Diploma Thesis

Fetal Arrhythmias
Diagnosis, Treatment and Outcome

submitted by
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0215423

in partial fulfilment of the requirements
for the degree of

Doctor of Medicine

at the
Medical University of Graz
Departement of Obstetrics and Gynecology

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December 2009

Affidavit

Hereby I, Brigitta Gombocz, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties.
Furthermore, I confirm that no sources have been used in the preparation of the thesis other than those indicated in the thesis itself.

Graz, December 2009 Signature: _____

Bonum certamen certavi, cursum consummavi, fidem servavi

Paulus, Zweiter Brief an Timotheus 4,7

Aknowledgements

First and foremost I would like to thank my loving husband, who has supported me in every imaginable situation and to whom I owe my beautiful daughter and my unborn son, the true joys of my life.

Furthermore I would like to thank my father who has taught me to be strong and persevering. I am deeply grateful for the love and encouragement received every step of the way.

I would also like to bestow my gratitude upon Prof. Dr. Martin Häusler, who provided me with some of the ultrasound images featured in the thesis and never minded my looking over his shoulder.

Last but definitely not least I would like to thank Prof. Dr. Wolfgang Schöll, my thesis advisor. He is has been a true mentor to me and taught me all I know about obstetrics and gynecology, never tiring of my endless questions. He was always patient and understanding and had an open ear for all my concerns.

Abstract

Fetal arrhythmias are a rare but serious condition occurring in an estimated 1-2% of pregnancies. In about 10% of those cases, morbidity or even mortality occurs. Depending on the type of arrhythmia, hydrops fetalis, neurological sequelae and fetal demise are to be anticipated.

There are three broad categories of arrhythmias; irregular fetal heart rhythm, tachycardias and bradycardias. Irregular fetal heart rhythm is mostly caused by premature atrial contractions, which are benign and require no further intervention other than monitoring. The most frequently observed forms of arrhythmia are supraventricular tachycardia, atrial flutter and complete heart block.

Sustained tachy- or bradycardias can become life threatening to the fetus, and the following forms of treatment should therefore be considered: observation, delivery or prenatal treatment.

In most cases, prenatal drug treatment is the recommended therapeutic approach, since it is associated with a better outcome in most instances. Prenatal drug treatment can be administered transplacentally (i.e. feto-maternal treatment) or directly (i.e. direct fetal treatment). Transplacental treatment is preferred, since conversion to sinus rhythm can be achieved in 80-100% of cases using different therapeutics. In drug refractory cases, direct fetal therapy should be considered.

A variety of drugs have been used over the past two decades, several of which were subsequently abandoned. Most centres now administer digoxin, sotalol, flecainide and amiodarone in varying dosage regimens.

Mortality can range from 8-50% depending on the underlying arrhythmia and the presence or absence of hydrops fetalis. Postnatal treatment is necessary in up to 80% of fetuses who displayed SVT. AF often resolves at birth, and recurrence is rare. Two thirds of the live-borns affected by CHB in utero will require pace-maker implantation by adolescence.

Zusammenfassung

Fetale Arrhythmien sind ein seltenes aber ernstzunehmendes Ereignis, das in ca 1-2% aller Schwangerschaften vorkommt. In 10% dieser Fälle kommt es zum Auftreten von Hydrops fetalis, bleibenden neurologischen Schäden oder dem Tod.

Arrhythmien kann man grob in drei Kategorien unterteilen: unregelmäßiger fetaler Herzschlag, Tachykardien und Bradykardien. Unregelmäßiger fetaler Herzschlag ist meist durch supraventrikuläre Extrasystolen bedingt und bedarf außer der Überwachung meist keiner Therapie. Die häufigsten Formen der Arrhythmien sind die supraventrikuläre Tachykardie, das Vorhofflattern und der komplette AV-Block.

Ist die Tachykardie anhaltend, kann sie für den Feten lebensbedrohlich werden und folgende Therapiemöglichkeiten sollten in Erwägung gezogen werden: Observanz, Entbindung oder pränatale Therapie.

Die pränatale Therapie kann entweder über die Mutter erfolgen, transplazentar, oder dem Feten direkt verabreicht werden. Durch den Einsatz verschiedener Medica kann bei der transplazentaren Therapie in 80-100% eine Konversion zum Sinusrhythmus erzielt werden, daher ist sie zu favorisieren. In den therapierefraktären Fällen ist die direkte fetale Therapie durchaus indiziert.

Viele Antiarrhythmika kamen in den vergangenen beiden Jahrzehnten zum Einsatz und nur einige wenige davon haben sich behaupten können. In den meisten Zentren kommen Digitalis, Flecainide, Sotalol und Amiodaron zum Einsatz.

Die Mortalität beträgt 8-50% und hängt primär von der zugrunde liegenden Arrhythmie und dem Vorhandensein von Hydrops fetalis ab. Eine Postpartale Therapie ist in 80% der Fälle von supraventrikulären Tachykardien notwendig. Vorhofflattern sistiert oft mit der Geburt, ein Wiederauftreten ist selten. Zwei Drittel aller Lebendgeborenen mit komplettem AV-Block benötigen bis zur Adoleszenz eine Schrittmacherimplantation.

Table of Contents

Figures and Tables

Abbreviations

aAo	Ascending aorta
ABC	ATP-binding casette
ADH	Antidiuretic hormone
AET	Atrial ectopic tachycardia
AF	Atrial Flutter
Af	Atrial fibrillation
ANP	Atrial natriuretic peptide
ART	Antidromic reciprocating tachycardia
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentry tachycardia
AVSD	Atrioventricular septal defects
bpm	Beats per minute
CAST	Cardiac arrhyhtmia suppression trial
CAVB	Complete atrioventricular block
CCO	Combined cardiac output
CHB	Complete heart block
COPD	Chronic obstructive pulmonary disease
CVO	Combined ventricular output
DEA	Desethylamiodarone
ECG	Electrocardiogramm
EDLS	Endogenous digoxin like substances
FHR	Fetal heart rate
FMCG	Fetal magnetocardiography
FMH	Feto-maternal hemorrhage
HFR	Heart forming region
IgG	Immunoglobulin G
IUD	Intrauterine death
IVIG	Intravenous immunoglobulin
LQTS	Long QT Syndrome
MDR1	Multi drug resistance protein 1
NND	Neonatal death
ORT	Orthodromic reciprocating tachycardia
Pgp	P-glycoprotein
PJRT	Permanent junctional reciprocating tachycardia
PW	Pulsed wave
SNP	Single nucleotide polymorphism
SVC	Superior vena cava
SVT	Supraventricular tachycardia
TDI	Tissue doppler imaging
TSH	Thyroid stimulating Hormone
VA	Ventriculoatrial
VSD	Ventricular septal defects
VT	Ventricular tachycardia
WPW	Wolf Parkinson White

Introduction

Fetal heart failure is a serious condition with a high morbidity and mortality. If left untreated, it may lead to hydrops fetalis, the accumulation of fluid in fetal tissues and body cavities.

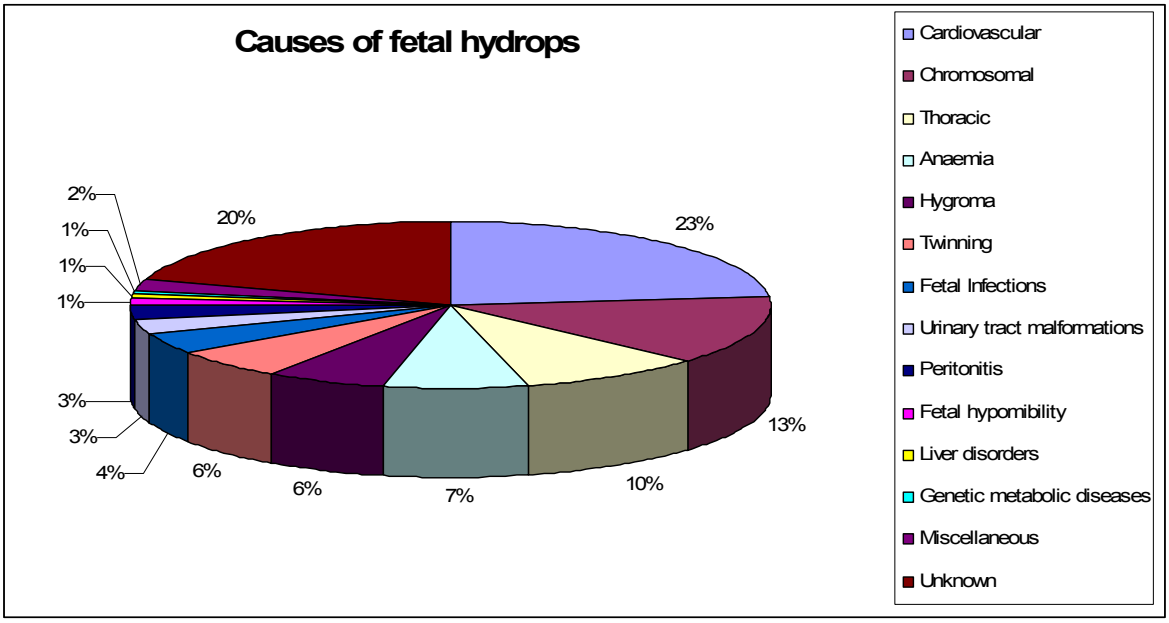


Figure 1: Causes of fetal hydrops

A large number of maternal, placental and fetal disorders can cause Hydrops, but in about 20% of the cases the etiology remains unknown.

In 1,585 reported cases of fetal hydrops cardiovascular disorders were responsible for 23.3%. Within this group, approximately 40% of the cases were caused by cardiac malformations, 32% by arrhythmias, 15% by high cardiac output due to tumors, and 13% by other causes. [1, 2]

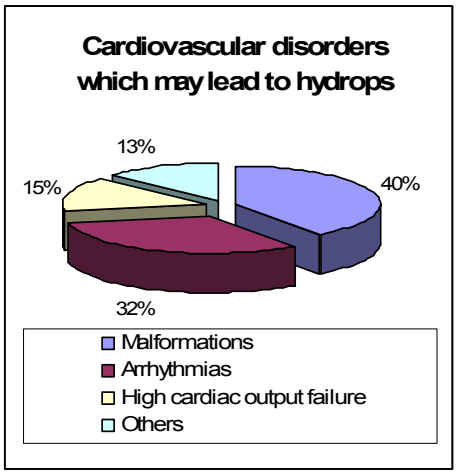


Figure 2: Cardiovascular disorders

Structural heart disease has been widely discussed, and the possibilities for prenatal intervention currently remain limited. Therefore, this thesis will focus on fetal arrhythmias, including diagnosis and current treatment options.

Fetal arrhythmias are a rare but serious condition occurring in an estimated 1-2% of pregnancies. About 10% of those cases result in morbidity or even mortality [3] Depending on the type of arrhythmia, hydrops fetalis, neurological sequelae and fetal demise are to be anticipated.

Although there are numerous studies dealing with fetal arrhythmias and their treatment, [4-9] the treatment strategies differ greatly. Thus the aim of this thesis is to provide a comprehensive summary of fetal arrhythmias, treatment options and subsequent outcomes.

Thesis objectives:

Introduction to the fetal cardiovascular system

Morphological and functional differences in fetal circulation affect the development and presentation of heart failure. This chapter will explain the differences between fetal and adult circulation and cardiac function.

Pathophysiology of heart failure in the fetus

Fetal arrhythmias may hemodynamically compromise the fetus through ventricular dysfunction and dilatation, secondary atrioventricular valve regurgitation and development of hydrops fetalis. This chapter will cover the pathophysiology behind fetal congestive heart failure.

Hydrops – immune and non-immune

The pathological accumulation of fluid in fetal tissues or body cavities is defined as hydrops fetalis if fluid accumulation is present in two or more compartments. Hydrops can be divided into immune and non-immune hydrops. This chapter will focus on the differences, incidence and causes of non-immune hydrops, excluding fetal arrhythmias. [1, 2]

Classification of arrhythmias and discussion of the underlying electrophysiology

In the past three decades, as diagnostic methods have evolved significantly, there has been an increased awareness of the need to detect and manage fetal arrhythmias. Although the majority of fetal arrhythmias detected during fetal heart monitoring or routine obstetric ultrasound are benign, some can lead to heart failure, hydrops fetalis and fetal demise. [3, 5] Fast, accurate diagnosis of the underlying electophysiological principle allows for targeted treatment. The aim of this chapter is to give a brief overview of the different kinds of arrhythmias and the underlying electrophysiology.

Treatment options

Once a diagnosis has been established, it is important to assess the need for treatment and to be aware of the different therapeutic options. This chapter will focus on different treatment options and when they should be implemented.

Review of the literature on pharmacological intervention in fetal arrhythmias

In the treatment of fetal arrhythmias, doctors have tried several different drugs, many of which were subsequently abandoned due to adverse effects or lack of effectiveness. [4-7] This chapter will describe the four antiarrhythmic agents currently employed by most centres and offer a detailed discussion of pharmacodynamics, pharmacokinetics, placental transfer, adverse effects, dosage regimens and clinical experience.

Long-term follow up of children who were diagnosed with an arrhythmia in the fetal period

This chapter focuses on the long-term outcome of children who were diagnosed with an arrhythmia in utero. Postnatal recurrence and the need for antiarrhythmic treatment will be discussed for each type of arrhythmia separately. The success rate of fetal treatment is usually measured by survival and rhythm control. Few studies deal with long-term neurodevelopmental outcome, although arrhythmias can lead to disturbances in the cerebrovascular autoregulation, especially in the hemodynamically challenged fetus. [10]

Material and methods

The aim of this thesis is to provide a current, systematic and thorough review of fetal arrhythmias, including diagnosis, treatment and outcome. The method chosen to accomplish this task is a systematic review of the literature that has been published to date concerning this area of research.

Appropriate literature was drawn from books and journals available at the Library of the Medical University of Graz, as well as from appropriate online databases, such as PubMed and Ovid. Full-text articles were only analyzed if they were either in German or English, while abstracts of relevant articles in other languages were included when available.

The list of search terms included, but was not limited to, the following words and combinations thereof:

- **fetus**
- **fetal**
- **arrhythmia**
- **dysrhythmia**
- **rhythm disturbance**
- **rhythm anomaly**
- **cardiac**
- **tachycardia**
- **supraventricular tachycardia**
- **reentry**
- **atrial ectopic tachycardia**
- **permanent form junctional**
- **orthodromic**
- **antidromic**
- **atrial flutter**
- **atrial fibrillation**
- **ventricular tachycardia**
- **long QT syndrome**
- **bradycardia**
- **atrioventricular block**
- **PR prolongation**
- **Mobitz**
- **Wenckebach**
- **first degree**
- **second degree**
- **third degree**
- **complete heart block**
- **conductive system**
- **heart failure**
- **congestive**

- high cardiac output failure
- hydrops fetalis
- hydropic
- morbidity
- mortality
- prenatal drug treatment
- transplacental
- materno fetal drug treatment
- Digoxin
- Cardiac glycosides
- β-methyl digoxin
- digitalis
- sotalol
- β-blockers
- flecianide
- amiodarone
- class III antiarrhythmics
- proarrhythmia
- pharmacokinetics
- dose
- placental transfer
- feto maternal ratio
- adverse effects
- outcome
- long term follow-up
- neurodevelopmental
- recurrence
- neurologic impairment
- periventricular
- echogenicity
- leucomalacia
- hemorrhage
- hemiplegia

Articles were selected if they included prenatal diagnosis of the mechanism of arrhythmia, form of treatment and outcome. Since the number of sources concerning certain types of arrhythmia are very limited (e.g. fetal VT), and since many studies are limited to a small number of cases, single-case reports were also included, in order to evaluate as many cases as possible and to report rare events, such as certain adverse effects.

A total of 227 full-text articles, book chapters and abstracts from 1931 to November 2009 were evaluated in the compilation of this thesis.

The fetal heart and circulatory system

Fetal heart development

The human heart originates from the mesoderm, which is one of the three germ cell layers that form in the early embryonic stages. The cardiac precursor cells constitute heart-forming regions (HFRs) on either side of the embryonic midline. These cells coalesce to form first the cardiac crescent and then the primary heart tube. The tube comprises the primordial heart chambers. At this point (21 to 22 days after conception), it begins to beat. Rapid growth forces the tube to bend upon itself, which results in the bulboventricular loop. Septa develop, thereby forming the left and right atria, the left and right ventricles and the two great vessels. By the end of the eighth week of gestation, partitioning is complete and the fetal heart is formed.

Initially, the fetal heart beat at a rhythm of 75-80 beats per minute (bpm). It then accelerates linearly to peak at 180 bpm in the 9th week, followed by a decrease to 150 bpm by week 15. From the 15th to the 20th week the average resting level is 140 bpm. Thereafter, beat-to-beat variability develops, and the average heart rate decreases to 120 bpm at term. [11]

Fetal circulation

Morphological and functional differences in the fetal circulation affect the development and presentation of heart failure. The fetus receives oxygen and nutrients from the maternal blood, which also carries away carbon dioxide and other waste products. The umbilical vein carries highly oxygenated blood to the fetal liver, but a portion of this blood bypasses the liver through the ductus venosus and enters the inferior vena cava, where it mingles with deoxygenated blood. Upon reaching the right atrium, a significant proportion of the blood is shunted directly into the left atrium through the foramen ovale. From here it passes

through the left ventricle and the aorta and supplies the myocardium and brain with oxygenated blood. The other portion of blood that reaches the right atrium, mainly from the superior vena cava, passes through the tricuspid valve and then on to the ductus arteriosus and lungs. Since the lungs are non functional and their vessels have a high resistance to flow, a minor portion flows through the pulmonary circuit. The larger amount is shunted into the descending aorta through the ductus arteriosus. From here, it passes into the lower regions of the body and on to the umbilical arteries, which carry the blood back to the placenta for reoxygenation.

The fetus has a clear right-heart dominance. A study showed that 59% of the combined cardiac output (CCO) was right cardiac output and 41% left cardiac output. This study also found that 33% of CCO is shunted through the foramen ovale, 46% through the ductus arteriosus, and a mere 11% is pulmonary flow. [12]

Thus, the fetal heart feeds two parallel circulations, rather than one sequential cycle. The left ventricle pumps more highly oxygenated blood to the upper body and cerebral circulation, while the right ventricle pumps more deoxygenated blood to the pulmonary circuit and the lower body via the ductus arteriosus.

Post-partum changes in the circulatory system

With the infant's first breath, oxygen reaches the alveolar tissue of the lungs. This triggers vasodilation in the pulmonary vessels, which reduces resistance and increases blood flow through the pulmonary circuit. Left atrial pressure increases with the increase of flow in the pulmonary veins. Once it exceeds right atrial pressure, the septum primum and septum secundum close the foramen ovale, which is then termed the fossa ovalis.

The ductus arteriosus closes within the first few days of life. It is replaced by connective tissue, which is known as ligamentum arteriosum. The umbilical vein and umbilical arteries degenerate and become the round ligament and the medial

umbilical ligaments, respectively. The ductus venosus is also converted into connective tissue, which is called the ligamentum venosum.

Structural and functional differences in the fetal heart

Due to the parallel arrangement, ventricular outputs can differ. If the output of one ventricle decreases due to an increase of the afterload, then the contralateral ventricle compensates by increasing its output. This compensatory mechanism can even reach the extent of having one ventricle supply the whole circulatory system alone. This leads to a frequently observed feature of congenital heart failure – the disproportionate growth of the unaffected side of the heart.

The fetal heart is structurally different from the adult heart. Comparisons in animal studies have shown that the fetal myocardium develops less active tension at similar muscle lengths. It has less T-tubular system, the myofibrils haven't reached the same levels of organization, and there are differences in the calcium uptake of the sarcoplasmatic reticulum. These differences have been used to explain the fetal myocyte's reduced ability to contract.

While the adult heart responds to an increased workload by increasing the size of myocytes (hypertrophy), the fetal heart responds by increasing the number of myocytes (hyperplasia). If the heart rate remains within a range of 50-200 beats per minute, the fetus can adapt combined ventricular output (CVO) to insure adequate tissue perfusion. Outside of this range, heart failure is known to develop. [13]

Heart failure in the fetus implies the heart's inability to sufficiently supply tissue perfusion with oxygenated blood. The fetus responds to this situation with excessive secretion of circulating catecholamines. Hormonal reflexes controlling the salt and water retention are triggered in an effort to increase cardiac preload and adrenocorticoid secretion. Ventricular end-diastolic pressure, atrial pressure and central venous pressure increase, and hydrops fetalis (i.e. end-stage fetal heart failure) develops.

Hydrops fetalis

History and Epidemiology

Hydrops fetalis was first described by Ballantyne in 1892 and is characterized by fluid accumulation in the fetal tissue. Fluids can accumulate in the abdominal cavity, ascites, pleural and pericardial spaces, effusions, and very prominently in the skin (edema). [14]

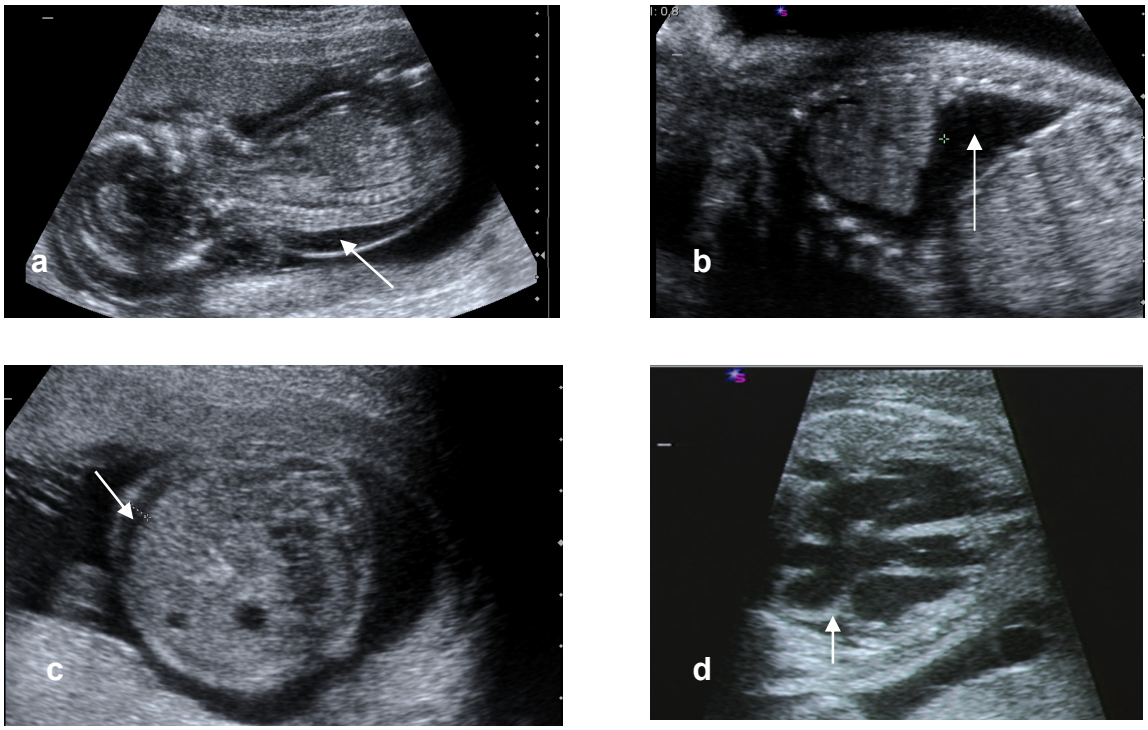


Fig. 3: Images show prominent skind edema (a), hydrothorax (b), ascites (c) and pericardial effusion (d). [154]

There are two forms of hydrops fetalis – immunologic or nonimmunologic. As early as 1943, Potter described fetal hydrops related to the incompatibility of fetal and maternal blood groups. Today, it is estimated that 75-90% of the cases of hydrops fetalis are of nonimmunologic origin. [14, 15] Fetal hydrops is a symptom of many fetal diseases. It has over 80 different known causes and affects 1 in every 3,000

pregnancies. [14] The causes can be divided into 6 main groups: cardiovascular, genetic abnormalities, intrathoracic malformations, hematological disorders, infectious conditions, and idiopathic forms. Although many underlying causes of fetal hydrops can be treated in utero, mortality can still be as high as 70%. [16]

The incidence of hydrops is hard to determine because many cases are not diagnosed until they present with fetal demise. Spontaneous intrauterine resolution has also been observed, making it impossible to give exact numbers. Incidence also varies greatly in different geographical regions. In southeast Asia, for example, hydrops is far more common, due to homozygous alpha-thalassemia or Bart's hydrops, which is rarely encountered in the western hemisphere. [1]

Pathophysiology

Since this thesis focuses on fetal arrhythmia, hydops fetalis will be used synonymously with end-stage heart failure.

Hydrops develops due to disequilibrium in the fetal fluid balance. The extracellular water content decreases with gestational age, while the tissue pressure increases. Fluid shifts from the intravascular to the extravascular compartment are determined by hydrostatic and oncotic pressure, as well as the fluid filtration coefficient. The fluid filtration coefficient is determined by the permeability of the capillary wall to water, which is higher in the fetus. Oncotic pressure within the capillary is largely determined by Albumin and increases with gestational age. All these factors contribute to fluid filtration out of the capillary bed and into the surrounding tissues. Thus lymphatic drainage is more important in the fetus. As the central venous pressure rises, lymphatic flow is increasingly hampered, which contributes further to the development of hydrops.

A decrease in systolic blood pressure and an increase in atrial and ventricular filling pressures trigger production of atrial natriuretic peptide (ANP) angiotensin II and antidiuretic hormone (ADH) also known as arginine vasopressin. These substances lead to increased capillary permeability and fluid retention. [13]

The development of high-resolution, transvaginal ultrasound imaging has aided the intrauterine diagnosis of hydrops fetalis based on sonographic findings, and the mean gestational age at diagnosis has fallen from 31-33 weeks to 24-29 weeks. However, classification of the underlying etiology still poses a great challenge. [17]

Immune fetal hydrops, or red blood cell alloimmunization

Alloimmunization involves the formation of maternal antibodies against fetal antigens. This results in the destruction of fetal erythrocytes and severe anemia. The antigen most commonly targeted is the Rhesus or Rh/D antigen.

The maternal blood type is described as ABO+/ABO- depending on the presence or absence of the Rh/D antigen. Alloimmunizaiton poses a risk if the mother is Rh- and the fetus Rh+. The maternal immune system will inevitablybe exposed to the antigen. Small amounts of fetal blood pass into maternal circulation in every normal pregnancy, and these amounts can be greater in the event of feto-maternal hemorrhage (FMH). Antigen exposure can also take place outside the context of pregnancy in the form of needle sharing or mismatched blood transfusions.

If exposure has taken place and the maternal immune system is functional, it will produce Immunoglubuline G (IgG) antibodies, which readily cross the placental barrier. Fetal red blood cells will be sequestered and haemolysed after being laden with maternal antibodies.

The incidence of alloimmunization dropped dramatically with the development of Rh/D Immunoglobulin in the 1960s. Prophylactic administration to all Rh- women at 28 weeks of gestation and post partum has dramatically reduced the incidence rate. Immunoglobulin should also be administered in cases of abortion (spontaneous or elective), ectopic pregnancy, diagnostic intervention (amniocentesis, chorionic villous sampling, fetal blood sampling), molar pregnancy, second- or third-trimester bleeding, intrauterine fetal demise, external version or abdominal trauma during gestation. [18]

Nonimmune fetal hydrops

Janiaux reports that hydrops fetalis diagnosed in early stages of pregnancy is more often related to chromosomal abnormality than hydrops diagnosed in the second half of gestation. An increase of nuchal translucency thickness is most likely the first sign of fetal hydrops. Skin edema is most clearly observed at the back of the fetal neck, where the thickness can reach up to 15-20mm. [17] Abnormalities of the fetal neck can be diagnosed from nine weeks of gestation. [17, 19]

Before 20 weeks of gestation, the most commonly associated feature with skin edema is placental edema. [20] Ascites is also commonly found in early hydrops, but pleural effusions are rarely observed before 15 weeks of gestation. [17] Isolated pleural effusions have been associated with Down Syndrome (Trisomy 21) and Ullrich-Turner-Syndrome (Monosomy X). [21]

Chromosomal anomalies, especially trisomy 21, monosomy X, trisomy 18 and trisomy 13, are known to cause cardiac malformations, the most common of which are atrioventricular septal defects (AVSD), ventricular septal defects and narrowing of either the isthmus or the truncus arteriosus. It is presumed that narrowing of the aortic isthmus causes congestive heart failure in all four conditions, leading to increased nuchal translucency thickness. [22] Fetuses with trisomy 21 that lack structural cardiac defects may present with hydrops due to transient myeloproliferative disorders. [23]

Hydrops that presents in the second or third trimester should lead to a maternal TORCH screen, which includes testing for antibodies directed against toxoplasma gondii, rubella, cytomegalovirus and herpes. Association of hydrops with infection increases from 1.4% in early pregnancy to 9.5% in late pregnancy. Other infections are also known to cause hydrops, especially parvovirus B19, treponema pallidum and trypanosoma cruzi. [24]

Inborn errors of metabolism and genetic syndromes are also associated with hydrops, since most affected fetuses suffer from cardiac defects, disorders of lymphatic drainage, impairment of red blood cell function or decreased venous return to the heart. Inheritance for most of these conditions is autosomal recessive. Although the prognosis is poor, accurate diagnosis is especially important in these cases, in order to enable parental counselling regarding the ongoing and potential future pregnancies.

The development of modern ultrasonsography has facilitated the diagnosis of hydrops. The real difficulty is the underlying etiology. Therapy should seek to treat the underlying cause of hydrops. Although outcome varies greatly, it is generally poor in hydropic fetuses. [1]

Diagnosis of fetal arrhythmias

In the past two decades, considerable progress has been made in ultrasound technology, which has enabled prenatal diagnosis of congenital heart disease. Historically, the examination of the fetal heart and circulatory system developed separately. Obstetricians employed Doppler to evaluate uteroplacental circulation, while cardiologists focused on the developing heart using M-mode and Doppler. [25]

Since fetal echocardiography has been well described, this chapter focuses solely on techniques and methods relevant to the diagnosis or differentiation of fetal arrhythmias.

When evaluating the fetal heart for rhythm anomalies, a complete echocardiography should be conducted to rule out structural heart disease. This includes:

- **Two dimensional real time evaluation of the heart (B-mode)**
- **M-mode assessment**
- **Doppler echocardiography**

Two-dimensional, real-time evaluation of the heart

Standardized planes should be referred to and should include:

- The four-chamber view
- The short-axis view
- The long-axis view
- The left and right chambers view
- The great-vessels view

Evaluation of these planes serves to rule out structural cardiac defects, which would greatly alter prognosis and outcome. Rhythm and AV-association can also be roughly assessed using this mode. [26, 27]

M-mode

Since fetal ECG is not easily derived, M-mode is used to distinguish the electrical events from the mechanical ones that cause them. Instead of a two-dimensional view of the heart, a recording of the variations along a single line is displayed. The M-mode curser line should be placed such that it intercepts both the atrial and ventricular walls. This allows appraisal of the atrial and ventricular rates, as well as the relationship between atrial and ventricular contractions.

M-mode has also been utilized to measure ventriculo-atrial (VA) and atrioventricular intervals, analogous to the RP and PR intervals of the extrauterine ECG, at peak atrial and ventricular wall motion. A long VA tachycardia is defined by a VA/AV ratio above 1. Long VA intervals have been associated with the permanent form of junctional reciprocating tachycardia and atrial ectopic tachycardia, which are usually incessant and unresponsive to most antiarrhythmic agents. [28]

Doppler echocardiography

Pulsed wave (PW) Doppler is used to analyse resistance and flow in a vessel using the Doppler effect. Recently, a simultaneous record of Doppler waveforms at the superior vena cava (SVC) and the ascending aorta (aAo) was identified as a useful method for assessing fetal cardiac arrhythmias. [9, 29] The beginning of reverse flow at the SVC (created by atrial contraction) and the beginning of forward flow at the aAo (created by ventricular contraction) are interpreted as the beginnings of the P and QRS waves of the extrauterine ECG. This method has

been shown to be more accurate in determining AV and VA intervals than measurements obtained from M-mode.

Simultaneous record of left ventricular inflow and outflow waveforms is another method to measure AV and VA intervals. AV contraction relation cannot be assessed after the onset of the tachycardia because E wave and A wave (first and second peak of the inflow pattern) cannot be distinguished in this condition. [11]

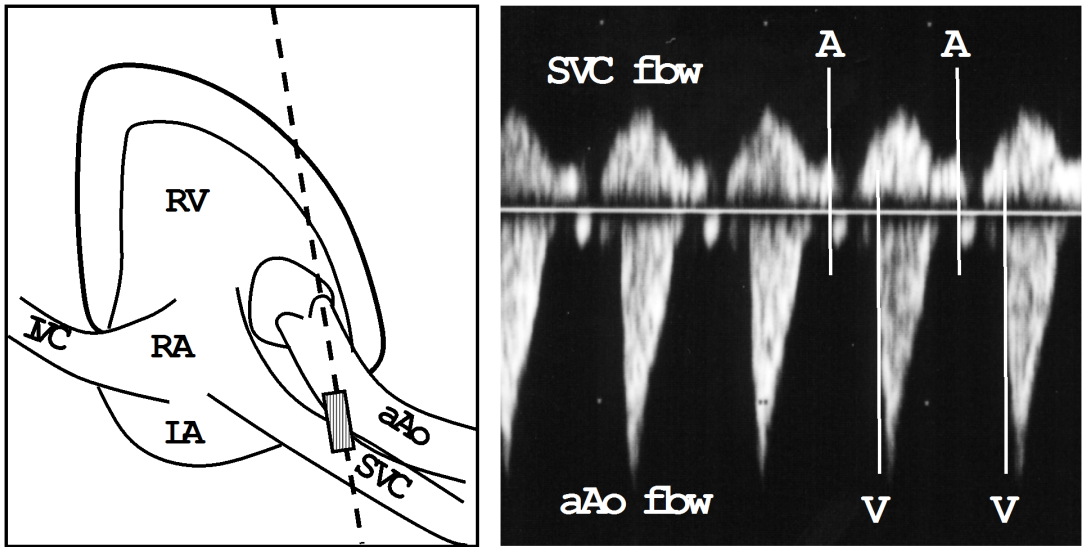


Fig. 4: Simultaneous Doppler trace of the ascending Aorta (aAo) and the superior vena cava (SVC). Beginning of reverse flow at SVC (A) and forward flow at the aAo (V) represent atrial and ventricular contraction respectively. [153]

Recent developments and outlook

Recent developments have made new diagnostic methods available that may help to accurately diagnose the underlying mechanism of arrhythmia.

Tissue Doppler imaging

Tissue Doppler imaging (TDI) is a new technique providing velocities of normal and pathologic myocardial structures during the cardiac cycle. Assessment of myocardial wall velocities with respect to timing and amplitude has been suggested as a method for quantifying global systolic and diastolic dysfunction. [30]

A recent study successfully diagnosed 27 fetuses using TDI. Simultaneous TDI curves of segmental motion were obtained by sampling the posterosuperior wall of the right and left atria and the right and left free wall insertions at the level of the atrioventricular annulus. Dysrhythmias were correctly diagnosed during the fetal period in 87% using M-mode, in 84% using PW Doppler and 100% using TDI. This was attributed to the fact that TDI is less dependent on cursor alignment and makes it possible to easily analyse the activity in any region of the heart and to obtain multiple tissue velocity curves within the same unique temporal domain. [31]

A previous study has also shown that TDI is a promising diagnostic tool when faced with fetal arrhythmias. [32]

Fetal Magnetocardiography

Fetal magnetocardiography (FMCG) permits non-invasive registration of fetal electromagnetic heart activity and documentation of the entire P-QRS-T waveform patterns from the second trimester onwards.

FMCG is recorded using a biomagnetometer inside a magnetically shielded room. In order to place the sensors as close to the fetal heart as possible, the exact fetal position should be ascertained using ultrasound prior to the examination. Simultaneous registration of a maternal single lead ECG allows the consecutive distinction between maternal and fetal P-QRS-T –waveforms. [33]

A number of studies have reported the use of FMCG and its value for the prenatal diagnosis and subsequent management of fetal arrhythmias. The major drawbacks of FMCG are that it is only available in very few locations, and the results can be affected by fetal presentation and movement. [33-37]

In conclusion, ongoing development in diagnostics (i.e. TDI, FMCG) will hopefully lead to further reductions in morbidity and mortality in the field of fetal arrhythmias.

Fetal arrhythmias

Fetal arrhythmias are a rare but serious condition occurring in an estimated 1-2% of pregnancies. In about 10% of those cases, morbidity or even mortality occurs. [3] Depending on the type of arrhythmia, hydrops fetalis, neurological sequelae and fetal demise can be expected. Although examination methods, especially fetal echocardiography, have greatly evolved in the past twenty years, morbidity and mortality are still high. Persistent fetal arrhythmias are associated with structural cardiac defects in about 15% of cases. [31]

The anxiety caused by the fetal cardiac rhythm irregularities, for both prospective parents and treating obstetricians, who often do not possess adequate experience and information in this field, is out of proportion to their clinical implication. The main concern is that sustained arrhythmia may lead to congestive heart failure, which can cause fetal hydrops and subsequently intrauterine death if treatment is not administered. The risk of intrauterine death, which varies greatly and depends on the underlying form of arrhythmia, is estimated to lie anywhere from 9% [38] to 50%. [39]

It has been postulated that fetuses displaying intermittent forms of tachycardia are at a lower risk for progression to sustained tachycardia and development of heart failure, [40] although there have been case reports where even intermittent forms have lead to hydrops fetalis within 10 days of initial diagnosis. [41]

Recently, the atrial contraction sequence has been identified as a parameter that might be of predictive value relating to possible fetal deterioration. If the left atrial contraction precedes the right atrial contraction by a fraction of a second, left atrial pressure will surpass right atrial pressure, resulting in a transient closure of the septum primum, the valve that ultimately closes the foramen ovale postnatally. Venous return is trapped in the right atrium and inferior vena cava, which leads to

a disproportionate increase in mean central venous pressure, thereby contributing to the development of hydrops. [42]

Predictors of hydrops fetalis have been controversially discussed in a number of studies. One study associated heart rates greater than 230 bpm with an increased incidence, [43] only to be contradicted by the next study, which suggested that neither the duration nor the heart rate were predictive of the clinical status at birth. [44] This was partially confirmed by Maxwell et al and Naheed et al. Their research found no correlation between heart rate and mechanism of tachycardia and hydrops, although they did find a positive correlation of hydrops to sustained forms of Tachycardias. [45, 46]

Many forms of arrhythmias, especially tachyarrhythmias, respond well to prenatal treatment with antiarrhythmic drugs, which greatly improves the prognosis. In a retrospective analysis of 127 cases of fetal tachycardia, the mortality rate of hydropic fetuses in whom the arrhythmia was controlled was 9.7%, compared to 56% in those in whom the arrhythmia was not controlled. [38] Therefore, it is of great importance to identify the underlying mechanism of the rhythm disturbance to allow initiation of adequate therapy.

There are three broad categories of arrhythmias:

- **Irregular fetal heart rhythms:** irregularities caused by premature atrial contractions. The average fetal heart rate is normal or near normal in most cases.

- **Tachycardias:** rhythms exceeding physiologic variation, more than 180 beats per minute (bpm), can be sustained or intermittent.

- **Bradycardias:** rhythms with less than 100 bpm.

Irregular fetal heart rate

Pemature atrial contractions lead to irregularity in the fetal heart rhythm by changing beat-to-beat variability. Average heart rate is usually normal or near normal. Premature atrial contractions may be followed by ventricular contraction resulting in an extrasystole. They may also be blocked in the atrioventricular node (AV node) if they occur early in diastole and the AV node is still in the refractory period, which leads to “skipped beats” and the perceived irregularities.

Bradycardia in the form of heart block may also result from premature atrial contractions if numerous contractions are blocked. This leads to a low ventricular rate, usually 70-100 bpm. [12]

Most cases of atrial ectopic beats resolve spontaneously; they are not a sign of fetal distress and treatment is usually unnecessary. In about 2% of fetuses that present premature atrial contractions and have normal ventricular contraction rates, this may lead to sustained tachycardia. Both supraventricular tachycardia (SVT) and atrial flutter (AF) have been observed. In fetuses with multiple blocked contractions, the resulting incidence of bradycardia is even higher. [11] This warrants weekly to bi-weekly monitoring to exclude the development of sustained arrhythmias.

Tachycardias

Tachycardias exceed normal physiologic variation with heart rates over 180 bpm, and typically over 220 bpm. They are often associated with abrupt changes. The mother is usually asymptomatic and does not notice changes in fetal activity.

A critical heart rate of approximately 210 bpm may lead to increased atrial and venous pressures and subsequent congestive heart failure. [46] Studies in fetal lambs have shown that the increase of systemic venous volume load is caused by shortening of the diastole, thereby decreasing atrial and ventricular filling time. This is accompanied by reversible systolic dysfunction and relative ischemia due to insufficient blood supply through the coronary arteries. Cardiac dilatation impairs contractility and causes atrioventricular valve regurgitation. These changes have been referred to as “tachycardia-induced cardiomyopathy”. [47]

Sinus Tachycardia is often caused by fetal distress, fetal infection, hyperthyroidism and sympathomimetic drugs. The fetus shows heart rates of up to 180-200 bpm with 1:1 atrioventricular (AV) conduction. There is beat-to-beat variability, in contrast to SVT. Treatment is always aimed at the underlying cause of the tachycardia. [42]

Pathological tachycardias can be divided into three main groups:

- **Tachycardias involving the specific conductive system**
- **Atrial tachycardias**
- **Ventricular tachycardias**

Supraventricular Tachycardias involving the conductive system

Supraventricular tachycardia is more commonly associated with significant clinical consequences than any other form of fetal cardiac arrhythmia [42] and accounts for approximately 73.2% of all fetal tachyarrhythmias. [48] SVT is defined by 1:1 AV conduction, a fetal heart rate above 180 bpm (typically between 240-260 bpm), and minimal beat-to-beat variability when associated with reentry mechanism. [11] Mean gestational age at point of diagnosis is 28-32 weeks, [48] although there has been a case report of an SVT diagnosed and treated as early as the 13th gestational week. [47]

SVT has been associated with ventricular septal defects (VSDs), Ebstein's Anomaly of the tricuspid valve, tricuspid valve dysplasia [38] and Tetralogy of Fallot. [28]

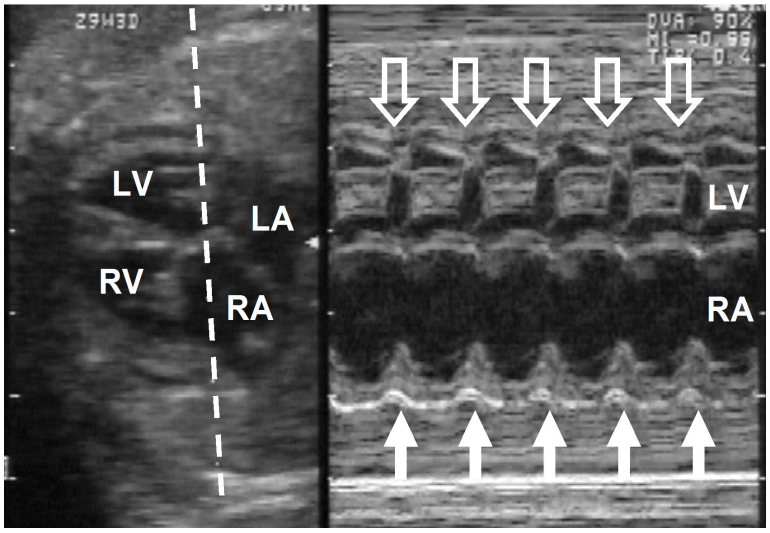


Fig. 5: Simultaneous M-mode recording of both ventricles and atria.

SVT with a 1:1 AV-conduction and a ventricular rate of 210. [153]

More than 90% of the cases of fetal SVT are attributable to atrioventricular reentry or reciprocating tachycardia. The anatomical substrate is an accessory pathway between the ventricle and atrium allowing the return of the cardiac impulse to the atrium due to the difference in conduction velocity and refractory period. While the physiological conductive tissue is still in the refractory period, the accessory pathway has already recovered its ability to allow the spreading of the electrical impulse. Upon reaching the atrium, the impulse is conducted antegradely through

the AV node, which has recovered conductivity by now, this is known as orthodromic reciprocating tachycardia (ORT). If the electrical energy is directed in the opposite direction, the arrhythmia is termed antidromic reciprocating tachycardia (ART). The electrical circus movement can be triggered by an appropriately timed extrasystole. [42]

This is also the underlying mechanism of the Wolff-Parkinson-White (WPW) Syndrome, which is confirmed in postnatal electrocardiograms in 8-10% of fetuses that are diagnosed with SVT. [38]

If the tissue that acts as accessory pathway is not located in the fibrous atrioventricular junction but rather in the AV node itself, the tachycardia is classified as AV nodal reentry tachycardia (AVNRT). This form of tachycardia is rarely found in the fetal period or infancy. [11]

Other mechanisms underlying the diagnosis of SVT include atrial ectopic tachycardia (AET), which arises from an atrial ectopic focus, and permanent junctional reciprocating tachycardia (PJRT), which is electrical reentry within the junctional tissue connecting atrium and ventricle. These forms of tachycardia are significantly rarer but also considerably harder to control; they are typically incessant and unresponsive to most antiarrhythmic agents. [42,11]

Prenatal diagnostic differentiation of the underlying mechanism can change the outcome of the fetus, as appropriate therapy may be initiated without delay. A valuable tool is measurement of atrio-ventricular (AV) and ventriculo-atrial (VA) time in M-mode echocardiography. SVTs with short VA times have been shown to be caused by an underlying AV-reentry mechanism. Long VA times have been associated with AET and PJRT, which were confirmed by neonatal electrocardiogram (ECG). [28]

Table 1: Characteristics of common tachycardias

Type	Heart Rate	AV conduction	VA time	Intermittent/Sustained
ORT	220-240 bpm	1:1	short	intermittent/sustained
PJRT	200-220 bpm	1:1	long	sustained
AET	200-220 bpm	1:1	long	sustained

M-mode echocardiography is limited by external factors, such as maternal obesity, fetal position and polyhydramnios. In hydropic fetuses, contractility is poor, and it is not always possible to distinguish atrial and ventricular contractions. An alternative approach to measuring AV and VA times is by simultaneous Doppler recording of flow velocities in the SVC and aAo. [9]

Therapeutic measures are aimed at slowing conduction in the AV node to disrupt the reentry mechanism and thereby restore sinus rhythm.

Atrial Tachycardias

Atrial Ectopic Tachycardia

AET is also a supraventricular tachycardia. In contrast to the other SVTs, there is no reentry through conductive tissue. It is believed to be caused by increased automaticity of nonsinus atrial foci. It is commonly incessant, and cardiac failure and tachycardia-induced cardiomyopathy have been observed. [5] Fetal heart rate is typically slower than in other tachyarrhythmias, ranging from 200-200 bpm. [11]

Atrial Flutter

AF accounts for 26.2% of all cases of fetal tachyarrhythmias. It typically shows fetal atrial contraction rates between 300-500 bpm and ventricular rates ranging

from normal to greater than 300 bpm, depending on the degree of atrioventricular block. Mean gestational age at point of diagnosis is 30-34 weeks. [48]

Congenital heart defects that have been reported in cases of AF are atrioventricular septal defects, hypoplastic left heart syndrome and pulmonary atresia.

Atrial flutter is also based on a reentry mechanism. In contrast to SVT, the “accessory pathway” is within the atrial wall. If tissue that is part of the conductive system is separated by electrophysiologically inactive tissue, circus movement is contained within the atrium itself. [42]

The detection or onset of this tachycardia is about two weeks later than SVT. It is believed that this results from the need for the atrium to reach a critical size to allow for intra-atrial macro-reentry. Critical size is reached at 27-30 weeks of gestation. [48]

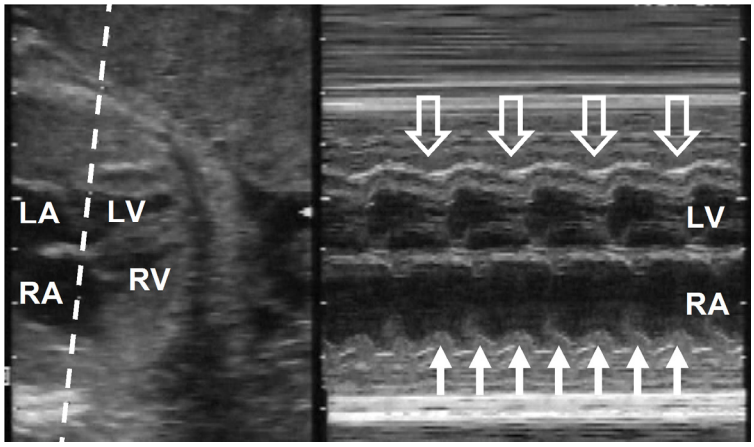


Fig. 6: M-mode trace of a fetus with AF and 2:1 AV conduction.

Atrial rate of 510 bpm and ventricular rate of 255 bpm. [153]

In contrast to SVT, ventricular rates are often irregular. This is due to atrioventricular block, which can result in fixed conduction rates (2:1, 3:1) or be variable, thereby leading to the irregularities in ventricular rates. [11] In 83.0% of AF there is a 2:1 AV block. The ventricular rate is of prognostic value; fetuses with higher ventricular rates are more likely to exhibit signs of hydrops. [48]

The aim of therapy is to restore normal sinus rhythm. If it is not possible to achieve this, it is desirable to reduce the ventricular response rate to ensure adequate ventricular filling and cardiac output.

Atrial Fibrillation

Atrial Fibrillation (Af) is rare in the prenatal period and is characterized by rapid disorganized electrical stimulation of atrial muscle. Cases of familial atrial flutter with fetal onset have been reported. [49] As with AF, conduction is blocked to a variable degree in the AV node. It is fundamentally important to abstain from digoxin-treatment, as this may inadvertently increase the ventricular response by decreasing the effective refractory period in accessory conduction tissue. [42]

Ventricular Tachycardia

Ventricular Tachycardia (VT) is another rarely encountered dysrhythmia in the fetal period. VT can be diagnosed if the ventricular rate exceeds the atrial rate. If retrograde conduction is present, VT can present as a tachycardia with 1:1 AV conduction, making it virtually impossible to discern from SVT. [11] A tachycardia with an atrial rate very close to the ventricular rate can be a VT with cardiac failure and reactional sinusal tachycardia. [50]

The underlying mechanism is a re-entrant electrical circuit that is contained within the ventricular myocardium. As with AF, electrophysiologically active tissue is separated by electrically inert tissue (presumably fibrosis or scar-tissue). Adults display this form of arrhythmia more commonly, since ischemic heart disease entails formation of scar-tissue.

VT in the fetus has been associated with iso-immune AV block [51], congenital long QT Syndrome (LQTS), which can lead to Torsade des Pointes Tachycardia and intermittent AV block, [52] and cardiac tumors. [53]

Bradycardias

Sinus Bradycardia

Sinus Bradycardia is an indication for fetal distress and is most frequently encountered during labour as a normal response to the uterine contractions or in association with placental insufficiency. Hypothyroidism should be considered if a fetus presents with a baseline of 110-120 bpm and no other pathology is present. [42]

Atrioventricular Block

AV block is the result of a functional impairment in the conductive tissue that lies between the Sinus node and the ventricles. The electrical impulse produced by the sinus node is passed on too slowly or not at all. This leads to bradycardia, which is the main reason for referral. AV block may be first degree, second degree or complete.

- **First degree AV block:** prolongation of the conduction time between the sinus node and the ventricular myocardium. Every atrial beat is conducted to the ventricle. In the fetus, it is defined as a PR interval prolongation over 150 ms.

- **Second degree AV block:** only some of the impulses generated by the sinus node are conducted through the AV node and His-Purkinje System. Fixed ratios, such as a 2:1 atrial to ventricular rate, are frequently observed.

- **Third degree or complete heart block (CHB, CAVB):** consists of complete dissociation of atria and ventricles. They contract completely independently of each other at different rates.

A fetus with first or second degree heart block often remains asymptomatic if the degree of blockage does not progress. [54] The majority of this chapter will focus on CHB, since it is more commonly associated with complications in the ante- and postpartum period.

Complete heart block

CHB is associated with structural heart disease in 57-59% of cases. [55, 56] The most common cardiac anomaly is left atrial isomerism, which occurs in 59-86% of cases. Other malformatios include discordant AV connections, hypoplastic right ventricle, tetralogy of fallot and rhabdomyomas. [55-57] Mean gestational age at diagnosis ranges from 25.6-29.5 weeks. [57, 58] Outcome of fetuses that display CHB related to structural heart disease is poor; fetal and neonatal death rate has been reported at 70-83%. [55, 56] Since this paper focuses on heart failure caused by arrhythmias, this chapter will concentrate on isoimmune CHB.

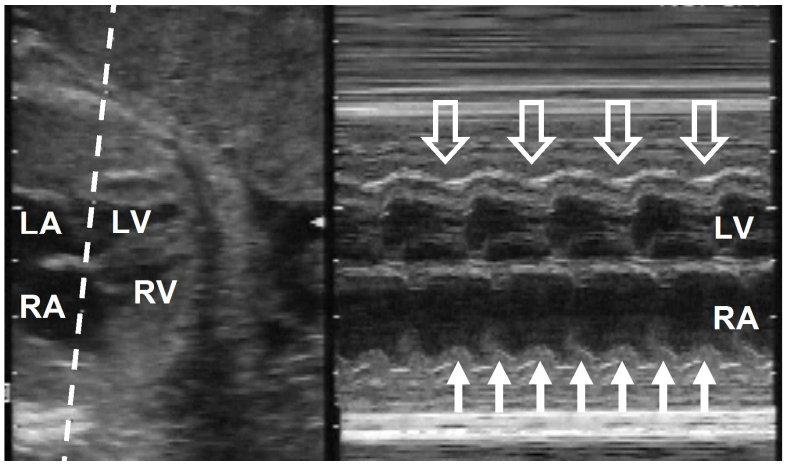


Fig. 7: Fetus with CHB.

M-mode tracing shows complete dissociation of atrial and ventricular contraction with a ventricular rate of 65 bpm.

If normal cardiac morphology is present, CHB is most likely due to maternal connective tissue disease. Circulating maternal anti Ro (SSA) and anti La (SSB) antibodies cause immune-complex mediated damage to the conductive system. These antibodies can also be found in the absence of clinical manifestation of connective tissue disease in the mother. [5] Jaeggi et al reported only 5 mothers with previously diagnosed autoimmune disease in 33 cases of maternal autoantibodies that led to CHB. [58]

Buyon et al suggested that complete AV Block may result from unresolved wound healing and scarring subsequent to transdifferentiation of cardiac fibroblasts into proliferating myofibroblasts, initiated by the specific maternal antibodies. [59] Viral infections and long-QT syndrome might be responsible for autoantibody negative cases of isolated CHB. [58]

Primigravidas with positive antibody status are confronted with an affected child in 2% of the reported cases. For women with previously affected offspring, the risk is up to 10-fold higher. Even though antibody titers were shown to be higher in mothers with affected fetuses, some researchers have suggested that high –titer antibodies alone are not sufficient to cause CHB, since most unaffected pregnancies display a similar profile. [60] Recent studies suggest that antibodies targeted at the 52-kd component of the Ro-antigen seem to be more likely to induce CHB than antibodies targeted at the 60-kd component. [61]

CHB associated with structural heart disease can be found early in pregnancy, whereas isoimmune or isolated CHB is rarely diagnosed before 18 weeks of gestation. This is due to the fact that the antibodies responsible are not transferred across the placenta prior to approximately 16 weeks of gestation. [54] It has been recommended to start assessment at least by gestational week 16, before irreversible AV node fibrosis has occurred. [62] The goal of intense monitoring would be to identify a biomarker of reversible injury, such as a PR interval > 150 ms (first degree AV block), moderate/severe tricuspid regurgitation, and/or an atrial echodensity. [60]

Recently, it has been suggested that anti-Ro52/SSA antibody-exposed fetal hearts have not only disturbed electrical conduction but also decreased mechanical performance in terms of contractility. [61]

The PR Interval and Dexamethasone Evaluation (PRIDE) Prospective Study was aimed at identifying early markers for CHB and finding effective therapy. Tricuspid regurgitation and atrial echodensities have been observed prior to development of hydrops fetalis and heart block. These findings are thought to be signs of

myocarditis and endocardial fibroelastosis. Fetuses exhibiting atrial echogenic foci have also been shown to develop late onset dilated cardiomyopathy. This occurs in 10-15% of affected fetuses, in utero or up to 9 years of age. [57, 60]

Some controversy has surrounded the questions of whether or not lesser degrees of AV block precede CHB and whether treatment of first and second degree AV block with fluorinated steroids is justified and effective to prevent progression to CHB.

Lopes et al found progression from second degree AV block in 6 out of 14 fetuses (42%). [57] Friedman et al identified three cases of CHB which were not preceded by lesser degrees of block. They opted to treat two fetuses with first degree AV block, based on the diagnosis of a prolonged PR interval with dexamethasone, which reversed the PR interval rapidly in both fetuses, possibly preventing development of CHB. [60] Another recent study reported 6 fetuses with first-degree AV block that were also treated with fluorinated steroids. There was no progression to second or third degree block and no development of second or third degree block in any of the other 64 fetuses whose mothers had autoantibodies. [63]

Poor outcome of CHB is related to a ventricular rate of less than 55 bpm [57], hydrops fetalis/heart failure and negative maternal anti Ro antibody status. [5] Primary fetal and neonatal mortality in presence of isoimmune CHB has been reported in 20-30% of cases, with 67% of surviving children requiring a pacemaker before adulthood. [60]

In women with a previously affected child, the recurrence rate of cardiac manifestation in a second child has been reported at 17%. Maternal health status, maternal steroid use, antibody status, severity of disease in the first affected child and sex of the second child are not predictive of outcome in the second child. [64]

Whereas inexperience with fetal CHB may lead to premature delivery, it is advisable to deliver near term in most cases. Buyon reported a loss of 52% of neonates born before 34 weeks of gestation. [59] Circumstances that should prompt delivery are deterioration of cardiac function and a fall in heart rate that results in

early hydrops. [5] Frequent follow-ups are recommended, as deterioration from sinus rhythm to CHB may occur in less than a week. [65]

Cesarian section is the widely preferred method of delivery. In a stable case of CHB delivered close to term, vaginal delivery is an option if the obstetrician is comfortable with monitoring the fetus during labor. [54]

Treatment

When faced with a fetus with an arrhythmia, many factors need to be taken into consideration when developing a treatment approach. The severity of the fetal condition and the resulting benefit of treatment must be carefully weighed against any potential fetal or maternal adverse effects caused by the treatment.

Since the majority of affected fetuses receive treatment, there is no data regarding the natural history of fetal arrhythmias. The rationale for treatment is that some fetuses who did not initially present with hydrops fetalis were found to develop hydrops if the arrhythmia was not treated.

There are three options for managing fetal arrhythmias:

- **Observation**
- **Delivery**
- **Prenatal treatment**

Observation

In near-term pregnancies with intermittent episodes of arrhythmia and without signs of fetal cardiac compromise, observation may be a viable option. Since there are no distinct predictors of hydrops, intervention is advisable in most other settings.

Delivery

While early delivery and postnatal treatment eliminates the uncertainty of placental drug transfer and efficacy, it is also associated with high mortality and numerous complications for the fetus if delivered preterm. Simpson reports a mortality of

9.7% of hydropic fetuses in whom the arrhythmia was controlled prenatally, compared to 56% for those in whom control of the arrhythmia could not be achieved. [38] Adding to the possibly compromised hemodynamic state are all of the complications of prematurity that have to be faced in early delivery.

In near-term, tachycardic fetuses, the decision on whether to expedite delivery or initiate prenatal drug therapy is still under dispute. This will always necessitate careful consideration of the individual situation at hand, assuming that there are no signs of fetal cardiac failure. Gestational age at delivery is significantly greater in fetuses who receive prenatal treatment, and the number of operative deliveries is lower. [46]

Prenatal drug treatment

Prior to initiating prenatal drug treatment a therapeutic goal needs to be defined. In most cases, a return to normal sinus rhythm is desirable. If this cannot be achieved, rate control may prove to be adequate to allow fetal cardiac recovery.

There are two methods of prenatal drug treatment:

- **Transplacental drug treatment: drugs are administered to the mother**
- **Direct fetal therapy: drugs are administered directly to the fetus**

Transplacental drug treatment

Although transplacental drug treatment is a well-established therapeutic option in fetal arrhythmias, treatment algorithms have never been tested in a controlled, prospective manner.

Each center has developed its own treatment algorithms, and some drugs have only been tried in a handful of cases, which makes it difficult to evaluate their potential. It is also virtually impossible to compare existing therapeutic approaches due to the large number of drugs that have been tried in differing dosages, combinations and administration schedules.

Another difficulty is the complexity of pharmacology in pregnancy. Therapeutic serum levels in the fetus are dependant on maternal serum levels. These are influenced by drug absorption, distribution, metabolism and clearance, all of which may be altered during pregnancy. [66]

Placental drug transporters

The human placenta is an important fetoprotective barrier when xenobiotics are administered during pregnancy. In recent years, placental transport proteins have been a subject of intense interest, since drug consumption during pregnancy is steadily increasing. [67]

Passive diffusion across the placental barrier is determined by the specific physicochemical characteristics of each drug. To some extent, most drugs can cross the placenta, depending on their molecular weight, lipid/water solubility and protein binding characteristics. [4]

A growing number of placental transporters have been identified, some of which are thought to contribute to the placental passage of pharmacotherapeutics. Some of these transporters show drug efflux activity, which decreases fetal exposure to their substrates, whereas others act as importers, thereby increasing fetal serum levels. Overlapping substrate specifity and affinity leads to the important conclusion that the net effects of all significant transporters must be considered in order to determine their effect on placental passage. [4]

Other factors that contribute to placental passage are the concentration gradient across the placenta, placental blood flow, plasma pH and protein binding differences in maternal and fetal environments, as well as placental metabolism and storage. As a steroid endocrine organ, the placenta has considerable capacity for sulfation, glucoronidation and gluthathione conjugation.

Expression of placental transporters is very variable, depending on gestational age, interindividual single nucleotide polymorphysms (SNPs), and individual variations between pregnancies. [66]

One member of the ATP-binding cassette (ABC) superfamily, P-glycoprotein (P-gp) (also known as multidrug resistance protein (MDR1)), is one of the most important transmembrane transporters in humans. It is expressed in intestinal epithelial cells, bile canaliculi, renal tubular cells, the placenta, and capillary endothelial cells in the brain and testes. [68] In the placenta, it is localized on the apical surface of the syncytiotrophoblast membrane, thus extruding substrates from trophoblast into maternal plasma. [69] It is also found in tumor cells, conferring a multi-drug resistance phenotype to cancer cells that have developed resistance to chemotherapeutics. [68]

P-gp substrates include immunosuppressive agents, HIV protease inhibitors, cardiovascular drugs, cytostatic drugs, antibiotics, sedatives, steroids and anticonvulsants. [66]

Expression is greatest in the first trimester of pregnancy and decreases with advancing gestational age. [70] Placental structure also changes as pregnancy

progresses. During the first trimester, the placenta forms a barrier to maternal-fetal exchange up to 20 µm thick. In the course of advancing gestation, the barrier will be reduced to 2-5 µm. [66] The fetoprotective role of the placental barrier is most distinct in early gestation, during the vulnerable period of organogenesis. [70]

P-gp/MDR1 gene and protein expression and activation *in vivo* in placental tissue can also be induced by administration of certain xenobiotics, such as antiretroviral agents. [71] *In vitro*, a number of substrates have been identified that increase P-gp activity and P-gp/MDR 1 gene expression. Co-administration of P-gp substrates may lead to significant drug-drug interactions. Various pharmacological substances, including verapamil, mifepristone, clotrimazole, diltiazem and isradipine, have demonstrated inhibition of digoxin secretion, thereby increasing serum levels. This may also be true of other P-gp substrates. [72]

Prescription and non-prescription drugs taken during pregnancy, either by choice (drug abuse), inadvertently or to treat maternal morbidity, will cause less harm to the developing fetus if they are extruded by drug efflux pumps.

If the fetus is the target of drug administration, as in fetal arrhythmia, placental drug transporters may add to the problem of achieving therapeutic serum levels in the fetus without causing maternal toxicity of the administered drug.

Further studies in this rapidly developing field may provide new options for optimizing pharmacotherapy for fetal arrhythmias by manipulating placental drug transporters, includig P-gp.

Fundamental Pharmacological Considerations

Due to the unique circumstances in transplacental drug treatment, there are two patients rather than one. This must be kept in mind, as the mother cannot be considered a passive compartment through which drugs are administered. She will experience all the effects and side effects of the employed drug.

In treating fetal arrhythmias, maternal cardiovascular health is of foremost importance. An ECG and Electrolyte Panel should always be conducted before initiating treatment. During treatment with antiarrhythmic agents, regular monitoring should be provided, since proarrhythmia is a common side-effect of most classes of antiarrhythmics.

The efficacy of any initiated therapeutic regimen should not be assessed before a steady state has been reached. Increasing the dosage before steady-state concentration is reached can lead to overshooting the desired concentration and cause maternal toxicity.

When administering drugs at the interval of one elimination half life, steady state concentration will be reached after approximately 4-5 half lives. As this would be too time consuming in most cases, loading doses are applied to reach the desired concentration more rapidly. If a change of drug is required, this must be considered carefully to ensure total clearance of the previously administered drug before introducing a new one, in order to avoid drug-drug interactions. [42]

Transplacental pharmacological intervention in tachycardias

In the past two decades numerous studies have described the use of antiarrhyhtmics to treat fetal tachycardias. All drugs that were used to treat fetal tachycardias are classified using the Vaughan-Williams classification of antiarrhyhtmics and inlcudde digoxin, sotalol, flecainide, amiodarone, procainamide, verapamil, propanolol, quinidine and adenosine. Use of many drugs has been abandoned again, either due to adverse effects for the mother or the fetus or inefficacy. The following chapter will deal with the four most commonly used agents at this time; digoxin, sotalol, flecainide and amiodarone.

All information listed in the sections on pharmacodynamics and pharmacokinetics are values referring to the mother and were obtained from women who are not pregnant, unless otherwise stated. Direct fetal therapy will be discussed in a separate chapter.

Digoxin

Pharmacodynamics and Pharmacokinetics

Digoxin is a cardiac glycoside. It can lead to an increase in cardiac output and decrease in heart rate by exerting direct and indirect effects on the myocardium, specific conduction system and autonomous nervous system. Its positive inotropic effect is of great value in heart failure. The increase of refractoriness in the AV node results in slower ventricular rates in AF, Af and can interrupt SVT's involving the specific conduction system. [73]

In accessory pathways, Digoxin can decrease the effective refractory period. This results in an increase of ventricular response if the antegrade conduction of the electrical impulse is through the accessory pathway. This does not seem to be the case in the fetus with an accessory pathway where digoxin is still the most frequently used monotherapy.

Digoxin has an elimination half life of 30-40 hrs and a therapeutic serum concentration of 0.8-2 ng/ml. During pregnancy, maternal blood volume and renal clearance increase, which necessitates higher doses to achieve therapeutic levels. [4]

Placental Transfer

It has been previously shown that fetal serum digoxin concentrations (determined from umbilical cord blood) can vary greatly. Fetal-to-maternal digoxin concentration ratio ranges from 0.1 to 0.9. [4] In hydropic fetuses, the placental transfer is severely restricted, and the concentration ratio is severely reduced. This frequently leads to non-conversion in hydropic fetuses receiving digoxin monotherapy. [5]

Adverse Effects and Monitoring

In animal studies utilizing rats and rabbits, digoxin did not induce malformations. [74-76] A neonatal death was reported due to severe maternal overdose and subsequent delivery in the 30th gestational week. [76, 77] Direct fetal or intra-amniotic administration of digoxin has also been applied to induce fetal demise prior to termination of pregnancy. [78]

Maternal adverse effects, which mainly result from overdosing, include gastrointestinal symptoms (nausea, vomiting, loss of appetite, diarrhea), central nervous system disturbances and cardiac arrhythmias (extrasystoles and AV block). [4]

Hypokalemia, hypomagnesaemia and hypercalcemia can alter digoxin's cardiac effects. It is contraindicated in maternal WPW-Syndrome. Other antiarrhythmics, such as flecainide, amiodarone, quinidine, propafenone and verapamil, can increase digoxin serum concentration. Close monitoring and dose adjustments are necessary when these drugs are combined. [4, 79]

Maternal serum digoxin levels and electrolytes should be evaluated regularly. In their protocol, Azancot-Benisty et al propose two controls in the first month and a subsequent monthly control. An ECG should be performed at the same interval. This is intended as a recommendation; each patient must be evaluated individually, and follow-up appointments should be arranged accordingly.

Side effects, such as nausea, diarrhea and headaches, do not necessarily imply treatment discontinuation. Bradycardia and first degree AV-block necessitate control of digoxin level and serum electrolytes and possibly dose adjustment. Second or third degree AV-block or any other form of arrhythmia require discontinuation and medical follow up of the mother. [80]

Dose

Since oral loading may take a week to achieve a steady state concentration, intravenous loading is preferred. Daily doses vary between 0.25-1 mg [4, 80] every 12 hours on the first day, followed by a maintenance dose of 0.125-0.5 mg every 12 hours.

Table 2: Digoxin doses administered in large studies

Author	Daily Dose	Doses/Day	Administration
Simpson [38]	0.75 mg	3	oral
Jaeggi [28]	2.0 mg loading dose over 2 days	n.s.	n.s.
	0.5-0.75 maintenance	n.s.	n.s.
Azancot-Benisty [80]	2.0 mg loading dose	2	i.v.
	1.0 mg 0.5-1.0 mg maintenance	2 2	i.v. oral
Cuneo [40]	1.0-1.5 mg	3-4	i.v.
Lisowski [81]	1.5 mg	3	i.v.
	0.5 mg	2	oral
n.s.: not specified, i.v.: intravenous			

Azancot-Benisty et al propose 1 mg digoxin i.v. every 12 hours for the first 24 hours, followed by 0.5 mg i.v. every 12 hours for the following 3 days. After the first 4 days, doses should be adjusted to digoxin through levels (< 2.5 ng/ml), maternal ECG and maternal clinical condition. [80]

The discovery of endogenous digoxin-like substances (EDLS) has made it difficult to interpret digoxin serum levels. ELDS can cross-react with digoxin assays and are found in patients with renal or hepatic impairment, pregnant patients and fetuses, especially those with cardiac abnormality. Weiner et al reported digoxin levels of up to 1.6 ng/ml in a hydropic fetus with SVT whose mother had not received digoxin. [82] In their protocol, Azancot-Benisty et al propose determining the maternal digoxin serum level prior to initiating therapy. [80] However, since EDLS levels may not be stable, pre-therapeutic EDLS levels cannot simply be subtracted from the attained digoxin serum levels to determine actual digoxin serum levels.

It is advisable to keep maternal serum levels as close to 2.0 ng/ml as possible without inducing serious side effects.

Clinical experience

Digoxin is the most frequently used monotherapy in treating cardiac arrhythmias in the fetus. Its effects on the mother and fetus have been well studied. One very thorough review evaluated 485 cases of fetal SVT and AF.

In fetal AF, digoxin was used as first-line treatment in 67.6% of cases, with a conversion rate of 45.1%. Conversion in hydropic fetuses (6.3%) was much lower than in non-hydropic fetuses (51.7%).

In 63.4% of the reported SVT cases, digoxin was used as first-line treatment and converted 51.5% to sinus rhythm. Here again, treatment tended to fail in hydropic fetuses, reaching a conversion rate of 24.6% compared to 65.4% in non-hydropic fetuses.

There was no difference in the success rate of digoxin in AF and SVT. Combining the data, digoxin converted 63.3% of non-hydropic and 19.5% of hydropic fetuses. [48]

With the differentiation of fetal SVT into long VA and short VA tachycardia, it has also become apparent that digoxin is the drug of choice in the short VA group, whereas it appears to be ineffective in the long VA group. [28]

Conclusion

Digoxin is a safe and well-studied drug in treating fetal cardiac arrhythmias. It is the only drug frequently employed with a positive inotropic effect, which may help alleviate signs of heart failure. For this reason, it is often used in combination with other drugs when monotherapy has failed. Its efficacy is not convincing in the presence of hydrops fetalis, where a combination with other drugs may be a more effective first-line approach. [7]

Sotalol

Pharmacodynamics and Pharmacokinetics

Sotalol is a noncardioselective, β-blocking (class II) agent with additional class III antiarrhythmic properties, which cause prolongation of the action potential duration and the refractory period. Sotalol has 20-50% of the β-blocking potential of propanolol, the reference agent. The electrophysiologic effects are dose dependant; class II effects can be observed at lower doses than class III effects. Clinical observation has also shown that sotalol is less negatively inotropic than other β-blocking agents.

Since orally administered sotalol does not undergo first-pass metabolism in the liver, it has a bioavailability of 90-100%. Elimination half life is between 7-15 hours, and Sotalol is excreted unchanged in urine. There is a linear relation between administered dose and plasma concentration. [83] Therapeutic plasma concentration ranges from 1.27-1.63 mg/l, but maternal blood level was not found to be a reliable predictor of therapeutic success. [79]

Placental transfer

Sotalol passes the placenta quickly and reaches a steady-state level almost identical to maternal plasma level. The fetal/maternal plasma concentration ratio is 1.11. Maternal blood levels can be used as an indicator for fetal blood levels.

Accumulation in the amniotic fluid but not the fetus itself has been observed with a cord blood/amniotic fluid ratio of 3.2. This suggests efficient renal excretion and a renal elimination rate that exceeds oral absorption in the fetus. [84]

Adverse Effects and Monitoring

Animal studies did not show an increased rate of malformations, but there was an increase in embryonic death, which is thought to be due to the arrhythmogenic effect sotalol had on the exposed fetuses. [85-87] One study conducted on canines showed that sotalol causes significantly greater prolongation of the QT interval in the neonatal heart than in adult hearts, putting the immature fetal or neonatal myocardium at greater risk for proarrhythmic events. [88]

Fetal mortality rates of up to 25-30% have been suggested in the setting of sotalol. [8] However, when interpreting this data, one must bear in mind that most intrauterine deaths occurred in severely hydropic fetuses that were at great risk of intrauterine demise without treatment. Therefore, it is not clear that sotalol aided or caused these deaths.

While growth restriction has been reported in the cases of other β-blocking agents [89], this does not seem to be the case with sotalol. [84]

Maternal side effects, which can be primarily ascribed to the β-blocking properties of sotalol, include fatigue, dizziness, dyspnea, chest pain, palpitations, asthenia, bradycardia, nausea and vomiting. These side effects lead to discontinuation of treatment in 16-18% of adults that are treated with sotalol. [83]

Class III antiarrhythmic agents posses arrhythmogenic potential due to the fact that they prolong repolarization. Proarrhythmia manifests as increased ventricular ectopy, impairment of AV conduction and ventricular tachycardia of the torsade de pointes type. Torsade des pointes tachycardia is a major point of concern with the use of class III antiarrhythmics and affects about 2.4% of patients. [90]

Most events occur 3-5 days after initial treatment or dose adjustment [83], and the risk increases substantially for total daily doses over 320 mg. [90]

Sotalol is contraindicated in patients with a QT interval greater than 450 ms, bronchial asthma, chronic obstructive pulmonary disease (COPD) or a creatinine clearance less than 40 ml/min. [91] Doses should be decreased if creatinine clearance is below 60 ml/min. [90]

Coadministration with other drugs that cause QT prolongation (e.g. cimetidine, tricyclic antidepressants, erythromycin) and electrolyte imbalances (e.g. hypocalcemia, hypomagnesemia) should be avoided. [79]

Prior to initiating therapy, maternal ECG and serum electrolytes should be determined in order to rule out pre-existing prolongation of the QT interval or imbalances. Maternal ECG should be monitored closely, especially in the first week. Sotalol should be withdrawn if the QT interval is greater than 500 ms. [83] Subsequent follow-ups should be scheduled at least once a week.

Unfortunately, it is not currently possible to monitor the fetal QT interval. Echocardiography should be performed at least weekly to discern drug-induced ventricular tachycardia.

Dose

Oral maternal dose should be initiated at 80 or 160 mg twice daily and can be increased to a maximum of 160 mg three times per day. [92]

Clinical experience

In the search for a second-line therapeutic to treat fetal arrhythmias, sotalol has gained popularity in the past few years. In the pediatric age group, it is recognized as an effective treatment for SVTs (89% conversion) and AF (74% conversion). [83]

Data in treating fetal arrhythmias is still limited but shows promising results. Oudijk et al reported conversion rates of 40% in SVT (60% after the addition of digoxin)

and 50% in AF (80% after the addition of digoxin) in a retrospective study including 21 patients. Three deaths occurred in the SVT group and one in the AF group. [92]

In a prospective study including 18 fetal patients, Oudijk et al reported 13 conversions to sinus rhythm out of 14 fetuses who were receiving sotalol as single therapy. In the remaining four fetuses, digoxin was added to sotalol treatment due to persistent tachycardia. There was one intrauterine death of a nonhydropic fetus and one neonatal death of an infant with massive hydrops. This study achieved a conversion rate of 72% with sotalol and 83% with the addition of digoxin. [84]

Both studies report unexplained fetal deaths, which may have been aided or even caused by the proarrhythmic effects of sotalol. Lisowski et al reported one sudden fetal death out of 14 fetuses with AF who were treated with sotalol. [81]

Sotalol is also effective in long VA tachycardia; it has successfully converted both PJRT and AET when co-administered with digoxin. [9]

Sotalol is equally effective in non-hydropic and hydropic fetuses, although hydropic fetuses still carry a higher risk of adverse outcome than non-hydropic fetuses. [92] In hydropic fetuses, the possible negative inotropic effect of the drug should be taken into account. In these circumstances, the drug should always be administered in association with digoxin. [93]

Conclusion

Sotalol is a very potent drug and shows high conversion rates in AF. In SVT, it shows conversion rates comparable to other studies. [84] Since its proarrhythmic effects are still a point of concern, it is not to be considered as a first-line drug in short VA tachycardias in non-hydropic fetuses, but rather as a second-line form of treatment in combination with digoxin if digoxin monotherapy has failed.

In hydropic fetuses with AF, it would be a very effective first-line choice in combination with digoxin. In SVT complicated by hydrops, the risks may outweigh

the benefits, and other strategies (e.g. digoxin and flecainide or amiodarone) may be more successful. In long VA tachycardias, it may be the drug of first choice, combined with digoxin in the presence of hydrops. [9]

Flecainide

Pharmacodynamics and Pharmacokinetics

Flecainide is a class Ic antiarrhythmic agent. By blocking sodium channels, it is very effective in depressing conduction in the myocardium (especially the His-Purkinje system) and in prolonging the atrial, AV-nodal and ventricular refractory periods. It is also negative inotropic. [39]

Bioavailability of orally administered flecainide is 70-90%. Elimination half life is 7-22 hours, with an average of 14 hours in patients with normal renal function. Flecainide is eliminated through renal excretion (40%) and hepatic metabolism through the Cytochrome P450 enzyme system (60%). [94] Therapeutic serum concentration is 500-1000 µg/l. [95]

Placental transfer

Flecainide passes the placental barrier easily, even in the presence of hydrops fetalis. Fetal to maternal concentration ratios from 0.5-0.97 have been reported. [7]

Adverse Effects and Monitoring

While administration of flecainide to experimental animals during pregnancy has been associated with adverse effects on development, [96, 97] this has not been the case in the human fetus.

The main adverse effect of flecainide is associated with is proarrhythmic ventricular tachycardia. Concerns were raised after the Cardiac Arrhythmia Suppression Trial (CAST), which demonstrated proarrhythmic effects and ventricular tachycardia with an increased death rate in post-myocardial infarction patients being treated for ventricular extrasystoles. [98] These effects have not been confirmed in young, healthy women. [95] The authors recommended flecainide only be used in life-threatening arrhythmias. Allan et al, the first group to publish a larger series on fetal SVTs treated with flecainide, reasoned that fetal tachycardia and heart failure is certainly a life threatening condition (mortality of up to 50%), thereby justifying the use of fleicainide. [39]

While intrauterine deaths during treatment with flecainide have been reported [39, 38], it is not clear whether these are attributable to flecainide or the serious condition with which the feutses presented.

Flecainide should not be used in AF, as it can lead to a 1:1 conduction by slowing the AF, thereby increasing the ventricular rate and inducing VT. Flecainide should not be used if there is maternal structural heart disease, ischemic heart disease, hypertrophic cardiomyopathy or severy bradycardia. [79]

Maternal side effects are dizziness, headache, visual disturbances, paresthesia, tremors, flushing, nausea and vomiting. [7] These were not encountered in a single case in two of the largest studies conducted. [39, 95]

Cardiac toxicity manifests predominantly as widening of the QRS intervals. This has been reported in a neonate who was treated for fetal SVT. In this case, unusually high flecainide levels were taken postnatally (1030 µg/l), and it was speculated that maternal concentration must have increased very late in gestation, since there is no evidence of flecainide accumulating in the fetus. Flecainide was discontinued, and on the third day neonatal ECG was normal. [99] For fetal and maternal reasons, flecainide levels should be monitored regularly throughout gestation.

Treatment with flecainide can cause the absence of accelerations and poor variability in the fetal heart rate (FHR). [100, 101]

Other adverse effects that have been reported include one case of neonatal transitional hyperbilirubinaemia [102], one case of neonatal QT prolongation after prenatal treatment with flecainide and digoxin [103] and one case of maternal prolongation of the QT interval after treatment with flecainide for fetal tachyarrhythmia. [104]

Treatment should be initiated in an inpatient setting. Following cardioversion, weekly follow-ups, including serum concentrations and maternal ECG, should be scheduled.

Dose

Recommended dosage varies from 200-600 mg per day in 2-3 doses. [12, 14, 28, 40] It is advisable to start with a small dose (100 mg twice daily) and increase the dose stepwise to reach the desired effect. A total daily dose of 600 mg should not be exceeded, as it increases the risk of adverse effects.

Clinical Experience

Numerous case reports [41, 101, 105, 106] have reported successful treatment of fetal tachyarrhythmias.

Allan et al were the first to describe a larger series of 14 fetuses that were treated with flecainide. Hydrops was present in all but one fetus. Twelve out of 14 fetuses converted to sinus rhythm within 5 days, most within 48 hours. The other two were converted using digoxin. There was one IUD, which occurred three days after initiating flecainide treatment and within 24 hours of chordocentesis. After successful conversion, treatment was stopped in 4 fetuses. There were three recurrences, which were again successfully converted with flecainide. Resolution

of hydrops, which usually occurs 1-2 weeks after rhythm control, was aided by drainage procedures in 6 fetuses. Nine fetuses were still in mild to moderate hydrops at delivery. [39]

Two other studies reported conversion rates of 100% in non-hydropic and 50-80% in hydopic fetuses. [107, 108]

The next largest series was reported by Simpson and Sharland, who treated 27 hydropic fetuses with flecainide. They achieved a conversion rate of 59% and a resolution of hydrops in 63% of the fetuses that had converted to sinus rhythm. Median time to control of arrhythmia was 3 days. There were 3 IUDs within 24 hrs of initiating flecainide, 1 IUD two weeks later, and 1 neonatal death of a hydropic newborn, who was delivered at 30 weeks of gestation. [38]

Krapp et al achieved cardioversion in 19 out of 20 fetuses (95%) using flecainide in combination with digoxin, and a reduction of heart rate in the remaining case. They were able to show that although 75% of fetuses convert into sinus rhythm after 7 days of flecainide therapy, a large proportion (25%) convert after up to two weeks. In these late converters, an initial decrease in heart rate can be observed, which should be interpreted as a therapeutic response that justifies treatment for a longer interval. No IUDs of NNDs were observed in this study. [95]

In a review evaluating 108 cases of prenatal flecainide treatment, 8 cases (7.4%) of sudden fetal death were identified in four studies. [109]

Conclusion

Flecainide is a safe and effective drug when used in healthy young women. In combination with digoxin, it has a very high success rate in treatment of fetal SVT, even in the presence of gross hydrops. This justifies the use of flecainide in combination with digoxin as a first-line treatment in hydropic fetuses with SVT. Due to the concern about proarrhythmic effects, it should be limited to second-line

therapy in non-hydropic fetuses. It should not be used in fetal AF, as it could lead to a 1:1 conduction and thereby increase the ventricular rate.

Amiodarone

Pharmacodynamics and Pharmacokinetics

Amiodarone is a class III agent which predominantly blocks potassium channels and prolongs repolarization. It also displays additional class I, II and IV effects. It is 37% iodine by weight. [4]

When administered orally, Amiodarone has a variable bioavailability of 20-80%. It is highly lipid soluble and accumulates in fat tissues. The terminal elimination half life is usually between 35-40 days, although up to 100 days have been observed in obese patients. [110] Amiodarone is metabolized to its active metabolite mono-N-desethylamiodarone (DEA) by the liver and excreted by the biliary and gastrointestinal route. The iodine is excreted in urine.

Maternal serum concentrations do not correlate with efficacy in short-term therapy, therapeutic range for long term treatment is 0.5-2.5 µg/ml. [79]

Placental transfer

Amiodarone and its active metabolite DEA cross the placental barrier, and fetal plasma concentration ratios from 0.1-0.5 have been documented. [4]

Adverse Effects

Amiodarone was not associated with increased congenital defects in animal studies. [111-13]

Although a number of adverse effects, including thyroid dysfunction, liver dysfunction, pulmonary toxicity, photosensitivity and bradycardia, can occur, transplacental amiodarone is well tolerated by both the mother and the fetus due to the short duration. [4, 79] Amiodarone-induced adverse effects are mainly dose dependent and rarely require discontinuation of the drug. [114] There has been one report of treatment discontinuation due to development of a photosensitive skin rash and thrombocytopenia in the mother. [115]

The main concern is transient hypothyroidism induced by the iodine load, to which the fetus is more sensitive, since it only acquires the capacity to escape from the acute Wolff-Chaikoff effect late in gestation. [116] Elevated levels of thyroid-stimulating hormone (TSH) at birth warrant follow up. In most cases, treatment is not necessary, and TSH levels return to normal within a short period of time. [115] If this is not the case, replacement therapy with L-thyroxine is indicated until euthyroism is achieved. Hyperthyroidism has only been reported in a small number of cases.

Transient hypothyroidism has been reported to occur in 9-24% of fetuses treated with amiodarone. [114-16] Neonatal examination should therefore include full thyroid function tests (i.e. TSH, free thyroxine and free triiodothyronine). Amiodarone-induced neonatal thyroid dysfunction is not related to dose, duration of therapy or placental transfer. [4, 114, 115]

Developmental delay has been reported in both hypothyroid and euthyroid infants that were exposed to amiodarone prenatally, which suggests a direct neurotoxic effect of amiodarone during fetal life. It is advisable to treat hypothyroidism as soon as it is diagnosed, even in utero. [116] This has been previously reported. A

weekly intra-amniotic installation of 250 µg L-thyroxine after hypothyroidism had been diagnosed prenatally led to a healthy infant with no developmental delay. [117]

Amiodarone is rarely associated with proarrhythmia in the form of torsade des pointes tachycardia related to a prolongation of the QT interval. [118] Nevertheless, maternal ECG and serum electrolytes should be monitored.

If coadministered with digoxin, amiodarone can increase digoxin through levels by 50-100%. [4] Digoxin doses should be reduced by 50% before initiating amiodarone therapy.

Dose

Maternal oral loading doses of 800-2400 mg per day, mainly 1800-2400 mg, have been used for 1-7 days, with a single dose not exceeding 800 mg. [9, 50]. If tachycardia persists, daily doses of 800 mg are advisable in order to ensure continued gradual loading for another 7 days. It can be reduced to the minimum effective dose, usually 200-400 mg daily, once sinus rhythm has been established, and discontinued 2-3 weeks later. [115]

Clinical Experience

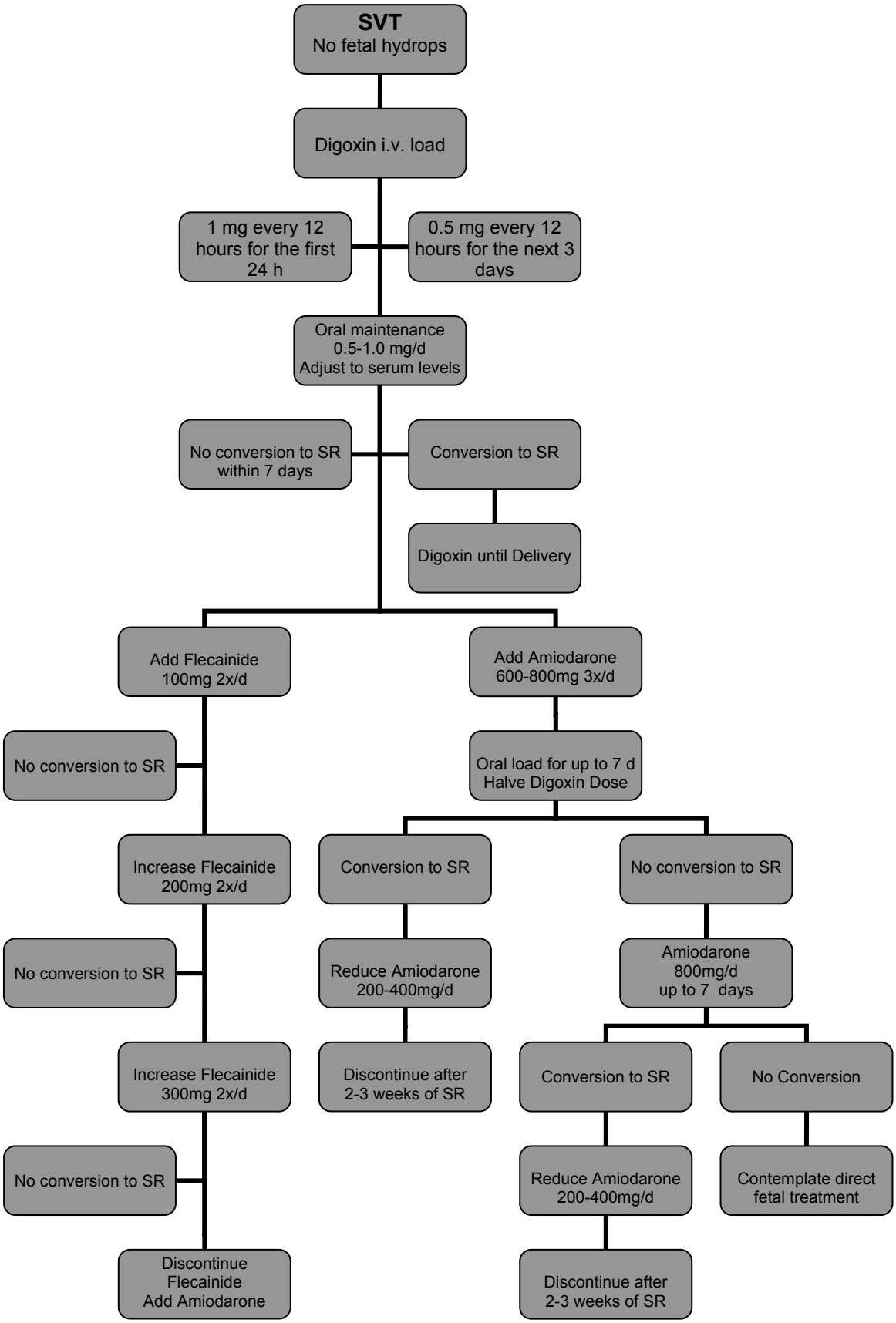
One review evaluated 37 cases of transplacental therapy using amiodarone. It was either administered alone or in combination with digoxin and/or sotalol and achieved conversion in 33 cases (89.2%). [109]

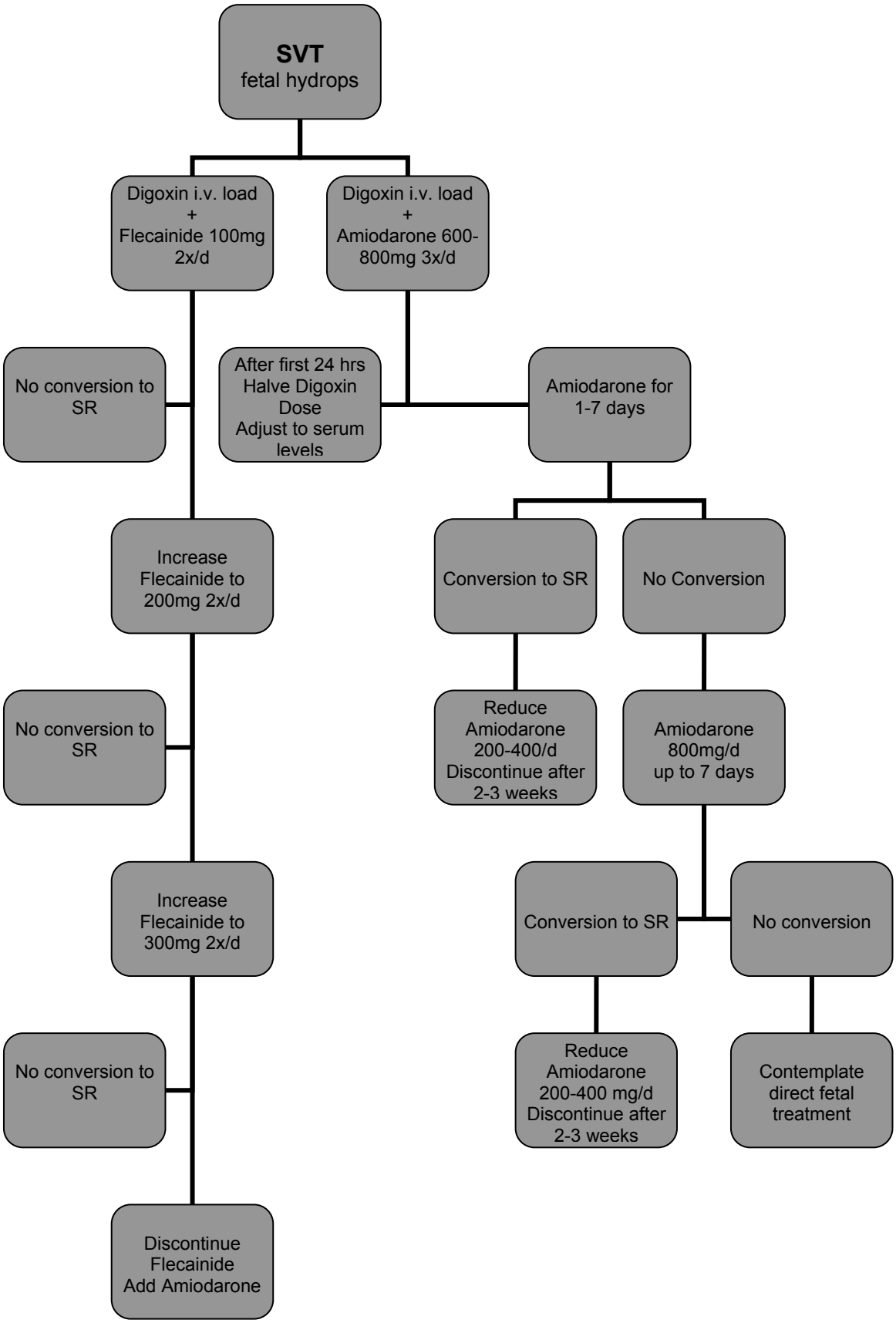
Success is high in SVT (conversion rate of 93%) and moderate in AF (conversion rate of 33%). Considering that amiodarone is usually administered as a third-line therapeutic in drug-refractory fetal tachycardias, these results are very promising, especially in hydropic fetuses with SVT that have not responded to other antiarrhythmic agents. [7]

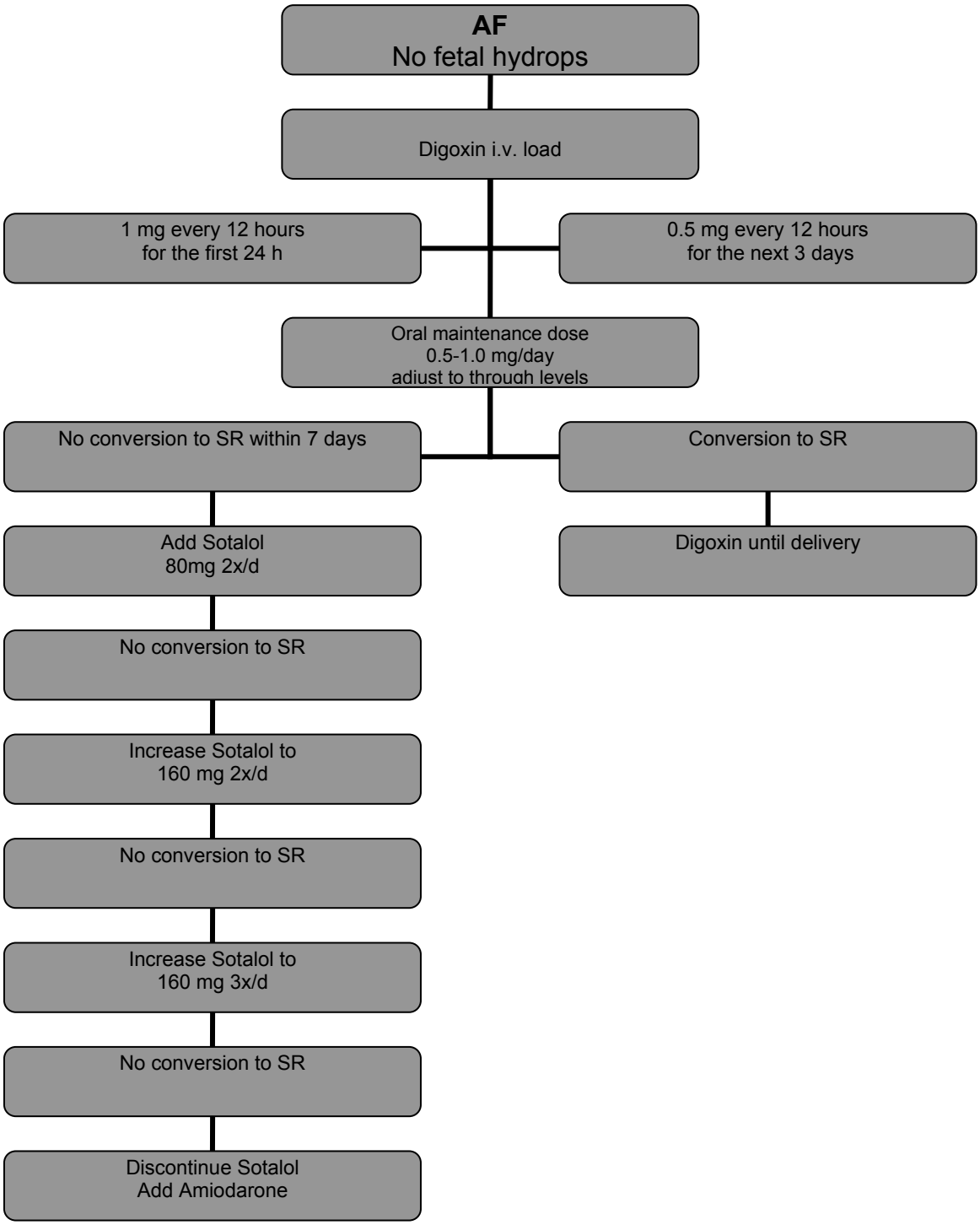
There are two cases of fetal VT that were also successfully converted using amiodarone, as monotherapy in one case [119] and in combination with digoxin in the other. [50]

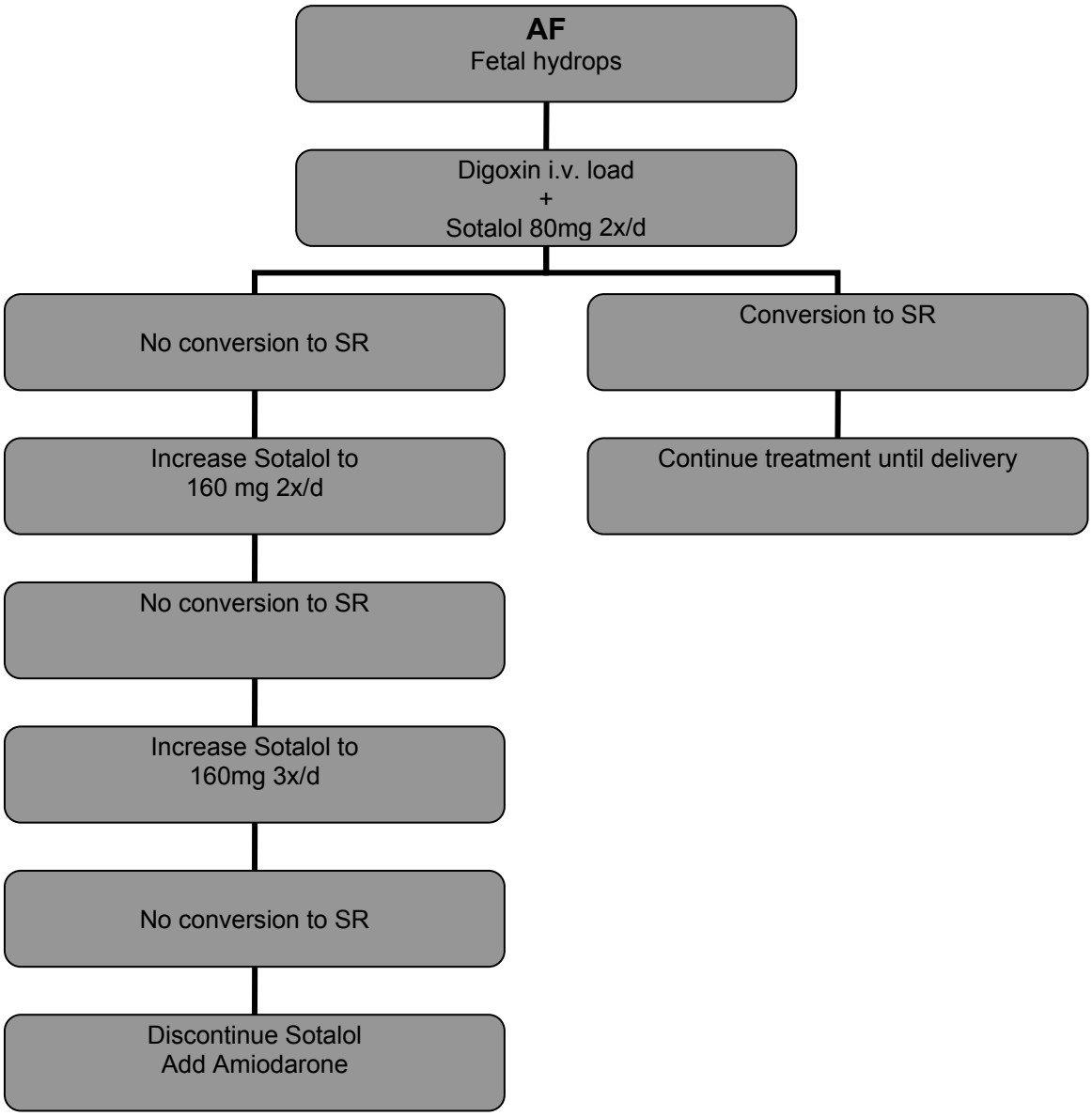
Conclusion

Amiodarone is a very potent drug with high conversions rates, especially in hydropic fetuses with SVT. Due to its large spectrum of adverse effects and long elimination half-life, it has been proposed as a drug of last resort. Considering the reports of sudden fetal deaths with sotalol [92] and flecainide, [109] it might be justified to recommend amiodarone as a second-line treatment in fetal SVTs complicated by hydrops and drug-refractory cases. Especially since reported neurodevelopmental delay is often described as the Non-verbal learning disability syndrome, an acceptable event when compared to fetal death.


SVT
No fetal hydrops
Digoxin i.v. load
1 mg every 12 hours for the first 24 h
0.5 mg every 12 hours for the next 3 days
Oral maintenance 0.5-1.0 mg/d Adjust to serum levels
No conversion to SR within 7 days
Conversion to SR
Digoxin until Delivery
Add Flecainide 100mg 2x/d
Add Amiodarone 600-800mg 3x/d
No conversion to SR
Oral load for up to 7 d Halve Digoxin Dose
Increase Flecainide 200mg 2x/d
Conversion to SR
No conversion to SR
No conversion to SR
Reduce Amiodarone 200-400mg/d
Amiodarone 800mg/d up to 7 days
Increase Flecainide 300mg 2x/d
Discontinue after 2-3 weeks of SR
Conversion to SR
No Conversion
No conversion to SR
Reduce Amiodarone 200-400mg/d
Contemplate direct fetal treatment
Discontinue Flecainide Add Amiodarone
Discontinue after 2-3 weeks of SR


SVT
fetal hydrops
Digoxin i.v. load + Flecainide 100mg 2x/d
Digoxin i.v. load + Amiodarone 600-800mg 3x/d
No conversion to SR
After first 24 hrs Halve Digoxin Dose Adjust to serum levels
Amiodarone for 1-7 days
Increase Flecainide to 200mg 2x/d
Conversion to SR
No Conversion
No conversion to SR
Reduce Amiodarone 200-400/d Discontinue after 2-3 weeks
Amiodarone 800mg/d up to 7 days
Increase Flecainide to 300mg 2x/d
Conversion to SR
No conversion
No conversion to SR
Reduce Amiodarone 200-400 mg/d Discontinue after 2-3 weeks
Contemplate direct fetal treatment
Discontinue Flecainide Add Amiodarone


AF
No fetal hydrops
Digoxin i.v. load
1 mg every 12 hours
for the first 24 h
0.5 mg every 12 hours
for the next 3 days
Oral maintenance dose
0.5-1.0 mg/day
adjust to through levels
No conversion to SR within 7 days
Conversion to SR
Add Sotalol
80mg 2x/d
Digoxin until delivery
No conversion to SR
Increase Sotalol to
160 mg 2x/d
No conversion to SR
Increase Sotalol to
160 mg 3x/d
No conversion to SR
Discontinue Sotalol
Add Amiodarone


AF
Fetal hydrops
Digoxin i.v. load
+
Sotalol 80mg 2x/d
No conversion to SR
Conversion to SR
Increase Sotalol to
160 mg 2x/d
Continue treatment until delivery
No conversion to SR
Increase Sotalol to
160mg 3x/d
No conversion to SR
Discontinue Sotalol
Add Amiodarone

Direct fetal therapy for fetal tachyarrhythmias

Direct fetal therapy has the obvious advantage of avoiding problems related to the transplacental transfer of the antiarrhythmic agents. Routes of administration include injection into the umbilical vein, the peritoneum, the amniotic fluid and fetal muscle tissue.

One major disadvantage of direct fetal therapy is the risk of the procedure, which will depend, in part, on any given centre's success and complication rates associated with invasive techniques. Since a single application of antiarrhythmic agents is rarely enough to convert the fetus to sinus rhythm permanently, repeated procedures are required in many cases.

Due to the risk, most centres only advocate direct fetal therapy when the transplacental approach has failed to convert the arrhythmia to sinus rhythm and the fetus exhibits signs of cardiac failure and hydrops fetalis. [11]

The various routes of administration have specific characteristics. Injection into the umbilical vein or the fetal heart secures direct access to fetal circulation, which results in a rapid reaction to therapy. Intra-peritoneal, intra-muscular and intra-amniotic administration provide a more sustained release of the therapeutic in the form of a maintenance dose. [7]

Direct fetal therapy should be combined with maternal administration of the drug to prevent it from simply passing from the fetal to the maternal compartment along the concentration gradient.

Table 3 summarizes the substances that have been administered and the respective doese. A number of other therapeutics have also been employed, including procainamide and flecainide. Exact time and dosage of administration are not always specified.

Table 3: Therapeutics used in direct fetal therapy

Drug	Route	Dose˚	Publication
Adenosine	umbilical vein	100-200 µg/kg	Simpson
	intracardiac	100-200 µg	Simpson
Amiodarone	umbilical vein	up to 40 mg/kg	Hansmann
		2.5-5.0 mg/kg	Hansmann
		up to 10mg/kg	Simpson
		15 mg/kg	Leirira
	intraperitoneal	9 mg/kg	Flack
Digoxin	umbilical vein	12 µg/kg	Hansmann
		30 µg/kg	Leirira
	intramuscular	88 µg/kg every 12 hrs (max. of 3 inj./d)	Parilla
		60-88 µg/kg every 12 hrs (max. of 3 inj./d)	Cuneo
Isoproterenol*	umbilical vein	0.05-0.1mg/min	Lopes
Propafenone	umbilical vein	6 mg/kg	Hansmann
Verapamil	umbilical vein	0.2 mg/kg	Simpson

˚ per kg of estimated fetal weight without hydrops
* Administered for CHB with a ventricular rate < 55bpm

Table 4 summarizes all of the cases of direct fetal treatment for fetal tachycardias that could be identified using the PubMed Database. Out of 74 reported cases, 50 were converted to sinus rhythm using differing medications, dosages and routes of administration. Considering that direct fetal therapy is normally used as a treatment of last resort for fetuses that are hydropic and have not responded to any other form of therapy, the conversion rate is very high.

Table 4: Effectiveness of direct fetal therapy in converting to sinus rhythm

Author	No. Of fetuses treated	Route of administration	Amiodarone	Digoxin	Propafenone	Verapamil	Other/ Combinations	Total	Intrauterine or Neonatal Death
Maxwell (1988) [45]	1	i.v.	-	-	-	0/1	-	0/1	1/1
Weiner (1988) [120]	1	i.m.	-	1/1	-	-	-	1/1	n.s.
Gembruch (1988) [121]	2	i.p.	-	-	-	-	2/2	2/2	n.s.
Hansmann (1991) [122]	13	i.v., i.p.	4/5	-	2/6	-	3/6	9/13	6/13
Hallak (1991) [123]	1	i.m	-	1/1	-	-	-	1/1	n.s.
Flack (1993) [124]	1	i.v., i.p.	1/1					1/7	0/1
De Catte (1994) [125]	1	i.v	1/1	-	-	-	-	1/1	0/1
Kohl (1995) [126]	1	i.v.	-	-	-	-	1/1	1/1	1/1
Parilla (1996) [127]	6	i.m.	-	6/6	-	-	-	6/6	0/6
Simpson (1998) [38]	4	i.v., i.p., i.c.	1/1	-	-	0/1	1/2	2/4	2/4
Jaeggi (1998) [28]	1	n.g.	-	-	-	-	0/1	0/1	1/1
Mangione (1999) [128]	1	i.v.	1/1	-	-	-	-	1/1	0/1
Cuneo (2000) [40]	17	i.m.	-	17/17	-	-	0/1	16/17	1/17
Lisowski (2000) [81]	1	i.v.	-	-	-	-	1/1	1/1	n.s.
Leiria (2000) [129]	1	i.v.	-	-	-	-	1/1	1/1	0/1
Vanbesien (2001) [117]	2	i.v.	2/2	-	-	-	-	2/2	0/2
Strasburger (2004) [115]	15	i.m.		0/15				0/15	0/15
Kolditz (2005) [130]	1	i.v.	1/1	-	-	-	-	1/1	0/1
Shand (2008) [131]	1	i.m.		1/1				1/1	0/1
Roest (2008) [132]	2	i.v.	2/2	-	-	-	-	2/2	0/2
Total	**73**		**13/14**	**26/41**	**2/6**	**0/2**	**9/15**	**49/73**	**12/68**
Percentage			92.86%	63.41%	33.33%		60.00%	67.12%	17.65%

Table shows number of fetuses converted to sinus rhythm/ total number of fetuses treated; i.v.: intravenous, i.m.: intramuscular, i.p.: intraperitoneal, i.c.: intracardial

It should be noted, however, that most studies were either conducted in a retrospective manner or consist of single-case reports, which limits their significance and the conclusions that can be drawn from them.

Nonetheless, the need for repeated invasive procedures and the fact that transplacental treatment options reach conversion rates of up to 100% make it advisable to employ direct fetal treatment only as a last resort. [7]

The treatment protocol should be individualised and will depend greatly on the protocol that was tried in the transplacental approach.

Treatment of bradycardias

Management of immune-mediated heart block is highly controversial. Sympathomimetics, Steroids, intravenous immunoglobulin, plasmapheresis and fetal pacing have been tried, with limited degrees of success.

Sympathomimetics

Sympathomimetics have been successfully applied to raise the fetal heart rate and to improve ventricular function. The substances that have been reportedly used are salbutamol, ritodrine, terbutaline and isoprenaline. Treatment is thought to be necessary at a ventricular rate of 56 bpm or less, as a ventricular rate of 55 bpm or less is associated with a poor outcome.

Groves reported a series of three trial cases in which isoprenaline was used as first-line substance and failed to produce a response in all three fetuses. All three did respond to high-dose salbutamol therapy, even to the extent of resolving hydrops in one affected fetus. [133] Similar reports have been published using ritodrine, which also lead to a higher ventricular rate and ameliorated signs of hydrops. [134] Most of these reports are single-case reports and therefore do not provide extensive insight.

Larger series utilising Terbutaline haven been reported. Terbutaline successfully raised ventricular rates and also resolved hydrops when administered at daily doses of 10-30 mg per os. It has also been postulated that Terbutaline acts locally, rather than influencing neural control of the fetal heart rate. [34]

In some cases, the fetus responds well to the sympathomimetic therapy, only to return to it's low ventricular rate, despite continuation and intensification of the administered regimen. [34, 135] Currently, it is still not clear why the effect is transient in these cases.

As with steroids (see below), the natural course of CHB may account for some of the observations made with Sympathomimetics.

Steroids

Steroids have been administered in the hope of alleviating symptoms of associated myocarditis and preventing onset or progression of AV block.

Prednisone, administered to mothers with manifest connective tissue disease, is not considered effective because it neither lowers antibody titers nor reaches the fetus in its active form. [60]

Fluorinated steroids, such as dexamethasone or bethametasone, have been studied extensively in the treatment of AV block. Obstetricians have long used dexamethasone in the form of a short pulse to advance lung maturity. Long-term administration bears maternal and fetal risks, which include hypertension, glucose intolerance, infections, oligohydramnios, growth retardation and possible central nervous system injury to the fetus. [57, 60]

While steroids have been proven to be ineffective if complete AV dissociation has occurred, it has also been shown that lesser degrees of block may revert to sinus rhythm under steroid therapy. The proposed daily dose is 4-8 mg/d per os for two weeks, followed by 2-4 mg/d for the duration of pregnancy. [58]

Based on the limited number of cases, it is hard to evaluate the benefit of fluorinated steroids in reversing or stabilizing first- or second-degree AV block, and decision to administer dexamethasone must therefore be weighed against the deleterious effects of prenatal corticosteroids. [136] Breur et al performed a meta-analysis of 93 fetal cases of CHB and concluded that dexamethasone was neither safe nor effective. [137]

Rein et al recently reported 6 cases of first degree AV block that were treated with fluorinated steroids. AV conduction normalized in all fetuses within 3-14 days, and none of them progressed to CHB or developed cardiomyopathy in the 1-6 year follow-up. [62]

However, a recent study that evaluated 116 cases of fetal AV block reported that these findings were in accord with the natural course of the disease. This study reported 3 cases of second degree AV block and one case of second degree with intermittent third degree AV block reverting to sinus rhythm spontaneously. [57]

Due to the rarity of this condition, a very large multicenter or even multinational, randomized, placebo-controlled trial would be necessary to evaluate the efficacy of treatment. An attempt by Friedman et al to conduct such a study failed because they were unable to secure the approval of the institutional review board within the necessary time frame. Furthermore, several women refused randomization because they were convinced that fluorinated steroids were the standard of care. [136]

Plasmapheresis

Plasmapheresis has also been suggested in the prophylactic treatment of women who have had a previously affected pregnancy. However, it has not proven to be effective and poses a considerable risk to the mother. [54]

Intravenous Immunoglobulin

The mechanism behind IVIG is increased elimination of maternal antibodies, decreased placental transfer and resulting reduction of inflammatory response and fibrosis in the fetal heart. [65] Due to the small numbers reported so far, the efficacy of this treatment has not been established.

Kaaja et al reported 8 cases of prenatal treatment with IVIG and prednisone to prevent recurrence of CHB in women who had previously delivered infants with

CHB. Seven of the 8 patients gave birth to a healthy child, while the eighth woman, who had refused treatment with prednisone, delivered a child with CHB. The treatment regimen was IVIG 1mg/kg at 16 and 18 weeks of gestation. Prednisone was started at 14 weeks of gestation at a dosage of 40 mg/d, which was tapered to 20 mg/d at 16 weeks and 10mg/d at 24 weeks, the dosage which was then administered for the remainder of pregnancy. The small number of patients limits the significance of this study. [138]

There is an ongoing trial for prevention of CHB in high-risk, pregnant women (positive anti-Ro/SSA and previous pregnancy with CHB). The proposed regimen is 0.4 g/kg administered at 12, 15, 18, 21 and 24 weeks of gestation. Enrolment is ongoing, and no data has been published to date. [65]

Direct fetal pacing

Direct fetal pacing has been attempted twice. As early as 1987, Carpenter describes ventricular pacing in a hydropic fetus with CHB. Although the placement of the lead was successful, the fetus died 4 hrs after the procedure. [139] In 1994, Walkingshaw reported an attempt at percutaneous transvenous pacing. Once again, it was possible to place the lead, but the fetus died shortly thereafter. [140]

In one case, a permanent pacemaker implantation was attempted by exteriorizing the fetus. This fetus also died following the procedure. [54,141]

Animal models have been described where in utero pacing has been successful. [142] Unfortunately, the complications are significant, and there have been no subsequent attempts to treat a fetus.

Outcome of children who were diagnosed with an arrhythmia in utero

Since fetal arrhythmias are associated with a high morbidity and mortality rate, this chapter will focus on two aspects of the long-term outcome in children who were diagnosed with an arrhythmia in utero:

- **Postnatal recurrence of the arrhythmia and the need for treatment**
- **Neurodevelopemental outcome in children who were diagnosed with fetal arrhythmia**

Mortality, postnatal recurrence and need for treatment

Depending on the underlying mechanism of arrhythmia, the mortality rate, rate of recurrence and need for postnatal treatment can vary greatly. The following chapter will therefore discuss each form of arrhythmia separately.

SVT

Overall mortality in SVT has been reported to be 8.9% [48]; mortality in hydropic fetuses with SVT can be as high as 37.5% [92]; 60% of deaths occur prenatally. Hydrops fetalis has been observed in 40.5% of cases. [48]

There is no consensus on the necessity of postnatal treatment of infants who do not display signs of persistent or recurrent arrhythmia. Prophylactic treatment is often prolonged for 6-12 months beyond the neonatal period. [48] Simpson et al showed that infants diagnosed with SVT prenatally required long-term treatment

with a median duration of 6 months in 57% of cases; in hydropic fetuses this number is even higher at 79% of survivors. [38]

For infants who are diagnosed with WPW-Syndrome, spontaneous resolution occurs by 1 year of age in 60-90%.

Postnatal control of the tachycardia can be achieved using direct current cardioversion (2 J/Kg) or antiarrhythmics (i.e. adenosine, digoxin, flecainide, amiodarone). The choice and dose depend on the drugs that were administered in the fetal period. [5]

AF

In AF, mortality does not differ greatly from SVT at 8.0% [48]; mortality in hydropic fetuses can be as high as 37.5%. [92] In contrast to SVT, only 20% of perinatal deaths attributed to AF occurred in utero. [48]

AF can be controlled by various drugs (digoxin, sotalol, amiodarone) or by direct current cardioversion. Spontaneous resolution of AF has been reported directly after birth. Once sinus rhythm is achieved, recurrence of AF is rare, and a “wait-and-see” approach is justifiable. [48] Lisowski et al reported prophylactic treatment in 58% of cases for a median duration of 7 months (range 3 weeks-12 months). Since then, the policy has been changed, and the current policy is not to treat prophylactically. [81]

Long VA-tachycardias: AET, PJRT

Since tachycardias with a long VA-interval are very rarely diagnosed in the fetal period, no definite numbers exist concerning mortality and late morbidity. However, there have been reports of an increased risk of mortality and morbidity, probably due to the fact that these arrhythmias are hard to control, both pre- and postnatally. Jaeggi et al reported that all survivors of the long VA group required

postnatal treatment and had recurrences of tachycardia despite prophylaxis with digoxin. [28] A study by Oudijk et al confirmed these findings; all of the 4 fetuses who had been diagnosed with PJRT in utero had recurrences of tachycardia in infancy and required more than one antiarrhythmic drug. Early ablation of the accessory pathway was recommended as a form of treatment if signs of congestive heart failure develop. [143]

CHB

Mortality in isolated CHB is very high and can reach up to 50% if both perinatal deaths (25-43%) [144, 58] and late mortality from cardiomyopathy are taken into account. [144] Mortality in hydropic fetuses can reach up to 100%. Only 73% of live-born fetuses reached 10 years of age. Risk factors for death are hydrops fetalis, endocardial fibroelastosis, delivery at < 32 weeks of gestation and a postnatal ejection fraction of ≤ 40%.

Since autoimmune mediated CHB causes irreparable damage, 69% of patients will require pacemaker implantation by adolescence. [145]

Neurodevelopmental outcome in children who were diagnosed with fetal arrhythmia

The success rate of implemented therapy in cases of fetal arrhythmia is generally measured by achievement of rhythm control and survival; few studies focus on the long-term neurodevelopemental outcome. [144, 146-150]

Neurological morbidity has been described in many reports of fetal rhythm disturbances and is most likely due to dysfunction of the cerebrovascular autoregulation in hemodynamically compromised fetuses. Cerebral autoregulation maintains a constant cerebral blood flow over a broad range of perfusion pressures by pressure-dependent activation of smooth muscle cells in the cerebral arterioles, inducing either vasoconstriction or vasodilatation. A pressure-passive

phenomenon results if autoregulation is disturbed, as cerebral blood flow increases or decreases with every change in mean arterial pressure. The fetus is exposed to ischemia in even moderate hypotension and suffers an increased risk of intracranial hemorrhage in even moderate hypertension. These findings have been associated with severe compromise of hemodynamics, as only found in hydropic fetuses.

Short recurrences of the arrhythmia with incomplete control of fetal heart rate may also contribute to the development of cerebral complications. Sudden changes of heart rate occurring during impaired cerebral autoregulation may have serious consequences for the sustenance of constant cerebral blood flow, again leading to periventricular ischemic lesions or hemorrhage. Swift and complete control of the arrhythmia should therefore be the highest therapeutic priority. [146]

Schade et al also proposed gestational age at presentation of the arrhythmia as a risk factor in the intrauterine onset of cerebral morbidity. In a study evaluating neurological outcome in 7 patients with fetal tachyarrhythmia, gestational age at presentation was lower in those who developed cerebral complications later (26.9 vs. 30.1 weeks). [146] Two other studies, which included a total of 55 children, were unable to support this finding. [147,148]

Tachyarrhythmias

There are few studies concerning the neurodevelopemental outcome of children who had been diagnosed with a tachyarrhythmia in utero. Patient numbers are small in most cases, and methods of assessment are not always specified or standardized, which restricts the ability to compare or draw definite conclusions. Neurodevelopmental morbidity has been reported in 1.6-16% of cases. [38, 149,]

In the largest study of fetal tachycardias, Simspon and Sharland reported neurological sequelae in only 2 of 127 (1.6%) fetuses, both of which were hydropic in utero. One child had mild hemiplegia, and the other one had severe neurodevelopmental delay. [38]

Oudijk et al reported the neurodevelopmental outcome of 11 fetuses who had suffered from tachyarrhythmias. In 8 cases, the outcome was good, and the development was normal. Three patients proved to have neurological complications. One of these three had complications that were severe enough to withhold further treatment, which lead to the infant's death on the second day of life; the second patient had a marked mental retardation, secondary to severe periventricular echogenicity; and the third patient showed mild hemiplegia with normal cognitive function and a good quality of life, although cranial ultrasound had shown parenchymal hemorrhage, which presented as a porencephalic cyst. Overall, the outcome exceeded expectations, with 73% of cases showing normal neurodevelopemental outcome. [147]

Lopriore et al reported normal neurodevelopmental outcome in 28 children who had suffered from either SVT or AF. Neurodevelopmental assessment was normal or even above average in all of them. It should be noted, however, that hydrops fetalis was only present in 39% of the fetuses affected by SVT and was not specified for fetuses affected by AF. [148]

In a study conducted by Boldt et al, neurological impairment was much higher in the SVT and AF group; 5 of 31 children(16%) displayed neurologic injury at follow-up. [149]

Special care must be taken when comparing results. Discrepancy may be partly due to different methods, selection criteria, and definitions of neurodevelopmental impairment. [148]

In conclusion, neurodevelopmental outcome is good in most cases, especially when the severity of the condition is taken into account. Impaired outcome is mainly associated with hydropic fetuses. Intrauterine rhythm control is of the utmost importance. Premature delivery should be the last resort, since it adds all the complications associated with prematurity to the already compromised state of the newborn.

Atrioventricular Block

There have only been a few studies evaluating neurodeveolpmental outcome in fetuses that were diagnosed with CHB. Most of the data focuses on survival and the need for pacemaker therapy.

Brucato et al evaluated 13 children with CHB, 11 of whom had been exposed to high doses of dexamethasone in utero. No negative effects on neuropsychological development were found. It has to be pointed out that only 2 fetuses displayed signs of cardiac failure in utero. [150]

Breur et al assed the long-term outcome in 10 fetuses with CHB and hydrops fetalis. The outcome was normal in all survivors (5/10). Mortality rate was extremely high (50%). There were 3 intrauterine deaths and 2 deaths due to dilated cardiomyopathy (at 9 months and 4 years). [144]

In a study conducted by Lopriore et al, which included CHB associated with structural heart disease, there were no patients with autoimmune associated CHB in the group of survivors. [148]

It is hard to draw conclusions from such small numbers, especially when methods of assessment are not always specified and rarely standardized. A big mulitcenter (or even multinational) study is needed to examine neurodevelopmental outcome in fetuses with CHB.

Discussion and Conclusion

The past two decades have brought substantial progress in both technology and knowledge in the field of maternal-fetal medicine. As therapeutic possibilities have also evolved significantly, the questions often posed are: which are the benefits and drawbacks of the different approaches, and which should be chosen?

Due to advances in research, the underlying electrophysiological mechanism of fetal arrhythmias can now be precisely diagnosed in the prenatal stage, thereby enabling accurate therapy.

The single most important predictor of fetal outcome is the presence or development of fetal hydrops. Conversion to sinus rhythm in the presence of hydrops is more difficult and hydropic fetuses are at a greater risk for adverse outcome, be it intrauterine demise or postnatal neurological impairment.

The most important conclusion revealed by a careful analysis of the reports published in this field is that there are many different therapeutic approaches that produce similar results. The quest for a “silver bullet”, a single drug that will convert all arrhythmias, is futile, since no such drug exists. Different underlying electrophysiology entails different therapeutic approaches for each form of arrhythmia. A fast, accurate diagnosis is therefore the key to a good outcome.

Fetal arrhythmias should be treated using a multidisciplinary approach, and therapy protocols should therefore be conceptualised in consultation with obstetricians, neonatologists and pediatric cardiologists. Each centre is bound to favour the drugs with which it has had the most experience.

Nonetheless, a systematic review of the available literature has shown that digoxin is still undeniably the drug of choice in non-hydropic fetuses with a short VA interval tachycardia. It is a drug that has been widely tried in the gestational setting

with good conversion rates and adverse effects that are well tolerated by both mother and fetus. However, in the state of fetal hydrops, digoxin does not cross the placental barrier readily enough to provide adequate treatment, therefore digoxin monotherapy is not advisable in hydropic fetuses.

It is also clear that treatment is preferable to observation in most cases, since hydrops fetalis can develop very quickly (less than 10 days), even in intermittent forms of tachyarrhythmia. Delivery should only be contemplated if the fetus is near term. Preterm delivery is associated with an adverse outcome, since all the complications of prematurity are added to the compromised state of the fetus. Most publications advocate delivery after the 35th gestational week.

Controversy starts when second-line treatment options or treatment options for hydropic fetuses with SVT are discussed. Most centres advocate either flecainide, sotalol or a combination of either of these drugs with digoxin. Amiodarone is also a very potent antiarrhythmic, and numerous studies have proven its efficacy in fetal arrhythmias. However, it remains unpopular, due to its long half-life, the induction of hypothyroidism and the fact that it has been associated with neurodevelopmental delay. Considering the fact, that several studies, concerning both sotalol and flecainide, have reported sudden fetal deaths that were possibly caused by proarrythmia, neurodevelopmental delay, caused by amiodarone, that has been described as reminiscent of the Non-verbal Learning Disability Syndrome seems to be an acceptable adverse effect. Several recent studies have advocated amiodarone as a second- or even first-line therapy. [151, 152]

In hydropic fetuses, flecainide or sotalol should always be combined with digoxin, in order to prevent the negative inotropic effects of these drugs from further compromising the hemodynamically challenged fetus. If digoxin monotherapy fails in the non-hydropic fetus and either of these antiarrhythmics is selected as a second-line treatment, combining them with digoxin is sensible to benefit from possible potentiation. When opting for amiodarone, digoxin doses must be reduced by half because of drug interaction.

In cases of AF in which digoxin monotherapy has failed or the fetus displays signs of hydrops, sotalol should be the drug of choice with digoxin. It has shown higher conversion rates than fleicainide or amiodarone, either alone or in combination with digoxin.

Tachycardias with a long VA interval are often incessant and hard to treat because the underlying arrhythmia is often PJRT or AET. Digoxin monotherapy is not very successful in converting these two types of arrhythmias, and a combination with another antiarrhythmic agent should therefore be employed as first-line therapy.

Direct fetal therapy should only be chosen in refractory cases because 60-100% of fetal tachycardias can be converted to sinus rhythm when digoxin, flecainide, sotalol, amiodarone or some combination of these drugs is administered transplacentally. [7] The recurrent risk of an invasive procedure is not justifiable if non-invasive therapeutic options have not been exhausted. However when non-invasive approaches have failed direct fetal therapy has been proven to be very effective.

The treatment protocols suggested in this thesis were drawn up in reference to the current literature and leave the choice of antiarrhythmic, (flecainide/sotalol or amiodarone) to the treating physician.

For the treatment of fetal CHB there are not as many options, and the main question is whether to treat lesser degrees of AV-block with fluorinated steroids or not. Considering that mortality in CHB caused by maternal antibodies can reach 50% (when counting late mortality due do cardiomyopathy), Treatment with betamethasone is justified. Due to the small numbers of reported cases, there is still some debate as to whether or not the administration of betamethasone or dexamethasone actually improves outcome. The same applies to sympathomimetics, which are often advocated if the ventricular rate is below 55-60 bpm, the adverse effects are not comparable to the benefit, given the administration proves to be effective.

Although fetal pacing could potentially be the most effective treatment for CHB, research in this area has not yet developed enough to offer viable solutions. While there has been some success in animal models, further research is necessary to develop a functioning therapeutic concept for the human fetus.

Fetal arrhythmias are relatively rare, affecting only 1-2% of all pregnancies. Nevertheless, this is common enough that any obstetrician could be confronted with an arrhythmia during a routine obstetric visit. Referral to an experienced centre, accurate diagnosis and fast initiation of appropriate therapeutic measures in a multidisciplinary approach are the keys to a good outcome.

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