [7, 9]. The fetal oxygen saturation gradually increases during the 2nd trimester to about 60%. To maintain an adequate circulation, the fetal heart adjusts continuously to the rise in circulatory blood volume and pressure load. The right and left ventricles work in parallel, adjusting their outputs via several prenatal shunts that will close in the immediate postnatal period.

3. Intrauterine Hypoxia

Intrauterine hypoxia is associated with a variety of maternal, placental, and fetal conditions which may manifest differently and have different outcomes. Kingdom and Kaufmann [29] suggested to classify hypoxic pregnancy conditions into 3 subtypes: (1) preplacental hypoxia, where both the mother and her fetus will be hypoxic (i.e., high-altitude, cyanotic maternal heart disease; etc.); (2) uteroplacental hypoxia, where the maternal oxygenation is normal but the utero-placental circulation is impaired (i.e., preeclampsia, placental insufficiency, etc.); (3) postplacental hypoxia, where only the fetus is hypoxic. We will focus on the first 2 subtypes as the post-placental hypoxia is mainly related to fetal diseases rather than to the direct impact of hypoxia onto the fetus.

3.1. Pre-Placental Hypoxia. Main causes of pre-placental hypoxia are a hypoxic environment (high-altitude) and pre-existing maternal cardiovascular disease such as cyanotic heart disease, heart failure, or pulmonary hypertension. Maternal anemia, infections, and chronic inflammation may further limit the maternal oxygen uptake and oxygen delivery to the fetus, thereby increasing the risk for adverse pregnancy outcomes.

Chronic hypoxia associated with placental insufficiency plays a key role in the etiology of intrauterine growth restriction (IUGR). High-altitude exposure mimics this condition and its adverse effects on birth weight exceed those of most other risk factors for IUGR, such as maternal low weight gain, smoking, primiparity, or preeclampsia [30]. A 1000 meter gain in altitude results in a natural average decline of the birth weight of 100 grams [30–32]. Intrauterine growth of the chronically hypoxic fetus generally begins to slow down between gestational week 25 to 31, a time when fetal growth normally increases exponentially [33]. Interestingly, high-altitude exposure appears also to be associated with an increased risk of pre-eclampsia that may further contribute to low birth weights in high-altitude populations [34]. Nevertheless, in most cases arterial hypertension during pregnancy at high-altitude is probably related to chronic hypoxia rather than to classic pre-eclampsia [34–36]. In line with this concept, pregnant women at high-altitude lack the physiological blood pressure fall at the beginning of the second trimester [36, 37]. A possible explanation is that chronic hypoxia diminishes the vasodilatory effect of nitric oxide while the sympathetic nervous system (α1-/α2-adrenergic receptor) is activated [10, 17, 18, 38–40]. In addition, potent vasoconstrictors like endothelin-1 and the hypoxia-inducible factor (HIF) are stimulated early in pregnancy by excessive generation of reactive-oxygen species (ROS) [41]. Altitude may also influence cardiac performance and the circulating blood volume. Cardiac output is lower presumably due to a lower heart rate and smaller stroke volumes related to a decreased blood volume of women living permanently at high-altitude [42, 43]. Finally, uterine arteries are typically smaller in diameter and less well perfused during pregnancy at high-altitude [44]. A direct association between uterine arterial flow and birth weight is supported by studies conducted in women from different origins [45, 46].

Women with congenital heart disease are at increased risk of developing pregnancy complications [47]. The probability of maternal complications has been classified as low,
intermediate, or high, with estimates of 5%, 25%, and 75%, respectively, of experiencing cardiac events such as arrhythmias, pulmonary edema, stroke, or cardiac death during pregnancy [48]. The highest risk is observed in mothers with severe left-sided obstructive lesions (i.e., aortic stenosis, coarctation), pulmonary hypertension, Marfan syndrome with aortic root dilatation, as well as with symptoms of moderate or severe heart failure (NYHA functional class III and IV). Increasing maternal hypotension is the most important factor associated with intrauterine growth restriction (20% to 25%) and prematurity (20% to 25%) [49]. Interestingly, un repaired or palliated cyanotic congenital heart disease does not belong to the high-risk group for an adverse maternal outcome but is associated with an increased risk of fetal loss. The live-birth rate is reportedly only 40% to 45% if the mother has cyanotic heart disease. This rate decreases to 10%–15% if the maternal oxygen saturation drops below 85%. In addition, extreme prematurity affects 35% to 40% of these pregnancies [50]. Fetal or neonatal death, brain hemorrhage secondary to maternal anticoagulation or to extreme prematurity, as well as IUGR are common findings in offspring of pregnant women with congenital or acquired heart disease [47, 48, 51].

Chronic pulmonary disease may have similar maternal-fetal consequences as chronic exposure to hypoxia [52]. Poorly controlled asthma is associated with pre-eclampsia, uterine hemorrhage, preterm delivery, and low birth weight [53, 54]. Among chronic lung diseases, cystic fibrosis (CF) and tuberculosis are the most common conditions: 5% of the world population is carrying the CF gene and 30% of humans have been infected with mycobacterium tuberculosis [55, 56]. Pregnancy in cystic fibrosis patients seems to have a positive effect on maternal long-term survival, despite the increased maternal risk for infections and insulin resistance and the increased fetal risk of prematurity and IUGR [57–61].

Acute respiratory infections during pregnancy are common. 1% of women experience symptoms of bronchitis or pneumonia during the course of pregnancy. Current antibiotic regimens have decreased maternal mortality from bacterial pneumonia dramatically, with the exception of cystic fibrosis. Nowadays viral pneumonias are responsible for the major part of maternal deaths during pregnancy [52]. The major risk for the fetus lies in maternal respiratory failure due to ARDS [52, 62, 63]. Fetal complications include stillbirth, spontaneous preterm labor, and a need for early delivery by Cesarean section to improve the effectiveness of maternal ventilation for respiratory failure.

Maternal hematological disorders may directly affect oxygen transfer. Iron deficiency anemia (IDA) is common in pregnancy and often related to malnutrition or micronutrient diets [64–67]. IDA is associated with increased risk for IUGR and prematurity [65, 68–70]. In contrast to IDA, the oxygen carrier capacity is altered in hemoglobinopathies. Sickle cell disease is particularly common in Africans and Afro-Americans [71, 72]. It may be present in combination with hemoglobin C or β-thalassemia (Hb S/C or Hb S/β). The most severe form (homozygous HbS) is called sickle cell anemia but any Hb S combination (Hb S/C or Hb S/β) can potentially cause vaso-occlusive crisis and hemolysis [73]. This problem is caused by the abnormal rigid sickle shape of the red blood cells with decreasing oxygen tension. Patients with sickle cell disease are at higher risk for maternal (i.e., preterm labor, preterm rupture of membranes, and postpartum infections) and fetal complications (i.e., abortion, prematurity, IUGR, low birth weight, and stillbirth) [74]. Close fetal monitoring during pregnancy and prophylactic exchange transfusion seem to be often effective in abolishing life-threatening intrauterine hypoxic events [75].

Thalassemia is an autosomal recessive blood disease which is particularly prevalent in Asians (α-form) and among Mediterranean people (β-form). The genetic defect results in a reduced synthesis rate of α- or β-globin chains that make up hemoglobin [73, 76]. Homozygous individuals present with severe anemia (Cooley’s anemia) and extramedullary erythropoiesis. Alpha-Thalassemia major (Hb Bart’s) is associated with hydrops fetalis, intrauterine death, and pre-eclampsia [71]. β-Thalassemia is a result of a mutation in the β-globin gene causing deficient or absent β chain production with absence of hemoglobin. The clinical picture of β-thalassemia varies in severity in function of the expression of Hb A. Pregnancy in thalassemia carriers is usually uncomplicated. Successful pregnancies in women with α- and β-thalassemia major have been reported but were associated with a higher incidence of IUGR, low birth weight, and prematurity [77–79].

3.2. Utero-Placental Hypoxia. Utero-placental hypoxia is related to abnormal placentation early in gestation and to placental vascular disease later in pregnancy. Abnormal placental implantation is a common finding in pregnancies complicated by IUGR, by gestational hypertension, and by pre-eclampsia. There exists an increased risk for both the mother and the fetus to develop cardiovascular disease later in life [68, 80–91].

Pre-Eclampsia. It is a complex multisystem disorder observed in human pregnancy. Maternal clinical manifestations range from mild hypertension and proteinuria to fully established HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelet count) or eclampsia with severe hypertension, proteinuria, and multiorgan involvement (pulmonary edema, CNS symptoms, oliguria, thrombocytopenia, and liver failure) [92–95].

Causes for its origin are largely unknown but may be the result of a systemic inflammatory response perhaps related to an immature maternal immune response [35]. Key abnormalities of pre-eclampsia include a rise in systemic vascular resistance, endothelial dysfunction, and activation of the coagulation system with enhanced platelet aggregation [92]. Endothelial dysfunction is responsible for the impaired generation and activity of vasodilators such as prostacyclin and NO and could explain surface-mediated platelet activation and fibrin formation in the uteroplacental circulation [96].

Depending on the severity of the pre-eclampsia, the condition may lead to intrauterine hypoxia and/or oxidative stress in the fetus. Pre-eclampsia is associated with IUGR and prematurity [89]. Fetal morbidity and mortality
increase significantly when pre-eclampsia develops prior to 33 gestational weeks [97–100]. Pre-eclamptic mothers and their offspring are at an increased risk for premature cardiovascular disease later in life [101].

3.3. Post-Placental Hypoxia. In post-placental hypoxia, only the fetus becomes hypoxic which is either related to diminished uterine artery flow (i.e., mechanical compression, rupture, and thrombotic occlusion), progressive fetal cardiac failure (i.e., complete congenital heart block, complex congenital heart malformations), or due to important genetic anomalies. As mentioned earlier, we will not further explore the post-placental hypoxia as it is mainly related to fetal diseases rather than to the impact of hypoxia onto the fetus.

3.4. Effects of Hypoxia on the Fetus. A main consequence of chronic hypoxia is the failure of the fetus to achieve its genetically determined growth potential. About 10% of all babies grow poorly inutero and are born small for gestational age. IUGR is associated with distress and asphyxia and a 6- to 10-fold increased perinatal mortality [102]. Frequent hypoxia-mediated complications include meconium aspiration, metabolic and hematologic disturbances, cognitive dysfunction, and cerebral palsy. Acute and chronic hypoxia is also associated with a variety of morphological and functional fetal cardiac changes that aim to compensate for the reduced oxygenation of vital organs or are the result of hypoxia-mediated fetal tissue damage [103–105].

3.4.1. Hemodynamic Consequences. At an initial stage, the human fetus may be able to adapt to hypoxia by increasing the blood supply to the brain, myocardium, and upper body and decreasing the perfusion of the kidneys, gastrointestinal tract, and lower extremities. This redistribution of blood allows preferential delivery of nutrients and oxygen to the most vital organs. Cerebral vasodilatation to spare the brain from hypoxic damage leads to a decrease in left ventricular afterload while systemic arterial vasconstriction of lower body vessels increases right ventricular afterload [106, 107]. In line with this concept, echocardiographic studies in the hypoxic fetus demonstrate an increased middle cerebral artery blood flow and a shift of the cardiac output in favor of the left ventricle [108, 109]. With further deterioration of the fetal oxygenation, this protective mechanism is overwhelmed by the decline in cardiac output and the emergence of fetal distress. The final stage is characterized by a decline in systolic and diastolic fetal cardiac function, secondary to myocardial ischemia [110]. Moreover, raised atrial contraction results in the transmission of atrial pressure waves into the venous duct and umbilical vein, causing end-diastolic umbilical vein, pulsation [111]. At this stage, reduced or reversed end-diastolic flow velocity may also be found in pulmonary veins and coronary blood flow may become visible with increased systolic-diastolic flow velocities (“heart sparing”). If not delivered, intrauterine death occurs usually within a few days [112].

In line with these findings in the hypoxic human fetus, in the hypoxic fetal sheep the cardiac output is reduced whereas the hemoglobin level is increased to maintain a near-normal oxygen delivery to the fetal myocardium [113, 114]. Moreover, in this hypoxic animal model, the coronary blood flow of the fetus is increased although there is no change in capillary/muscle fiber ratio, capillary volume density, or capillary diameter, and myocardial contractility is reduced [113–117].

While chronic hypoxia has detrimental consequences for the fetal heart, chronic anemia appears to have less detrimental effects because the higher oxygen affinity of fetal hemoglobin allows to compensate for this problem. In maternal anemia-related hypoxia, the fetus is able to increase the cardiac output and to increase the transplacental oxygen transfer by actively interfering with the iron metabolism of the mother.

Surviving babies seem to be particularly susceptible to the development of arterial hypertension and cardiovascular disease later in life. An association between low birth weight and early onset of essential arterial hypertension has first been postulated by Barker in the “fetal origins of adult disease hypothesis” [118]. Barker’s theory states that physiologic adaptations that enable the fetus to survive a period of intrauterine deprivation result in permanent reprogramming of the development of key organs that may have pathological consequences in postnatal life. In older children and adults, a low birth weight has been linked with increased arterial stiffness, systolic blood pressure, premature coronary heart disease, stroke and diabetes [68, 83–85, 87, 119–129], and ischemia/reperfusion injury (139–45). Despite the strong epidemiologic evidence that supports the concept of “fetal programming”, we still do not know its underlying mechanisms.

3.4.2. Teratogenicity. Recently it has also been suggested that hypoxia early in gestation may be teratogenic to the human embryo. As such, maternal asthma exacerbation during the first trimester of pregnancy reportedly increased the risk for congenital malformations including the risk of cardiovascular malformations [130]. As described above, maternal blood enters the intervillous space of the human placenta only after 10 to 12 gestational weeks and until this moment the placental metabolism is anaerobic [3, 7]. Yet, the human heart forms early in the period of anaerobic metabolism between day 15 and day 60 postconception. Interestingly, if animal embryos are exposed to chronic hypoxia, cardiac malformations seem not occur more frequently.

3.4.3. Cellular Effects of Hypoxia. In rats, early fetal hypoxia triggers cardiac remodeling associated with enhanced apoptosis and a significant increase in binucleated myocytes [131]. At the age of 4 months, fetal hypoxia was associated with increased heart/body weight ratio presumably due to hypertrophy of myocardium in presence of slowed fetal growth, increased β-α-myosin heavy chain ratio, increased collagen I and III expression, and lower matrix metalloproteinase-2 activity. The consequences of these changes are higher end-diastolic pressure related to less compliant left ventricle and a reduced capability to recover from ischemia.
Apoptosis is a controlled active physiologic process that removes unwanted or defective cells by intrinsic programmed cell suicide [105]. In rat hearts exposed to oxidative stress, it could be shown that many genes that affect cell communication, survival and signaling were downregulated [105, 131]. This downregulation is believed to be partly responsible for the long-term consequences of intracellular hypoxia and leaves a persistent cardiovascular "imprint" that leads to cardiovascular disease in later life. The transcription of the heat shock gen Hsp70 might be an example of this observed cardiac programming phenomenon. Hsp70 is a protein that protects against myocardial ischemia and stress (hyperthermia) and inhibits apoptosis by preventing the formation of caspase-9 [132–134]. In chronic intracellular hypoxia conditions, the expression of Hsp70 is down-regulated [135]. This effect persists into adulthood and may explain why some adult hearts are more vulnerable against ischemia/reperfusion injury [132–138]. The expression of endothelial nitric oxide is also important for the long-term cardioprotection of the cardiomyocytes. eNOS levels are also decreased in rat hearts who were exposed to intracellular hypoxia [139]. Similar changes were observed in the regulation of the β-adrenoreceptors (βARs) and the coupling G proteins. β2AR and Gsα are upregulated in adult rat hearts that were in utero exposed to chronic hypoxia. This upregulation preserves cardiac contractility in hypoxia, but the regulatory mechanism appears to be lost in adulthood presumably due to wrong prenatal programming [140, 141].

4. Conclusion

Hypoxia does not play a major role in the early development of structural cardiac malformations probably because early embryogenesis already takes place under anaerobic conditions. Only during the second and third trimester, oxygen becomes more important for the normal fetal organogenesis and growth. If at that stage exposed to hypoxia, the fetus has a number of protective options. Immediate protection against oxidative stress is established by up-regulation of genes. Stimulation of nitric oxide synthesis enhances cell signaling for defense mechanisms, platelet inhibition, and regulation of apoptosis. β2AR and Gsα will be up-regulated to maintain a sufficient cardiac output. With persistent hypoxia, premature exit of cell cycle is initiated, together with enhanced apoptosis resulting in fewer, but hypertrophied cardiomyocytes. This process aims for better energy efficiency during hypoxic conditions but also results in less compliant ventricles. Altered regulatory gene expression in response to in-utero hypoxia appears to extend into adulthood and mimics the changes that are found in adults with chronic heart failure. Hypoxia slows fetal growth, and growth restriction is now considered a risk factor of premature arterial hypertension and cardiovascular disease, probably secondary to endothelial dysfunction. Further investigations are needed to explore preventative strategies such as the early use of antioxidants and selective vasodilators to limit the effects of intrauterine hypoxia.

References


Review Article

Impact of Congenital Heart Disease on Brain Development and Neurodevelopmental Outcome

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Advances in cardiac surgical techniques and perioperative intensive care have led to improved survival in babies with congenital heart disease (CHD). While it is true that the majority of children with CHD today will survive, many will have impaired neurodevelopmental outcome across a wide spectrum of domains. While continuing to improve short-term morbidity and mortality is an important goal, recent and ongoing research has focused on defining the impact of CHD on brain development, minimizing postnatal brain injury, and improving long-term outcomes. This paper will review the impact that CHD has on the developing brain of the fetus and infant. Neurologic abnormalities detectable prior to surgery will be described. Potential etiologies of these findings will be discussed, including altered fetal intrauterine growth, cerebral blood flow and brain development, associated congenital brain abnormalities, and risk for postnatal brain injury. Finally, reported neurodevelopmental outcomes after surgical repair of CHD will be reviewed.

1. Introduction

Congenital heart disease (CHD) has been reported to occur in 5 to 8 per 1000 live births [1]. It is by far the most common birth defect and a significant cause of childhood morbidity and mortality. Over the past several decades, advances in cardiac surgical techniques and perioperative intensive care have led to improved survival in babies with CHD [1]. While it is true that the majority of children with CHD today will survive, up to half of surviving children will have impaired neurodevelopmental outcome across a wide spectrum of domains [2–5]. While continuing to improve short-term morbidity and mortality is an important goal, recent and ongoing research has focused on defining the impact of CHD on brain development, minimizing postnatal brain injury in this vulnerable population, and improving long-term outcomes for survivors. This paper will review the impact that CHD has on the developing brain of the fetus and infant. Neurologic abnormalities detectable prior to surgery will be described. Potential etiologies of these findings will be discussed, including altered fetal intrauterine growth, cerebral blood flow and brain development, high prevalence of congenital brain abnormalities, and risk for postnatal brain injury in babies with CHD. Finally, reported neurodevelopmental outcomes after surgical repair of CHD will be reviewed.

2. Preoperative Neurological Status in Babies with CHD

Traditionally, studies of neurological outcomes in children with CHD have focused on factors related to surgery, when cerebral perfusion may be compromised during cardiopulmonary bypass. However, the fact that these infants are at risk for adverse outcome before entering the operating room is supported by an increasing body of literature. Brain abnormalities are detectable by preoperative neuroimaging and neurological examination in a significant percentage of infants with CHD. These findings are multifactorial, contributed to by intrauterine hemodynamic alterations, congenital brain abnormalities, and acquired brain injury related to prolonged cyanosis or hypoperfusion after birth.
2.1. Clinical and Radiographic Evidence of Impaired Preoperative Neurological Status. Limperopoulos et al. reported neurobehavioral abnormalities prior to surgery in 56 newborns (<1 month at surgery) and 70 infants (between one month and two years) with complex CHD of a variety of lesion types [6, 7]. In this series, more than 50% of newborns and 38% of infants were found to have abnormalities. In newborns, findings included hypotonia, hypertonia, jitteriness, motor asymmetry, and absent suck. Sixty-two percent had poor behavioral state regulation, 34% feeding difficulties, and 5% seizures. In infants, abnormalities included hypotonia, head preference, lethargy, restlessness, agitation, motor asymmetry, and feeding difficulties. Autistic features were also found. Microcephaly was present in 36%. Newborns with acyanotic lesions were more likely to demonstrate abnormalities than those with cyanotic defects. However, cyanotic infants with an oxygen saturation <85% had a higher incidence of abnormalities. In another report, these authors described preoperative neurological examinations and electroencephalograms (EEG) in 60 infants with CHD. Prior to surgery, 19% of infants had epileptiform activity, and 33% had disturbances in background activity that were moderate or diffuse [8]. EEG abnormalities were associated with abnormal findings on neurological examination, and severe abnormalities were predictive of death. Other authors have likewise reported neurological findings prior to surgery in cohorts of patients with CHD. Chock et al. reported the incidence of an acute neurological event defined as seizure, tone abnormality, or choreoathetosis, to be 19% preoperatively in patients of mixed lesion types [9]. Glauser et al. reported that 38% of infants with hypoplastic left heart syndrome (HLHS) had an abnormal neurological examination or seizures prior to surgery [10].

Structural abnormalities and acquired lesions can be detected by neuroimaging performed prior to surgery in a significant percentage of patients with CHD. Preoperative head ultrasounds can detect abnormality in 15–59% of patients with congenital heart disease [9, 11, 12]. Brain magnetic resonance imaging (MRI) performed prior to surgery also demonstrates a high incidence of preoperative brain abnormalities ranging from 25–53% in some series [13–15]. Lesion types detected preoperatively by ultrasound and MRI may be either developmental and/or acquired. In addition to detecting abnormalities, newer imaging modalities may also shed light on pathogenesis. Emerging MR techniques including diffusion tensor imaging (DTI) and advanced MR spectroscopy (MRS) have lead to quantifiable methods to describe brain injury. Miller et al. described results of preoperative DTI and MRS evaluation of 41-term newborns with CHD compared to healthy control newborns without CHD [16]. Decreased ratio of N-acetylaspartate to choline, increased lactate to choline ratio, and decreased white matter fractional anisotropy values were found, similar to profiles measured in preterm infants. This similarity to the preterm brain led the authors to suggest that infants with CHD have abnormal brain development in utero. This concept is further supported by studies of in utero cerebral blood flow in fetuses with CHD.

2.2. Intrauterine Factors That Impact Cerebral Flow and Neurodevelopment. The association of complex CHD with intrauterine growth retardation has been well established in numerous reports over the past six decades [17–26]. Biometric data from a regional, population-based, case-controlled study revealed that infants with CHD had abnormal in utero somatic growth compared to matched controls [19]. The study demonstrated that infants with transposition of the great arteries (TGA) had normal birth weights, but small head circumferences relative to birth weight. Newborns with HLHS had birth weights, lengths, and head circumferences that were less than normal and had head volumes that were disproportionately small relative to birth weight. Finally, infants with tetralogy of Fallot (TOF) had normal proportions, but birth weights, lengths, and head circumferences that were less than normal. There are two theories that have been proposed with regards to the etiology of growth retardation in babies with CHD. First, fetuses with altered growth may have an increased risk of developing cardiac abnormalities [17]. Second, and perhaps more likely, the altered circulation which occurs as a result of the specific structural cardiac abnormality can lead to flow disturbances that may affect in utero growth and brain development [19, 26]. This second theory has been further explored in Doppler ultrasound studies of animal and human fetuses.

2.2.1. In Utero Cerebral Flow Characteristics and Compensatory Mechanisms. The fetal circulation has been described in detail in both animal and human studies and is depicted in Figure 1(a). Fetal lamb studies have shown that right ventricular output is twice left ventricular output, and oxygen saturation of blood delivered to the cerebral circulation is higher than that delivered to the body through the ductus arteriosus. Deoxygenated blood from the superior vena cava is directed into the right ventricle, across the ductus arteriosus and to the placenta. The Eustachian valve and atrial septum move together to direct deoxygenated blood from the hepatic inferior vena cava into the right ventricle, and oxygenated blood from the ductus venosus across the foramen ovale, through the left ventricle, and to the aorta and cerebral circulation. In the human fetus, the path the blood takes through the heart is identical. Right ventricular output is greater than left, though the difference is not as substantial as in the fetal lamb [27].

In situations where fetal oxygenation is compromised, there is a redistribution of blood flow to the cerebral circulation as a “brain sparing” response [28, 29]. This hemodynamic phenomenon is represented by increased diastolic flow in the cerebral arteries and decreased diastolic flow in the descending aorta and umbilical arteries. Specific regions of the fetal brain may be more protected than others. In a study by Dubiel, interrogation of the middle, anterior, and posterior cerebral arteries was obtained in pregnancies complicated by maternal hypertension and placental dysfunction [29]. Cerebral vasodilation was found in the anterior cerebral artery in 41%, in the posterior cerebral artery in 30%, and in the middle cerebral artery in 24% of fetuses evaluated. Thus, there is an enhanced autoregulatory response of the anterior cerebral arteries, and redistribution
of blood flow favors perfusion of the frontal lobes. The middle cerebral arteries, however, have been found to be less reactive and lose reactivity sooner during long-standing compromise.

Paradoxically, this autoregulatory mechanism has been found to be a harbinger of adverse neurological outcome. Since cerebral vasodilation occurs in the face of compromised fetal oxygenation, the detection of this finding reflects a high risk in utero environment and/or aberrant fetal circulation. In other words, this protective mechanism may be inadequate to maintain normal brain growth and development in situations of prolonged in utero stress. Doppler ultrasound studies have elucidated normative data on blood flow characteristics in human fetuses, and abnormalities have been shown to be predictive of adverse perinatal outcome [30–38]. Resistance and pulsatility indices can both be calculated from Doppler waveform tracings of the cerebral vessels obtained during imaging of the fetus. The resistance index is defined as the systolic flow velocity (SV) minus the diastolic velocity (DV) divided by the mean velocity (MV). These indices are considered to be representative of the resistance to flow distal to the point of measurement and can be measured in the cerebral as well as umbilical arterial vessels. Normative information for these indices has been established and lower than normal values have been associated with growth retardation [31, 34, 36, 38] and adverse neurological outcome [33, 36]. A cerebral to umbilical artery ratio of these indices, reflecting degree of “brain sparing” response, is more predictive of intrauterine growth restriction and poor outcome than either index alone. Arbeille showed in normal fetuses that after 15 weeks gestation the cerebral and umbilical resistance both decrease linearly, but the cerebral resistance always remains higher than the umbilical resistance. For the duration of pregnancy the normal cerebral/umbilical resistance ratio is >1.0. In his study, 97% of normal fetuses had cerebral/umbilical ratios >1.0, and 88% of growth-retarded fetuses had ratios <1.0 [38]. In a study by Gramellini, a cerebral/umbilical pulsatility ratio <1.08 after 30 weeks gestation in high-risk pregnancies had a diagnostic accuracy of 70% for growth retardation and a predictive value of 90% for poor perinatal outcome [36].

Another ultrasonographic finding indicative of poor outcome is reversal of diastolic flow in the aortic isthmus. In the fetus, the ventricles function in parallel with two distinct shunt pathways: the foramen ovale and ductus arteriosus. These connections equalize pressures in the aorta and in the great vessels. Differences between right and left ventricular impedance can be explained by the aortic isthmus which is the narrowest segment of the arch located distal to the left subclavian artery and proximal to ductus arteriosus insertion [27]. Hemodynamically, the fetal aortic isthmus is the bridge between the left ventricular and right ventricular outputs. Normal isthmus blood flow is toward the ascending aorta in diastole. Reversed diastolic flow in the isthmus in the absence of CHD is likely due to an altered cerebral/placental resistance ratio caused by placental disease and/or a reflex dilation of the cerebral vasculature in response to hypoxia. Doppler interrogation with reversed flow at the isthmus has been shown to be a predictor of poor neurological outcome in high-risk fetuses [39–41].

2.2.2. Alterations in Cerebral Blood Flow in Fetuses with CHD. Several studies have characterized in utero blood flow using Doppler ultrasound in human fetuses with CHD. These ultrasonographic findings and their pattern in CHD infants are summarized in Table 1.

Donofrio et al. published the first multicenter, prospective study that assessed cerebral blood flow by imaging fetuses with CHD at four-week intervals and comparing results to normal controls [42]. Sixty-three studies in 36 heart disease fetuses and 47 studies in 21 normal fetuses were analyzed. Blood flow characterization by lesion type, changes during gestation, and comparisons of indices in CHD versus normal control fetuses were described.

Normal fetal circulation directs oxygenated blood to the brain and deoxygenated blood to the placenta (Figure 1(a)). Fetuses with HLHS likely have increased resistance to cerebral flow as blood flows retrograde across a hypoplastic aortic isthmus to reach the brain. Due to intracardiac mixing, relatively deoxygenated blood supplies the cerebral circulation (Figure 1(b)). Fetuses with left ventricular outflow tract obstruction have varying degrees of resistance to aortic flow, with minimal intracardiac mixing (Figure 1(c)). Fetuses with TGA have venous blood from the cerebral circulation directed back to the brain (Figure 1(d)). In fetuses with TOF and hypoplastic right heart syndrome relatively deoxygenated blood enters the cerebral circulation due to intracardiac mixing (Figures 1(e) and 1(f)). Thus, lesion type affects not only the source of cerebral blood flow but also the degree of deoxygenated blood distributed through the cerebral circulation.

Donofrio demonstrated that the cerebral/umbilical resistance ratio versus gestational age relationship was different between normal and heart disease fetuses. Plotting of the data revealed a more quadratic effect in fetuses with heart disease versus the linear relationship in fetuses without CHD. The resistance ratio nadir for heart disease fetuses was at 24-week gestation (Figure 2). This finding is significant since brain development enters a critical period at approximately 24–26-week gestation. Rudolph showed that in normal lamb fetuses, blood flow to the brain begins to increase at a gestational age which correlates to a human age of 26 weeks [27]. Mari showed that cerebral pulsatility decreases in normal fetuses after 24 weeks, indicating increased blood flow to the brain [34]. From 20 to 24 weeks, neuronal proliferation and migration occur, and by 24 weeks the human cerebral cortex has its full complement of neurons. After neuronal migration, the major gyri form between 24–28 weeks gestation with the most rapid increase occurring at about 26 weeks [43]. Thus, autoregulation of cerebral blood flow in fetuses with CHD occurs during a time of brain development when increased perfusion is needed the most to compensate for cerebral hypoxemia.

Overall, mean cerebral artery resistance and mean cerebral/umbilical resistance ratios were lower for fetuses with heart disease compared to normal. When comparing individual groups, mean cerebral/umbilical resistance ratios...
Figure 1: (a) Normal fetal blood flow. (b) Hypoplastic left heart syndrome. (c) left ventricular outflow obstruction. (d) Transposition of the Great Arteries. (e) tetralogy of fallot. (f) hypoplastic right heart. Red arrows: oxygenated blood; blue arrows: deoxygenated blood.

were lower for fetuses with HLHS compared to normal. Fetuses with TGA had the second lowest mean ratios, with a trend towards significance. The percent of fetuses in each group with at least one abnormal cerebral/umbilical resistance ratio during gestation was different when comparing normal and heart disease groups (5% versus 44%, resp.). In this analysis, fetuses with hypoplastic left and right heart syndrome had the highest incidence of abnormal cerebral/umbilical resistance ratios (58% in HLHS and 60% in hypoplastic right heart syndrome). Fetuses with TOF and TGA were less affected (45% and 25%, resp.), and no fetus with left ventricular outflow tract obstruction had an abnormal resistance ratio. Mean head circumference of fetal weight ratio trended towards being smaller when comparing normal and heart disease fetuses. Abnormal cerebral/umbilical resistance ratios at fetal weights around 2 kg were associated with smaller head circumferences in CHD fetuses.

The second study to evaluate cerebral blood flow in fetus with CHD was a cross-sectional, prospective analysis of fetuses with HLHS (n = 28), and defects with left (n = 13) or right (n = 17) heart obstruction compared to 114 normal controls published by Kaltman [44]. Cerebral (CPI) and umbilical pulsatility indices (UPI) were measured, and comparisons were made using Z-scores generated from published normative data. When comparing groups, the HLHS group had a lower mean CPI while the right sided obstruction group had a higher CPI than normal. The left-sided obstruction group was not different from normal. The right-sided obstructive lesions had a higher mean UPI while both other heart disease groups were not different from normal. Of note, the UPI/CPI ratio was not different when comparing groups. The finding of increased CPI in fetuses with right sided obstructed flow was different from the results of Donofrio’s study. It is possible that cerebral resistance is increased in these defects because antegrade
flow from the aorta is unobstructed and perhaps increased from normal. The increase in cerebral resistance may be due to cerebral autoregulation to limit excessive flow. The difference between the findings of the two studies may be in part attributable to the fact that in Kaltman’s study, fetuses with right sided obstruction included those with TOF which were analyzed separately by Donofrio. Kaltman’s fetuses had an increased umbilical resistance that was also not found in Donofrio’s study. In a study by Meise [45] umbilical resistance was abnormal in some fetuses with heart disease. The true prevalence of altered placental flow in fetuses with CHD is not known. Of note, in Meise’s study no difference was found in cerebral resistance when comparing normal to CHD fetuses; however defects were not separated into physiologic subtypes for analysis.

Other studies have revealed similar findings. In a study by Jouannic [46] cerebral flow in fetuses with TGA was evaluated. CPI in TGA fetuses (n = 23) was compared to 40 normal matched controls. In this study the CPI was significantly lower in TGA fetuses compared to normal fetuses. Umbilical Doppler (including UPI) and ductus venous flow were normal. This study confirmed the trend seen in Donofrio’s study and suggests that fetuses with TGA have cerebral vasodilation likely from cerebral hypoxia related to the structural cardiac abnormality. In a study by Modena’s [47], CPI in 71 fetuses with CHD was compared to matched controls. Cardiac lesions were grouped into defects with intracardiac mixing of deoxygenated and oxygenated blood versus those that were considered to have nonmixing lesions. Abnormal CPI was found in 7% of fetuses with CHD, versus none with normal hearts. All abnormal CPI occurred in fetuses with intracardiac mixing suggesting that hypoxemia plays a role in cerebral vasodilation. Guorong [48] evaluated 45 fetuses with CHD and compared findings to 275 controls. CPI, UPI, and UPI/CPI ratios were calculated and converted to z-scores similar to the study of Kaltman. They found that fetuses with CHD had normal CPI; however UPI/CPI ratios were elevated suggesting a redistribution of the circulation towards the head. Fetuses with CHD complicated by congestive heart failure had low CPI compared to normal suggesting cerebral vasodilation. They concluded that cerebral dilation occurs as a result of cerebral hypoxemia from limited perfusion and that it is both heart function and type of CHD that have an impact on fetal cerebral blood flow distribution and postnatal neurologic outcome.

The results of these studies all demonstrate that alterations in the intracardiac circulation caused by specific cardiac defects result in changes in cerebral blood flow characteristics that can be documented by Doppler ultrasound. The mechanism is complex and likely is related to both the cerebral oxygen content of blood and also the oxygen delivery which is dependent on cardiac function and total combined cardiac output. In Donofrio’s study, hypoplastic left and right heart fetuses were the most affected. These defects both have a single ventricular chamber with intracardiac mixing of blood and thus lower oxygen content in the blood that is delivered to the brain. This relative cerebral hypoxemia may stimulate a decrease in cerebral vascular resistance that in the presence of an unchanged placental resistance results in cerebral vasodilation and abnormal cerebral/umbilical resistance ratios. It has been shown that the fetal myocardium delivers less active tension, generates a lower maximum force of contraction, and responds less to increased preload than mature myocardium [49]. The single ventricular chamber may not be able to increase combined ventricular output enough to compensate for the cerebral hypoxemia caused by intracardiac mixing of blood. This may lead to abnormal brain development despite cerebral autoregulation. In HLHS, cerebral perfusion is likely also limited by the increased resistance caused by the hypoplastic aortic isthmus. Since the cerebral circulation is supplied retrogradely, the isthmus may restrict the amount of blood that can be delivered to the brain, despite the protective autoregulatory mechanism of the cerebral vascular bed. This may contribute to the higher incidence of neurodevelopmental abnormalities found in these children. In contrast, fetuses with TGA and TOF were less affected than those with single ventricles. In these defects, there is intracardiac mixing of blood in the presence of two ventricles with no obstruction to antegrade cerebral flow. These hearts may be able to compensate for the cerebral hypoxemia by increasing combined ventricular output. Of note, fetuses with left ventricular outflow tract obstruction were not affected. These fetuses likely have cerebral blood with near normal oxygen content and adequate antegrade aortic flow to support cerebral perfusion.

Ultimately, what is of utmost importance is how much oxygen and substrate actually reach the brain in fetuses with CHD. Chock et al. reported that elevated nucleated red blood cell counts measured after birth (presumably a marker of the erythropoietic response to chronic in utero hypoxia) was a significant risk factor (odds ratio 7, P = .02) for a perioperative acute neurological event [9]. Multiple factors including cardiac output, oxygen content, and hemoglobin content are all critical factors that will impact on the oxygen and substrate delivery to the brain, in addition to the relative resistances of the distal vascular beds. Given the findings of neurological abnormalities after birth and before surgery in these infants (including smaller head circumference, clinical neurological abnormalities, and radiographic abnormalities), it appears that there is inadequate fetal cerebral oxygen delivery to support normal brain development even in the presence of the autoregulatory “brain sparing” response. Further studies are needed to correlate these alterations in fetal circulatory dynamics with postnatal neurodevelopmental outcome and to see if intervening in cases where significant abnormalities are detected may improve outcome for this population.

2.3. Congenital Brain and Developmental Abnormalities.
Structural and functional brain abnormalities have been identified in babies born with CHD in the neonatal period prior to surgical repair. In addition, there have been studies showing that similar abnormalities can be found in fetuses. These brain abnormalities represent a spectrum of disease processes with multiple potential etiologies. Abnormalities indicative of altered development have been noted in addition to abnormalities relating to injury from embolic events
or hypoxia. In addition, genetic abnormalities have been incited in both the cause of structural brain defects as well as leading to fragility of the brain which may increase the potential for injury.

2.3.1. Genetic Abnormalities Associated with CHD. Genetic syndromes that have associated neurological abnormalities are present in many children with CHD [50]. For example, infants with Trisomy 21, DiGeorge, velocardiofacial (VCFS), Turner's, and William's syndromes have common congenital heart abnormalities and varying degrees of associated developmental delay. The incidence of CHD in patients with Trisomy 21 is approximately 40%, with the most common being defects of the endocardial cushion and ventricular septum. All infants with Trisomy 21 have mental retardation, ranging from mild to severe. DiGeorge syndrome and velocardiofacial syndrome, both caused by a microdeletion on chromosome 22 and associated with developmental delay, are also associated with conotruncal defects including interrupted aortic arch and truncus arteriosus. Turner's syndrome (due to absence of an X chromosome) is associated with mildly decreased intelligence quotient (IQ) scores and abnormalities of the aortic valve and coarctation. Finally, in William's syndrome, which is due to a chromosome mutation on 7q11 and associated with cognitive and behavioral abnormalities, common cardiac defects include supravalvar aortic stenosis and peripheral pulmonary branch stenosis. Other genetic factors may also place certain patients at higher risk for CNS injury. There is increasing evidence that Apolipoprotein E (APOE) is important for neuronal repair. APOE e2 allele carriers were found to have significantly lower Bayley PDI at one year of age after cardiac surgery compared to those without the allele, suggesting a genetic susceptibility to brain injury [51].

2.3.2. Clinical Presentation of Preoperative Brain Abnormalities. Abnormalities on neurological exam have been detected preoperatively in neonates with CHD. Chock reported an incidence of an acute neurological event defined as seizure, tone abnormality, or choreoathetosis, to be 17% in patients with CHD prior to surgery [9]. In a study of infants with HLHS by Glaucer, 38% were reported to have an abnormal neurological exam or seizures prior to surgery [10]. A prospective study of babies with CHD by Limperopolous revealed preoperative neurological abnormalities in 50% of newborns and 38% of infants [6]. Abnormalities included hypotonia, hypertonia, jitteriness, motor asymmetry, and absent suck. Sixty-two percent had poor behavioral state instability. In another study by Limperopolous, 19% of newborns and 38% of infants [6] had disturbances in consciousness regulation, 34% feeding difficulties, and 5% seizures. In infants, abnormalities included hypotonia, head preference, lethargy, restlessness and agitation, motor asymmetry, and feeding difficulties. Autistic features were found. Abnormalities were independent of hemodynamic instability. In another study by Limperopolous, 19% of infants had epileptiform activity, and 33% had disturbances in background activity on electroencephalogram (EEG) that were moderate or diffuse [8].

2.3.3. Structural Brain Abnormalities in Newborns with CHD. It is well described that there is a high incidence of brain malformation in babies with CHD in the absence of a defined genetic syndrome [52, 53]. These brain findings may be due to undefined genetic abnormalities or may relate to alterations in the circulation leading to injury or abnormal or delayed brain development. In one autopsy study, multiple congenital brain anomalies were found in a significant proportion of babies with HLHS [53], including marked microcephaly (brain weight > 2 standard deviations below the normal mean) in 27%, abnormal cortical mantle formation in 27%, and overt central nervous system malformations such as agenesis of the corpus callosum or holoprosencephaly in 10%. The absence of dysmorphic features did not preclude the presence of central nervous system malformations, and conversely, the presence of dysmorphic features did not reliably predict the presence of a brain abnormality in this study. These structural abnormalities have been detected in living patients by physical exam and neuroimaging performed

<table>
<thead>
<tr>
<th>Table 1: Doppler indices of cerebral blood flow.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doppler Ultrasound Finding</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Cerebral Pulsatility Index (CPI)</td>
</tr>
<tr>
<td>Cerebral Resistance Index (CRI)</td>
</tr>
<tr>
<td>Cerebral/Umbilical Pulsatility Ratio</td>
</tr>
<tr>
<td>Cerebral/Umbilical Resistance Ratio</td>
</tr>
<tr>
<td>Reversal of diastolic flow in the aortic isthmus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Finding</th>
<th>Definition</th>
<th>Significance</th>
<th>Congenital Heart Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Pulsatility Index (CPI)</td>
<td>(SV-DV)/MV</td>
<td>Lower value associated with higher mortality, growth retardation, and poor neurological outcome</td>
<td>Lower in HLHS and higher in right-sided obstruction lesions compared to normal [44], lower in TGA [46], lower in CHD with intracardiac mixing [47], lower in CHD fetuses with CHF [48]</td>
</tr>
<tr>
<td>Cerebral Resistance Index (CRI)</td>
<td>(SV-DV)/SV</td>
<td>Lower value associated with growth retardation</td>
<td>Lower in CHD infants compared to normal [42]</td>
</tr>
<tr>
<td>Cerebral/Umbilical Pulsatility Ratio</td>
<td>CPI/UPI</td>
<td>Ratio &lt;1 associated with growth retardation and poor perinatal outcome</td>
<td>No difference [44], increased in CHD [48]</td>
</tr>
<tr>
<td>Cerebral/Umbilical Resistance Ratio</td>
<td>CRI/URI</td>
<td>Ratio &lt;1 associated with growth retardation</td>
<td>Lower in CHD infants compared to normal, lowest in HLHS (58% with ratio &lt;1) [42]</td>
</tr>
<tr>
<td>Reversal of diastolic flow in the aortic isthmus</td>
<td>Blood flow away from the descending aorta</td>
<td>Predicts poor neurological outcome</td>
<td>Present in HLHS and severe left ventricular (LV) outflow obstruction with LV failure</td>
</tr>
</tbody>
</table>
prior to surgery. In a study by Limperopoulos, preoperative evaluation of babies with CHD excluding HLHS revealed microcephaly in 36% and macrocephaly in 13% of babies evaluated [7]. Head ultrasound has detected abnormality in patients with CHD including cerebral atrophy [11], echodensities or calcifications in the basal ganglia [11, 12], and widened ventricular or subarachnoid spaces [9, 12, 52, 53].

Brain MRI performed prior to surgery has also demonstrated a high incidence of preoperative brain abnormalities. In a study by Mahle, 24 patients with CHD were studied, and the only brain anomaly believed to be congenital in origin was an open operculum which was present in 17% [14]. In a study by Licht in 25 babies with CHD, 53% with CHD had developmental and/or acquired brain lesions including microcephaly (24%), incomplete closure of the operculum (16%), and PVL (28%) [15]. Miller, using MRS and diffusion tensor imaging (DTI) in neonates with CHD, found abnormalities similar to the preterm population [16]. Utilizing biochemical ratios, a higher ratio of lactate/choline and a lower ratio of N-acetylaspartate/choline were found in CHD patients with TGA or single ventricle physiology compared to controls. N-acetylaspartate is a marker of neuronal integrity found in high concentrations in neurons and is known to increase with maturation. In contrast, lactate decreases with increasing maturity. These results suggest findings of an immature brain in full-term neonates with CHD. In the same cohort it was also noted that average diffusivity was increased in the CHD neonates. Average diffusivity decreases with development; this is thought to be due to decreased water content and increased membrane growth in neuronal and glial cells that accompany brain maturation. In a study by Licht [54], infants with HLHS and TGA were evaluated by MRI with outcome measures being head circumference and total brain maturation score. The brain maturation score is a published scoring system that evaluates four parameters that include myelination, cortical infolding, involution of glial cell migration bands, and the presence of germinal matrix tissue. In this study, the mean head circumference was one standard deviation below normal and the mean total maturation score for the cohort was significantly lower than reported normative data suggesting a delay in maturation of one month for babies with CHD. Limperopoulos evaluated 55 fetuses with CHD using MRI and MRS and compared results to 50 normal fetuses [55]. Fetal intracranial cavity volume, cerebrospinal fluid volume, and total brain volume were calculated using 3-dimensional volumetric MRI, and cerebral N-acetyl aspartate/choline ratios and cerebral lactate levels were determined using MRS. Gestational age at study ranged from 25 to 37 weeks. MRI analysis showed a progressive decline in age-adjusted total brain volume and intracranial cavity volume in fetuses with CHD relative to controls. N-acetyl aspartate/choline ratios increased in CHD fetuses but were slower to rise than what was seen in normal fetuses. On multivariable analysis, the cardiac diagnosis and percentage of combined ventricular output through the aortic valve were independently associated with total brain volume. Predictors of lower acetyl N-acetylaspartate/choline ratios included cardiac diagnosis, absence of antegrade aortic arch flow, and evidence of cerebral lactate. These results suggest that in the third trimester fetuses with some forms of CHD, in particular those with diminished aortic output, have evidence of impaired development and brain metabolism and have total brain volumes that are lower than normal. These findings noted on fetal MRI by Limperopoulos, and on neonatal preoperative MRI by Miller and Licht, suggest that the altered circulation that attends the fetal circulation in specific CHD may delay brain maturation and growth and play a role in the neurodevelopmental impairments of these patients.

2.4. Acquired Preoperative Brain Injury. In addition to the developmental lesions previously mentioned, acquired lesions may be detectable in babies with CHD before surgery representing injury due to hemodynamic compromise with or without hypoxia. There have been several studies that have revealed the presence of hypoxic ischemic injury before surgical intervention. In an autopsy study, Glauser found that 45% of babies with HLHS, half of whom did not undergo surgery, had hypoxic ischemic lesions and/or intracranial hemorrhage [10]. Hypoxic ischemic injury included cerebral necrosis, periventricular leukomalacia (PVL), and brainstem necrosis. Lesions detected by cranial ultrasound studies include intraventricular hemorrhage [9], cerebral atrophy [11], echodensities or calcifications in the basal ganglia [11, 12], widened ventricular or subarachnoid spaces [9, 12, 52, 53], and ischemic changes [10, 12]. Licht found PVL in 28% of CHD patients imaged with MRI preoperatively [15]. In Mahle’s study, 25% of patients had clear evidence of ischemic injury including PVL or infarct on brain MRI done before surgery. Over 50% of patients had elevated lactate on MR spectroscopy, further evidence of brain ischemia [14]. In one of the most recent and largest cohort of 62 patients studied prospectively with MRI, McQuillen described radiographic evidence of brain injury in 39% of patients, most commonly stroke followed by white matter injury [13]. The high incidence of white matter injury, particularly PVL, is notable in this population and atypical of the pattern in term newborns who suffer hypoxia-ischemia from other causes. This finding suggests that some of the acquired brain injuries in babies with CHD may be related to an abnormality of the cerebral vascular bed and/or brain development. It is possible that babies with CHD have white matter cell lines that are particularly susceptible to injury, similar to the vulnerability of these cells in preterm infants, manifesting in different patterns of injury compared to other term infants who suffer hypoxic ischemic injury.

In addition to neuroimaging evidence of preoperative brain injury, various serum biomarkers reflecting systemic and neurological compromise have been examined in patients with CHD. Serum lactate as a marker of global hypoperfusion has been followed and found to be elevated preoperatively in patients with CHD [56]. Proinflammatory cytokine profiles (with elevated IL-6 and decreased IL-10) have been detected in infants with cardiac disease preoperatively [57]. The glial-derived protein S100B has been evaluated in infants and adults with cardiac disease
Figure 2: Cerebral to placental resistance ratio versus gestational age for normal fetuses and fetuses with Congenital Heart Disease (CHD). *P is significant normal versus CHD.

and is believed to be a marker for cerebral ischemia [58–60]. S100B levels have been found to be elevated in infants with CHD before surgery, possibly reflecting preexisting neurological injury [60]. Infants with HLHS had the highest levels before surgery, and the S100B concentration correlated inversely with the size of the ascending aorta. This finding complements the Doppler studies that suggest that the amount of antegrade flow in the aorta in fetuses and infants with HLHS impacts cerebral perfusion and may leave these infants particularly prone to ischemic injury even before surgery.

3. Neurodevelopmental Outcome after Surgical Repair of CHD

There is an increasing body of literature reporting intermediate and long-term outcomes from various cohorts of patients with CHD. Generalizations are problematic since there is heterogeneity amongst these reports in regards to surgical/medical era, patient population, type of cardiac lesion, age at followup, and type of assessment tool used. Given the advances in care including improved medical and surgical techniques and brain protection strategies, the more historical data reported may not reflect the improved outcomes that we hope to see with patients in the current era. Nevertheless, outcome data has provided some general knowledge about these patients postoperatively, both in the short-term and for long term survivors.

3.1. Short-Term Neurological Outcome after Surgery. Postoperative short-term outcomes include a significant incidence of neurological abnormalities. Miller performed postoperative neurological examinations in 91 infants who had undergone heart surgery and found 15% had clinical seizures, 34% had hypotonia, 7% had hypertonia, 5% had asymmetry of tone, and 19% had decreased alertness at hospital discharge [61]. The aforementioned study by Limperopoulos that detected high incidence of preoperative neurological findings also reported that these abnormalities generally persisted or worsened postoperatively, with additional findings of cranial nerve abnormalities and choreoathetosis [6]. Chock reported the incidence of an acute neurological event to be 25% within the first week after surgery and 56% after the first week [9]. In other reports, the incidence of clinical post-operative seizure was 4–11% and was detected by continuous EEG monitoring in up to 20% of patients in the 48 hours following surgery [62–67]. Swallow dysfunction [68] was another significant finding in patients with CHD following surgery, as feeding performance has been shown to be an early indicator of later neurodevelopmental outcome [69].

3.2. Neurodevelopmental Outcomes for Survivors at School Age and Beyond. Reports of long-term followup have limited applicability as technological advances in medical management and surgical repair techniques make outcomes reported from procedures done in previous decades less insightful. For example, of note when interpreting results of the outcomes from the Boston Circulatory Arrest Trial is that during the time period of the study the alpha stat strategy, hemodilution to 20% hematocrit, and currently outmoded hardware for bypass were utilized. Thus, consideration must be made to surgical era when interpreting results from historical cohorts. Despite this, some general themes have arisen from reported long-term outcomes in patients with CHD.

Long-term survivors, although they frequently have limitations, are actually quite functional. Several studies have demonstrated that while patients with CHD have significantly lower mean IQs than age-matched controls, their IQs still fall within the normal range [4, 5, 70–94]. These reports, however, also describe highly prevalent gross and fine motor, attention, and school problems. The prospective cohort originally described by Limperopoulos was followed through school age by Majnemer and found to have high incidence of gross and fine motor abnormalities (49 and 39%, resp.) and abnormal neurological examination (28%) [2]. Highly prevalent behavioral and school problems are reported from the Boston cohort [5, 91]. Overall long-term cognitive outcomes reported from various studies are presented in Table 2. Special attention should be paid to
Table 2: Reported long-term cognitive outcomes for patients with congenital heart disease.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Reference</th>
<th>Number of Patients</th>
<th>Mean age at assessment (range)</th>
<th>Cohort prospectively identified</th>
<th>Surgical era</th>
<th>Full scale IQ (mean ± SD) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD-mixed</td>
<td>Clarkson, 1980 [89]</td>
<td>72</td>
<td>4y (2.4–7y)</td>
<td>No</td>
<td>1969–71</td>
<td>93 ± 16</td>
</tr>
<tr>
<td></td>
<td>Miatton, 2007 [75]</td>
<td>43</td>
<td>8y</td>
<td>No</td>
<td>1995–99</td>
<td>96 ± 15</td>
</tr>
<tr>
<td>TGA</td>
<td>Clarkson, 1980 [89]</td>
<td>22</td>
<td>4y (2.4–7y)</td>
<td>No</td>
<td>1969–71</td>
<td>90 ± 18</td>
</tr>
<tr>
<td></td>
<td>Newberger, 1984 [74]</td>
<td>33</td>
<td>5.8y (5.5–6.3y)</td>
<td>No</td>
<td>1968–72</td>
<td>102 ± 15</td>
</tr>
<tr>
<td></td>
<td>Hesz, 1988 [84]</td>
<td>10</td>
<td>(6.5–14y)</td>
<td>No</td>
<td>1967–84</td>
<td>92 ± 12</td>
</tr>
<tr>
<td></td>
<td>Oates, 1995 [73]</td>
<td>30</td>
<td>(9–10y)</td>
<td>No</td>
<td>1972–82</td>
<td>100 ± 17</td>
</tr>
<tr>
<td></td>
<td>Ellerbeck, 1998 [88]</td>
<td>54</td>
<td>8y</td>
<td>No</td>
<td>1981–90</td>
<td>90 ± 21</td>
</tr>
<tr>
<td></td>
<td>Miatton, 2007 [75]</td>
<td>43</td>
<td>8y</td>
<td>No</td>
<td>1995–99</td>
<td>96 ± 15</td>
</tr>
<tr>
<td></td>
<td>Brosig, 2007 [90]</td>
<td>13</td>
<td>(3.5–6y)</td>
<td>No</td>
<td>1996–99</td>
<td>110 (90–126)</td>
</tr>
<tr>
<td></td>
<td>Clarkson, 1980 [89]</td>
<td>17</td>
<td>4y (2.4–7y)</td>
<td>No</td>
<td>1969–71</td>
<td>88 ± 14</td>
</tr>
<tr>
<td>TOF</td>
<td>Oates, 1995 [73]</td>
<td>51</td>
<td>(9–10y)</td>
<td>No</td>
<td>1972–82</td>
<td>100 ± 17</td>
</tr>
<tr>
<td></td>
<td>Miatton, 2007 [76]</td>
<td>18</td>
<td>8y</td>
<td>No</td>
<td>1994–99</td>
<td>95 ± 14</td>
</tr>
<tr>
<td></td>
<td>Clarkson, 1980 [89]</td>
<td>16</td>
<td>4y (2.4–7y)</td>
<td>No</td>
<td>1969–71</td>
<td>93 ± 15</td>
</tr>
<tr>
<td>TGA/TOF</td>
<td>Wright, 1994 [70]</td>
<td>29</td>
<td>9.5y (7–12y)</td>
<td>No</td>
<td>1979–84</td>
<td>94 ± 15</td>
</tr>
<tr>
<td></td>
<td>Hovels-Gurich, 2006 [83]</td>
<td>20</td>
<td>7y (5–12y)</td>
<td>Yes</td>
<td>1993–99</td>
<td>93 ± 12</td>
</tr>
<tr>
<td>SV</td>
<td>Wernovsky, 2000 [71]</td>
<td>128</td>
<td>11y (3.7–41y)</td>
<td>No</td>
<td>1973–91</td>
<td>96 ± 17</td>
</tr>
<tr>
<td></td>
<td>Uzark, 1998 [72]</td>
<td>32</td>
<td>2.5y (1.5–9.5y)</td>
<td>No</td>
<td>1986–94</td>
<td>98 ± 12</td>
</tr>
<tr>
<td></td>
<td>Goldberg, 2000 [85]</td>
<td>51</td>
<td>5y (2.8–8y)</td>
<td>No</td>
<td>1989–96</td>
<td>101 ± 5</td>
</tr>
<tr>
<td></td>
<td>Forbes, 2002 [87]</td>
<td>34</td>
<td>5 y</td>
<td>No</td>
<td>1993–2000</td>
<td>90 ± 16</td>
</tr>
<tr>
<td></td>
<td>Goldberg, 2000 [85]</td>
<td>26</td>
<td>5y (2.8–8y)</td>
<td>No</td>
<td>1989–96</td>
<td>94 ± 7</td>
</tr>
<tr>
<td></td>
<td>Mahle, 2006 [77]</td>
<td>48</td>
<td>12y (8–17y)</td>
<td>No</td>
<td>1986–94</td>
<td>86 ± 14</td>
</tr>
</tbody>
</table>

outcomes reported for two specific populations: those with single ventricles and TGA. Patients with single ventricles, especially those with HLHS, have higher risk for adverse outcome based on their underlying physiology and hemodynamics as well as complexity of surgical repair. Meanwhile, patients with TGA have been the most extensively and reliably studied.

3.3. Neurodevelopmental Outcomes in Children with Single Ventricles. Children with a single functioning ventricle who undergo a series of palliative surgical procedures culminating in the Fontan operation are at the highest risk of developmental compromise. In addition to the frequent hemodynamic instability accompanying the complex cardiac physiology in these patients, surgical repair often involves multiple operations requiring bypass and circulatory arrest. Children with HLHS are at particular risk for neurodevelopmental abnormalities, in part because the repair involves a period of hypothermic circulatory arrest that in the past has been longer than 30–40 minutes. There have been several reports of neurodevelopmental outcomes in these patients although none involved prospectively identified cohorts. Forbess reported outcomes from the registry of outcome data maintained by the group at Boston Children’s Hospital. He reported that patients with single ventricle lesions had significantly lower full-scale and performance IQ and had lower scores on multiple domains of memory, learning and visual-motor testing, when compared to patients undergoing biventricular repair [87]. Wernovsky evaluated 133 patients who had a Fontan operation between the years 1973–91 [71]. For 128 patients who underwent cognitive testing, the mean full scale IQ of 96 was lower than the population
mean. Mental retardation was found in 8%. Children with HLHS scored lower on all parameters compared to children with other single ventricle lesions. Mahle reported results of outcomes for patients with HLHS who underwent surgery in 1984–1991 [78]. In 28 children, the median full scale IQ was 86, lower than the general population mean. Performance IQ was lower than verbal (83 versus 90). Full scale IQ scores in the mental retardation range were found in 18%. Cerebral palsy with hemiparesis was documented in 17%, microcephaly in 13%, fine motor abnormalities in 48%, gross motor abnormalities in 39%, and speech deficits in 30%. Goldberg reported IQ scores reflecting outcomes for HLHS in the time period between 1989–94 [85]. Children with HLHS fell within the normal range for full scale IQ as measured by the Weschler test but scored lower than children with other single ventricle lesions. For the whole group, IQ was 101, for HLHS 94, and for other single ventricles 107. Brosig reported the most recent outcome data for patients who underwent surgery between 1993–99 [90]. Median IQ was 97 in 13 patients evaluated at 3.5 to 6 years. When compared to patients with TGA, patients with HLHS had more problems with visual-motor skills, expressive language, attention, and externalizing behavior.

3.4. Neurodevelopmental Outcomes in Children with TGA. The majority of neurodevelopmental outcome reports come from cohorts of patients retrospectively identified and recalled for developmental assessments, leading to inherent selection bias. There are few prospective studies which have provided more reliable outcome information. The Boston Circulatory Arrest Trial evaluated differences between two groups of babies with TGA based on bypass strategy and provided insight into the outcomes of babies with TGA in general after surgical repair [5, 91–93]. The overall study population had significantly lower mean IQ than the general population although still within the normal range. Verbal IQ was higher than performance IQ. Although mean scores on most outcomes were also within normal limits, the cohort as a whole was performing below expectations in several domains including academic achievement, gross and fine motor, working memory, attention, and higher-order language skills. There was high prevalence of hearing deficits (12% and 8% in the circulatory arrest and low flow bypass groups, resp., \( P = .43 \)) at four years [91] and abnormalities on neurological exam (circulatory arrest 71% and low flow bypass 64%, \( P = .23 \)) at eight years [5]. At 8 years following repair, 30% of the population were receiving remedial services in school, and 10% had repeated a grade.

In another longitudinal prospective study in Germany, Hovels-Gurich et al. followed 60 patients with TGA through school age and have reported outcomes for their group at a mean of 10 years [4, 82, 94]. While they found that overall IQ scores were not significantly different than population norms (different from the Boston cohort), they reported high rates of gross and fine motor dysfunction (>20%), reduced expressive and receptive language (around 20%), and speech abnormalities (40%).

4. Conclusion

Advances in medicine, including prenatal diagnosis and evaluation, innovations in cardiothoracic surgical techniques, and improvements in perioperative management have contributed to the increased survival of infants with CHD. Greater attention is now being directed toward understanding how in utero hemodynamics affect cerebral development, how the conduct of the operation can best be manipulated to maximize cerebral oxygen delivery and utilization, and how perioperative care, including the incorporation of neuromonitoring, can be optimized. Although as a group IQ appears to be in the normal range for CHD survivors, rates of neurodevelopmental impairment continue to be significant. Neurodevelopmental evaluation in patients with CHD should be standard practice to not only identify those with impairments who would benefit from intervention services but also to continue to identify risk factors and strategies to optimize both short- and long-term outcomes in these high-risk children. In the future, fetal management and intervention strategies for specific defects may ultimately play a role to improve in utero hemodynamics and increase cerebral oxygen delivery to enhance brain growth and improve early neurodevelopment.

References


[40] J.-C. Fouron, J. Gosselin, C. Amiel-Tison et al., “Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcome between the ages of 2 and 4


