Fetal Tachycardia

Diagnosis and treatment

and

The fetal QT interval in hypoxia

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Proefschrift

Ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de Rector Magnificus, Prof. Dr. W.H. Gispen ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op dinsdag 18 maart 2003

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Martijn Alexander Oudijk
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Mi piaccion quelle cose
che han sì dolce malia,
che parlano d'amor, di primavere;
che parlano di sogni e di chimere,
quelle cose che han nome poesia.
Lei m'intende?

Voor mijn ouders

Table of contents

Chapter 1

General introduction

The fetal heart rate has been utilized as a method of determination of fetal well-being since the late 19th century, both antenatally as well as intrapartum. Prenatal detection of disorders in fetal heart rhythm should be examined in a specialized center as they may be life-threatening. Methods for detailed examination of the fetal heart rhythm include Doppler and M-mode echocardiography and fetal magnetocardiography (FMCG). These methods are described in Part I of this thesis for the purpose of the detailed diagnosis of fetal tachycardia. Aspects of the consequences of fetal tachycardia, the necessity for prenatal treatment and the choice of specific drugs are discussed in *Part I*.
Evaluation of the fetal heart rhythm by means of a direct electrode is possible during labour through an electrode attached to the presenting fetal part. A single lead fetal ECG (FECG) is derived and specific intervals on the ECG can be investigated. Changes in RR intervals and in T waves are used clinically to detect fetal hypoxia and asphyxia. The QT interval, a measure of repolarization and cardiac electrical stability, may provide additional information on the physiology and condition of the fetal myocardium. The influence of intrapartum hypoxia on the QT interval of the FECG is presented in Part II of this thesis.

Part I
Fetal Tachycardia

The normal fetal heart rate ranges are approximately 120-160 bpm at 30 weeks and 110-150 bpm at term [1, 2]. Frequencies up to 170 bpm are considered mildly abnormal, whereas overt tachycardia is usually defined as a heart rate exceeding 170 bpm [1] or 180 bpm [3]. Fetal tachycardia was first recognized in 1930 by Hyman et al. [4] and is a condition that occurs in 0,4-0,6 % of all pregnancies [5].
In the extrauterine situation, rhythm disorders are usually detected by a surface ECG. Atrial depolarization, resulting in atrial contraction, is shown as the P wave on the ECG. The electrical impulse is delayed in the atrioventricular (AV) node and consequently conducted to the ventricles, where the depolarization of the ventricles results in the QRS complex. Repolarization of the ventricles results in the T wave.
However, attempts to derive an adequate fetal ECG have thusfar failed, due to interference from the maternal ECG. In the absence of a reliable fetal ECG, other modes of investigating the fetal cardiac rhythm are being used. The development of Doppler and M-mode echocardiography have greatly improved the knowledge on rhythm disorders in the fetus [6-9]. The real time image of the fetal heart, motions of the cardiac

chambers and flow dynamics can actually be considered a mechanical and dynamic ECG [3]. Fetal tachycardias are thus divided by M-mode echocardiography in supraventricular tachycardia (SVT), atrial flutter (AF) and ventricular tachycardia (VT), depending on the site of origin. This will be further discussed in **chapter 2 and 3**. A detailed examination of the M-mode echocardiography however, can result in further differentiation in type of tachycardia.

Aim 1

Further delineation of fetal tachycardia by detailed examination of M-mode echocardiography: diagnosis of persistent junctional reciprocating tachycardia in the fetus (Chapter 3)

The development of new techniques in the diagnosis of fetal tachycardia is ongoing, with fetal magnetocardiography as its most recent and promising addition. Fetal magnetocardiography is a technique that records the magnetic field generated by the electrical activity of the fetal heart [10]. Detection occurs non-invasively by sensors cooled by liquid helium positioned several centimeters above the maternal abdomen in a magnetically shielded room. As the maternal heart generates magnetic activity as well, a maternal ECG is recorded simultaneously and substracted from the FMCG. This way, an averaged one lead FMCG is obtained which allows for a more detailed differentiation of the type of tachycardia [10-12].

Aim 2

Diagnosis of specific types of fetal tachycardia by fetal magnetocardiography (Chapter 2)

Consequences of fetal tachycardia

Fetal tachycardia may hemodynamically compromise the fetus, through ventricular dysfunction and dilatation, secondary atrioventricular valve regurgitation and fetal hydrops. This may ultimately lead to fetal death. Congestive heart failure is usually defined if fluid accumulation exists in the fetal body, such as pericardial effusion, pleural effusion, ascites or skin edema. Fetal hydrops is usually defined if fluid accumulation exists in 2 or more of these compartments. It is unclear which factors play a role in the occurrence of hydrops and it is difficult, if not impossible, to determine the likelihood of the development of hydrops in a particular case. These factors and their possible use in clinical practice will be discussed in more detail in **chapter 4 and 5**.

Fluid accumulation occurs in the amniotic fluid compartment as well, resulting in polyhydramnios. This predisposes the fetus to preterm delivery and neonatal complications of prematurity [13].
Fetal tachycardia may also result in neurological damage [14-17]. The cerebrovascular autoregulation that ensures adequate cerebral perfusion during postnatal life does not function adequately in the distressed newborn and most probably also not in distressed fetuses. A disturbance in rhythm resulting in hemodynamic compromise predisposes the fetus to cerebral ischemia in periods of moderate hypotension and to intracranial hemorrhage in periods of moderate hypertension [15]. Although this has been described in several case-reports, little is known on the outcome of the group hydropic fetuses as a whole.

Aim 3
Neurological follow-up of children who were treated for fetal tachycardia complicated by hydrops (Chapter 4)

Treatment
The decision to initiate pharmacological intervention in the case of fetal tachycardia depends on several factors and must be weighed against possible maternal and/or fetal adverse effects inherent to the use of antiarrhythmics. Although prenatal treatment in advanced cases of fetal tachycardia is widely accepted, the necessity for treatment in milder cases is still a point of discussion [18, 19]. The necessity for treatment will be discussed in **chapter 5**. However, in the absence of reliable predictors of adverse outcome of fetuses, most centers have opted for initiation of treatment as soon as the diagnosis of fetal tachycardia has been established.
Several treatment protocols have been developed, in which different modes of pharmacological intervention, indirect (transplacental, through oral or intravenous maternal therapy) or direct (intra-umbilical, intra-amniotic, intra-peritoneal and intra-muscular fetal therapy) have been proposed.

Aim 4
Review of the literature on pharmacological intervention of fetal tachycardia (Chapter 5)

The optimal treatment protocol however, has not yet been designed and the search for other effective drugs continues. Sotalol is a potent Bèta-blocking agent with additional class III antiarrhythmic properties and a mild to absent negative inotropic effect [20, 21]. It has proven to be

safe and efficacious in the treatment of tachycardia in adulthood [22, 23] and infancy [24-26]. Based on these findings, we hypothesized that sotalol could be a safe and effective antiarrhythmic agent for the treatment of various forms of fetal tachycardia. The success of transplacental treatment of fetal tachycardia depends largely on the transplacental passage, maternal pharmacokinetics and pharmacodynamics of the administered drug, influenced by various physiologic changes in pregnancy. These properties of sotalol are therefore also investigated.

Aim 5
To investigate the transplacental pharmacokinetics, pharmacodynamics, effectiveness and safety of sotalol in the treatment of fetal tachycardia (Chapter 6 and 7)

Part II
Fetal ECG in labour, aspects of the intrapartum QT interval

The evaluation of the electrophysiology of the fetal heart through a direct electrode is for the first time feasible during labour. Fetal ECG (FECG) analysis has formed the basis for electronic fetal monitoring for decades. So far the FECG assessment has been limited to RR interval measurements only. Among other time constants, the relationship between PR and RR intervals has also been extensively investigated. A PR shortening with RR lengthening is present during clinical FHR decelerations and bradycardia [27] and experimental hypoxia [28]. Clinically, these measurements are not of additional value [29]. The morphology of the FECG including the ST segment and T wave configuration has been shown to provide specific and clinically useful information of fetal cardiovascular adaptation to experimental hypoxia and as an adjunct to standard FHR monitoring in labour [30-32].
The last interval of the ECG complex, the QT interval, has been the subject of many studies in the neonate, during infancy and adulthood, as a prolonged QT interval, either genetic or acquired, predisposes to ventricular tachycardia and to recurrent (pre-) syncope or sudden cardiac death [33-36]. The genetic origin of this arrhythmia lies in malfunctioning myocardial ion channels as a result of mutations in genes encoding these ion channels. The aqcuired form may be the result of drug therapy, myocardial infarction or cardiomyopathy. The QT interval is a dynamic parameter and is subject to different physiological processes. Many studies have shown changes in its properties in situations of

exercise, stress, infection and heart failure among others [37-43]. The dynamics of the QT interval during labour are unknown as the technology to measure this interval was not available until recently. The development of the STAN® technology, designed to perform analysis of the fetal ST waveform to improve fetal surveillance, has provided us with the means of evaluation of specific features on the fetal ECG, including the QT interval. We hypothesized that the QT interval on the FECG, representive of repolarization, could provide information on the physiology of the fetal myocardium and may provide additional information on the fetal myocardial adaptation to the ultimate stress of labour [44].

Aim 6
The evaluation of the effects of hypoxia and asphyxia on the fetal QT interval (Chapter 9 and 10)

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Part 1
Fetal Tachycardia

Diagnosis of Fetal Tachycardia

Chapter 2

Fetal Tachycardia

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Maria J. Peters
Gerard H.A. Visser
Erik J. Meijboom

Introduction

Fetal tachycardia, first recognized in 1930 by Hyman et al [1], is a condition occurring in approximately 0,4-0,6% of all pregnancies [2]. The necessity of therapeutic intervention in this condition is still a matter of discussion focused on the natural history of the disease. The spectrum of opinions varies from non-intervention [3-5] based on a number of cases in which the tachycardia subsided spontaneously [6], to aggressive pharmacotherapeutic intervention [7, 8] based on reports of deterioration of the fetal condition ultimately ending in significant neurological morbidity [9-11] or fetal demise [12-14]. Prenatal treatment through indirect, maternally administered drug therapy seems to be the preference of most centers [15-21].

The choice of the specific pharmacotherapeutic agents and the chances on success of therapy depend largely on the type of tachycardia. The determination of the type of tachycardia is therefore of the utmost importance [20, 22], however, the available diagnostic armamentarium is limited. The most widely used method of diagnosis of fetal tachycardia, M-mode echocardiography, provides a time related documentation of function of the various cardiac structures. The current subdivision in supraventricular tachycardia (SVT), atrial flutter (AF) and ventricular tachycardia (VT) derived from M-mode echocardiography is not sufficient enough for differentiation according to the electrophysiologic mechanism. Several attempts have been made in the last years to increase the accuracy and reliability of M-mode echocardiography by measurement of atrioventricular (AV) and ventriculoatrial (VA) intervals [23, 24] and the addition of Doppler echocardiography [25]. New methods registrating the actual electrophysiologic events in the fetus are in development including noninvasive techniques such as magnetocardiography [26] and direct intrapartum techniques such as the ST-analyzer (STAN®, Neoventa Medical, Gothenburg, Sweden) [27, 28]. Characteristics of the most common types of fetal tachycardia are described and examples of M-mode echocardiography and FMCG are presented.

Definitions of tachycardia

The normal fetal heart rate ranges are approximately 120-160 bpm at 30 weeks and 110-150 bpm at term [29, 30]. Frequencies up to 170 bpm are considered mildly abnormal, whereas overt tachycardia is usually defined as a heart rate exceeding 170 bpm [29] or 180 bpm [22]. These rhythm abnormalities of the fetus are usually noticed at routine prenatal visits. Fetal echocardiography is used to exclude structural cardiac and used to position the M-mode sampling line to intercept both the atrial and ventricular walls. The relationship between peak atrial and ventricular systolic excursions currently provides a division in SVT, AF and VT.

Fetal magnetocardiography, a technique recording the magnetic field generated by the electrical activity of the fetal heart [26], offers a more precise delineation of the fetal electrophysiology. Detection occurs non-invasively by sensors cooled by liquid helium positioned several centimeters above the maternal abdomen in a magnetically shielded room. As the maternal heart generates magnetic activity as well, a maternal ECG is recorded simultaneously and substracted from the fetal MCG. This way, an averaged one lead fetal MCG is obtained and allows for a more detailed differentiation of the type of tachycardia.

Premature Atrial Contractions

Premature atrial contractions (PAC's) do not qualify as a form of fetal tachycardia, and are associated with good outcome. However, in approximately 0,4 % of cases, it may progress to runs of tachycardia and even become persistent. It is therefore recommended that these patients are monitored weekly by doptone to exclude the presence of runs of tachycardia [12, 16]. M-mode echocardiography will show premature atrial contractions not followed by a ventricular contraction and a subsequent 'drop' in heart rate *(Figure 1)*.

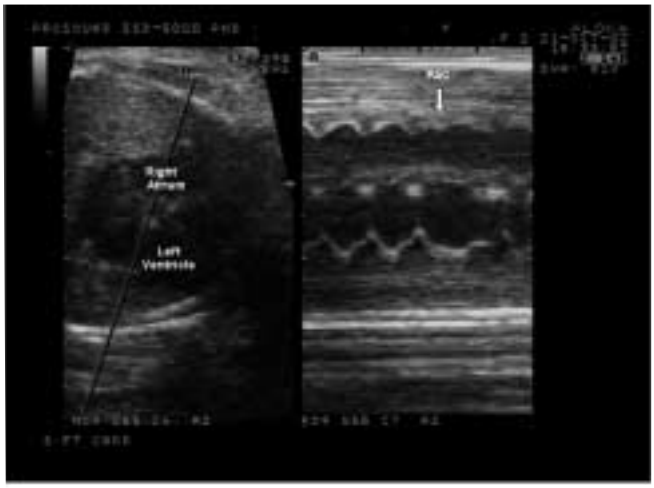

Figure 1

M-mode echocardiography of a premature atrial contraction (PAC).

The FMCG will show a premature P-wave not followed by a QRS complex *(Figure 2)*.

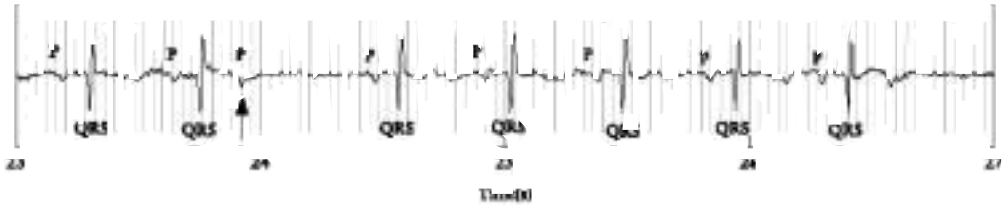

Figure 2

FMCG of a PAC (black arrow).

Atrial Flutter

AF is a condition that accounts for approximately 21 – 50 % of fetal tachycardia and may be associated with structural abnormalities [14, 21, 31]. It is defined as an atrial rate ranging from 250 up to 500 bpm with a fixed or variable AV block, as the AV-node is not able to conduct every

contraction of the atrium which results in a 2:1 or 3:1 conduction to the ventricles. Rarely in some cases paroxysmal 1:1 conduction is seen. It may be either paroxysmal or incessant in nature and is reported to be associated with fetal hydrops in 7 – 43 % of cases [14, 18, 31, 32]. The most common electrophysiologic mechanism in AF is a re-entry circuit confined to the atrium. M-mode echocardiography will show typical atrial contractions that are followed by ventricular contractions every 2 or 3 atrial contractions *(Figure 3)*.

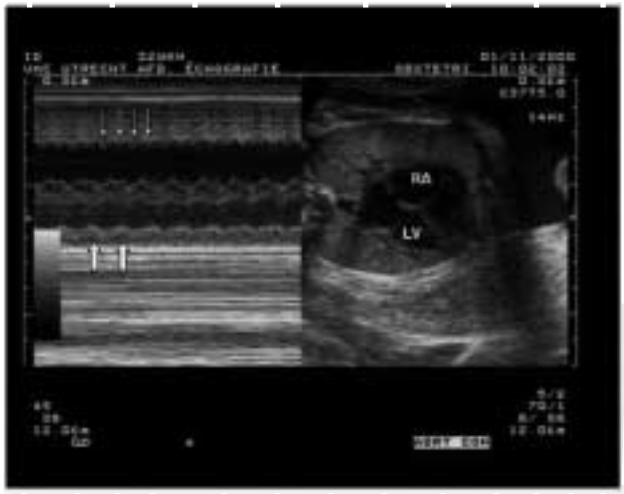

Figure 3

M-mode echocardiography of AF. Flutter contractions of the atrium are indicated by the small arrows; atrioventricular conduction is 2:1 and ventricular contractions are indicated by the large arrows. (RA = right atrium, LV = left ventricle)

FMCG will show typical flutter waves (P-waves) followed by QRS complexes every 2-3 P-waves *(Figure 4.1)*.

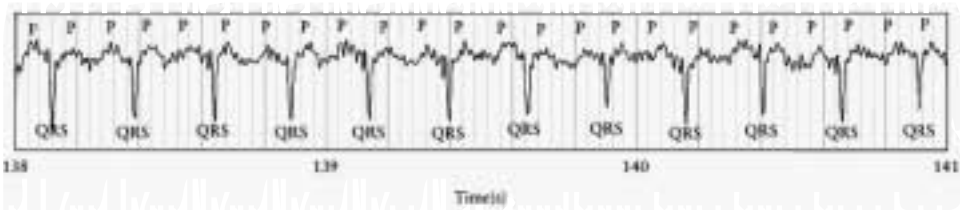

Figure 4.1

Raw FMCG trace of atrial flutter with 2:1 conduction.

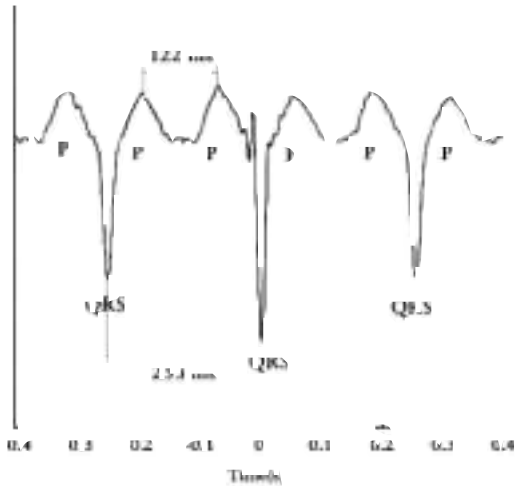

Figure 4.2
Averaged FMCG trace of atrial flutter with 2:1 conduction.

Transplacental pharmacological intervention with digoxin is reported to be successful in 45 % [31] , with sotalol 63 %, reaching 79 % after the addition of digoxin [21].

Supraventricular tachycardia

SVT is reported to account for 47 – 68 % of cases of fetal tachycardia [14, 18, 21] and is associated with a low percentage of structural abnormalities in 2 % of cases. It is defined by a 1:1 atrioventricular conduction in which the atrial contraction precedes the ventricular contraction. Heart rates in SVT most commonly range from 200-300 bpm, is either paroxysmal or incessant in nature and associated with fetal hydrops in 36 - 64 % [14, 33]. The condition has several different underlying electrophysiologic mechanisms, such as re-entry using an accessory atrioventricular connection (AVRT), which may be either apparent or concealed. Other possibilities include primary atrial tachycardias and re-entry within the AV node [34].

The diagnosis of these specific types of fetal tachycardia is difficult, if not impossible, with the most widely used current technology, M-mode echocardiography. As mentioned in the introduction, several studies have been conducted to allow for a more specified diagnosis using Doppler and M-mode echocardiography. These techniques are based on the relationship in time between atrial and ventricular wall excursions on M-mode, and flow patterns over the AV and semilunar valve orifices. In most re-entry tachycardias, conduction through the accessory connection is fast, as in the Wolff-Parkinson-White syndrome (WPW). This results in a short RP interval on the postnatal ECG, comparable to a short VA interval on M-mode (*Figure 5.1*). In several patients, slow conduction is observed in the accessory pathway, as in Persistent Junctional Reciprocating Tachycardia (PJRT) resulting in a long RP interval on the ECG, comparable to a long VA interval on M-mode echocardiography (*Figure 5.2*). In the literature there has been one case diagnosed as JET by Doppler echocardiography [35]. It is extremely rare and we have not encountered JET in the prenatal situation at our center.

Figure 5.1

M-mode echocardiography of a SVT with a short VA interval. First white line placed on the peak excursion of the left atrium wall, second line placed on the peak excursion of the right ventricle wall, third line on the consecutive peak atrial wall excursion. The AV interval is markedly longer than the VA interval.

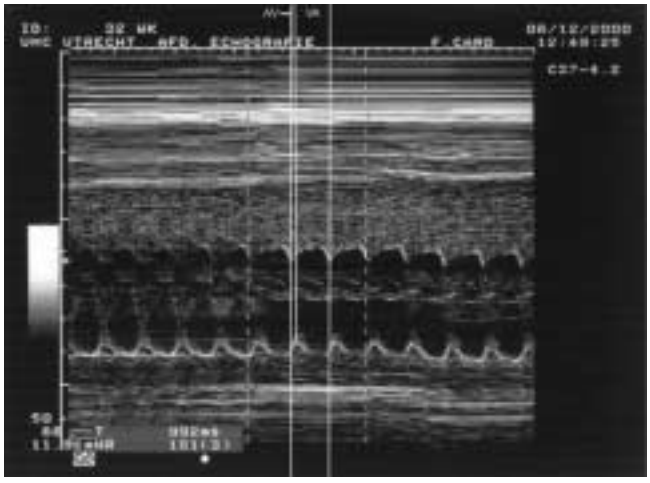

Figure 5.2

M-mode echocardiography of a SVT with a long VA interval.

The detailed electrophysiological events however, are irretrievable by M-mode echocardiography. Specific types of fetal tachycardia have been detected and published using FMCG [36-38]. A more detailed configuration, comparable to the postnatal ECG is obtained. An example of this category of fetal SVT's is shown in *Figure 6*.

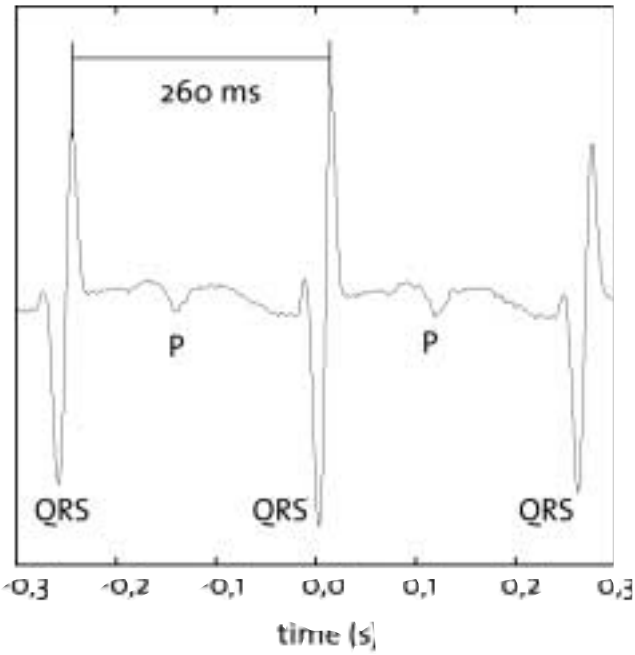

Figure 6

FMCG of a fetal SVT, the RR interval is 260 ms, FHR = 231 bpm

The electrophysiologic events are clearly defined in this situation, however, a precise diagnosis is still debatable. The SVT shown in *Figure 6* for instance, may be AVRT using a concealed accessory pathway, but could also be attributed to represent a PJRT.

Ventricular Tachycardia

VT in the prenatal situation is rare and has only been reported occasionally in the international literature [5, 16]. It is usually paroxysmal in nature and outcome depends on the electrophysiologic mechanism. Of the utmost importance is the diagnosis of the congenital Long QT syndrome (LQTS). The origin of this arrhythmia lies in malfunctioning myocardial ion channels as a result of mutations in genes encoding these ion channels. It is characterised by prolongation of the QT interval and the occurrence of polymorphic ventricular arrhythmia (such as torsade de pointes). Patients with the LQTS are predisposed to ventricular fibrillation and sudden death [39, 40]. The prenatal diagnosis is focused on fetuses of mothers with prolonged QT syndrome to document the possible presence of this syndrome in the fetus. In addition, in fetuses pre-

senting with (baseline) bradycardia or intermittent ventricular tachycardia of the torsade de pointe type, the diagnosis of LQTS must be considered as well, as spontaneous mutations have been reported. The suspicion of fetal LQTS may be raised in case M-mode echocardiography shows (baseline) bradycardia varying from 60-110 bpm and intermittent ventricular tachycardia in which there is atrioventricular dissociation. FMCG shows a prolonged QT interval (*Figure 7*), and the possible presence of intermittent VT [38].

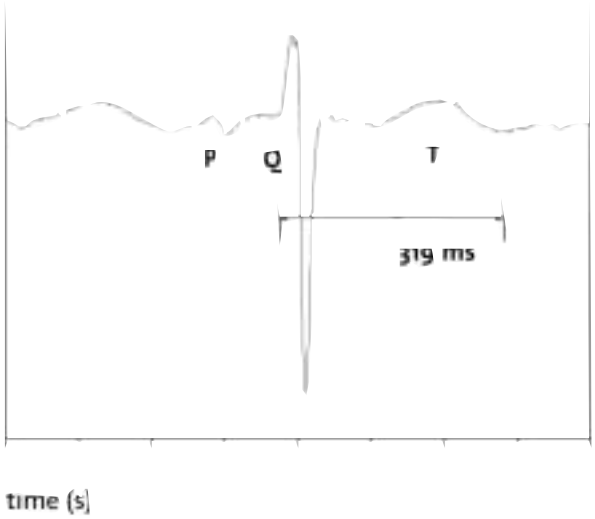

Figure 7
The QT interval is 319 ms, RR interval is 430 ms, QTc interval is 486 ms.

A prolonged QT interval may be detected during labour with STAN® (*Figure 8*) and identify fetuses predisposed to LQTS. A postnatal ECG is warranted in these cases to confirm these findings during labour.

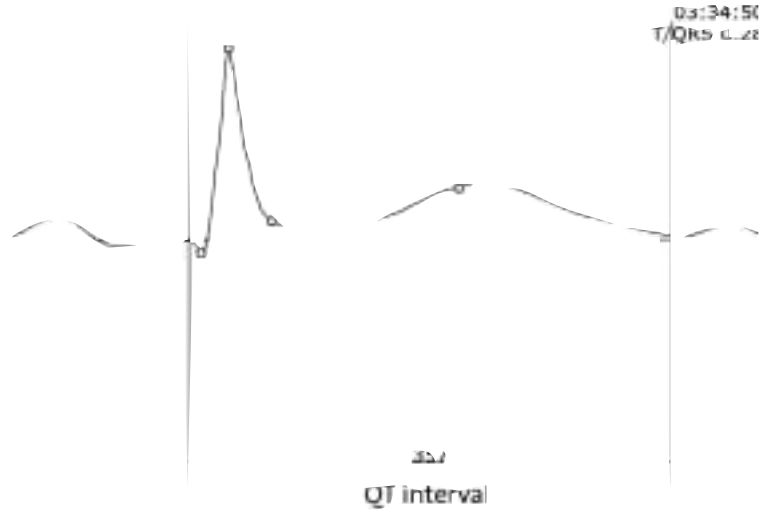

Figure 8

Fetal ECG during labour. The QT interval at 120 bpm is 357 ms, corresponding to a QTc interval of 504 ms.

Discussion

Fetal tachycardia is a rare disorder, in which difficulties are encountered in the diagnosis of the exact underlying electrophysiological mechanism and is therefore probably underreported.

The spectrum of pathologic symptomatology varies from an infrequent paroxysmal tachycardia to a persistent form, which may deteriorate in fetal hydrops, neurological morbidity and even fetal demise. The presence of fetal tachycardia therefore deserves more attention and requires a specialized evaluation to define its electrophysiologic diagnosis.

Fetal atrial flutter is a frequently encountered form of fetal tachycardia and can be well diagnosed by either M-mode echocardiography or FMCG. This type of tachycardia has all the symptomatic properties described above and therefore deserves pharmacological intervention. Numerous agents have been described, but in our opinion sotalol medication seems to provide the best clinical result [21]. Fetal SVT remains the most complicated form of fetal tachycardia, both in diagnosis as in treatment. The difficulty in delineating an accurate diagnosis of the specific form and the relative therapy resistance of the various subtypes of this tachycardia, for instance PJRT, makes the deve-

lopment of an optimal treatment protocol complicated.
The most infrequent encountered form of tachycardia is fetal VT, however, if present, it has very serious implications for the fetus. In utero management is complicated and yields a limited success but it is also predictive for an uncertain future after birth. Improved prenatal diagnostic techniques may support a better understanding of the pathophysiology, but does not necessarily result in an improved outcome.

Implications of technical developments for prenatal diagnosis and treatment

FMCG is still in an ongoing phase of development, but it is clear that specific subtypes of tachycardias can be diagnosed by the technique and its development will undoubtedly have a great impact on the classification of fetal tachycardias. The task ahead contains several aspects:

- The classification and identification of the characteristics of each specific subtype of tachycardia in the prenatal period. Important features are the risk on congestive heart failure, development of fetal hydrops, response to different antiarrhythmics and outcome. Normal values of the intervals on the MCG in the fetus will have to be obtained from large studies, to allow for the accurate diagnosis of for instance the long QT syndrome.
- Comparative studies on the treatment of specific subtypes of fetal tachycardia will have to be performed, by preference in the setting of multicentre trials, in order to identify the optimal antiarrhythmic agent for each subtype of tachycardia.
- The development of a specific treatment protocol for each specific subtype of fetal tachycardia.

In addition to FMCG, the interpretation of the fetal ECG in labour (STAN®) may provide the clinician with valuable information on the electrophysiology of the fetal heart. Besides its purpose in fetal monitoring, it may have additional value in identifying fetuses with a predisposition to the LQTS.
Studies on these new techniques will hopefully result in a further reduction of morbidity and mortality in the field of fetal tachycardia.

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Chapter 3

Persistent Junctional Reciprocating Tachycardia in the Fetus

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Abstract

Background

Persistent junctional reciprocating tachycardia (PJRT) tends to be a persistent arrhythmia and requires aggressive therapeutic management. Diagnosis and management of this infrequently occurring tachycardia in the fetus at an early stage is of importance for the prevention of congestive heart failure (CHF).

Methods

A retrospective study of four fetuses with supraventricular tachycardia (SVT) of the PJRT type was performed.

Results

All had sustained SVT (mean of 228 bpm) at a mean gestational age of 34^{+5} weeks, with CHF present in two. Three fetuses had prenatal characteristics of PJRT on M-mode echocardiography with a ventriculo-atrial (VA)/ atrio-ventricular ratio >1 on M-mode echocardiography suggesting a slow conducting accessory pathway. All four fetuses had postnatal confirmation of the diagnosis. Transplacental treatment with flecainide was effective in one patient, sotalol as a single drug or in combination with digoxin was partially effective in the remaining three. Two developed sinus rhythm, with short intermittent periods of tachycardia and decreasing signs of CHF, one case showed a minimal decrease in heart rate. Oral propranolol therapy converted two patients postnatally, in the remaining two patients radiofrequency ablation was performed at the age of 5 months and 6 years.

Conclusions

The characteristics of our prenatal PJRT cases include a sustained heart rate not exceeding 240 bpm with a long VA interval, presence of CHF and therapy resistance. Transplacental treatment should be initiated, possibly with a combination of sotalol and digoxin in nonhydropic cases, or flecainide, especially in case of fetal hydrops. Pharmacological therapy is to be preferred postnatally, but radiofrequency ablation seems indicated in therapy resistant cases with CHF, even in the first months of life.

Introduction

Persistent or permanent junctional reciprocating tachycardia (PJRT), originally described by Coumel et al. in 1967 [1], is an infrequent form of re-entrant supraventricular tachycardia (SVT) in which retrograde conduction occurs via a slowly, decrementally conducting concealed accessory pathway, frequently located near the coronary sinus orifice. The electrocardiogram (ECG) is characterized by an often incessant tachycardia at a rate of 120-250 beats per minute (in infancy and adulthood) with inverted P waves in the inferior leads and a P-R interval shorter than the R-P interval, consistent with slow retrograde conduction. PJRT tends to be unresponsive to most antiarrhythmic agents and is associated with tachycardia induced cardiomyopathy [2,3]. Although the original reports deal with adult patients, it has also been described in the pediatric age group [3]. More recently, techniques have been described to assist in the prenatal diagnosis of this arrhythmia [4]. This technique allows for a more specific differentiation of the diagnosis of tachycardia in utero by M-mode echocardiography than has been reported previously [5-11].

Although some reports exist on fetuses diagnosed with supraventricular tachycardia that proved to be PJRT postnatally [9, 12, 13], little is known about the characteristics of prenatally diagnosed PJRT. This retrospective study reports on 4 fetuses diagnosed with supraventricular tachycardia of the PJRT type. Characteristics and outcomes are reviewed and suggestions as to management are made.

Methods

This retrospective study includes 4 out of 30 mothers presenting with fetuses referred for supraventricular tachycardia to the University Hospital of Utrecht, the Netherlands.

Definitions of supraventricular tachycardia

Supraventricular tachycardia is a condition with several different underlying mechanisms. The most common mechanism in infancy is re-entry using an accessory atrioventricular connection, other less common possibilities include primary atrial tachycardias and re-entry within the AV node [14]. In most re-entry tachycardias, conduction through the accessory connection is fast, as in the Wolff-Parkinson White syndrome (WPW), resulting in a short RP interval on the ECG and a short VA interval on the prenatal M-mode echocardiography. However, in a

portion of patients slow conduction is observed in the accessory pathway, such as in PJRT. This results in a long RP interval with a shorter PR interval on the ECG, consistent with a long VA interval on the prenatal M-mode echocardiography. In primary atrial tachycardia, such as atrial ectopic tachycardia (AET), the primary focus of the tachycardia lies within the atria, resulting in a P wave preceding the QRS wave and therefore a short PR interval and a longer RP interval as is observed in PJRT. In tachycardias with re-entry within the AV-node there is no consistent 1:1 relationship between the atria and ventricles and periods of AV dissociation are present.

Prenatal situation

The patients underwent echocardiographic monitoring for approximately 30 minutes, reviewing the mechanism of tachycardia by M-mode echocardiography, measuring heart rates, reviewing or monitoring signs of congestive heart failure and evaluating the general condition of the fetus. Fetal tachycardia was defined as a ventricular heart rate exceeding 180 beats per minute (bpm). Fetuses with atrial flutter (defined as an atrial rate > 250 bpm with a fixed or variable AV block, resulting in a variable ventricular response), or tachycardia with atrioventricular dissociation were excluded from this study. On the M-mode echocardiography, the ventriculo-atrial (VA) and atrioventricular (AV) intervals, analogous to the RP and PR intervals of the extrauterine ECG, were measured at peak atrial and ventricular systolic excursions. Slow conduction was concluded from a long VA interval and defined by a VA/AV ratio above 1 as described by Jaeggi et al. [4] (*Figure 1*). PJRT was considered a possible cause of the tachycardia in case of 1:1 atrioventricular conduction with slow conduction through the retrograde pathway. Congestive heart failure was diagnosed if fluid accumulation existed in the fetal body, such as pericardial effusion, pleural effusion, ascites or skin edema. Fetal hydrops was diagnosed if fluid accumulation existed in 2 or more of these compartments.

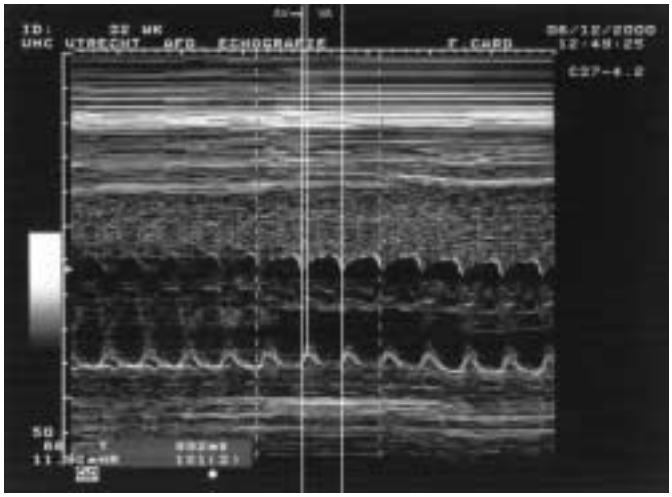

Figure 1.

Fetal M-mode echocardiography, through the four chamber view.

Above are the contractions of the atrium and below the contractions of the ventricles. The ventriculo-atrial (VA) and atrioventricular (AV) intervals, analogous to the RP and PR intervals of the extrauterine ECG, are measured at peak atrial and ventricular systolic excursions. Measurements show a short AV interval and a long VA interval, consistent with slow retrograde conduction through the accessory pathway, as is seen in PJRT.

Prenatal treatment

After establishing the diagnosis of fetal SVT and after evaluation of the maternal ECG for possible abnormalities, the first fetus was treated through oral maternal flecainide at a G.A. of 31 weeks initiated in a dosage of 75 mg 2x/day, which was increased to 100 mg 3x/day. The 3 following fetuses were treated according to a newly installed protocol with oral maternal sotalol 160 mg 2x/day and the addition of digoxin in case rhythm control was not achieved [11]. Fetuses were regularly monitored during treatment, varying from two to three times a week.

Postnatal situation

All patients were delivered in the hospital and postnatal ECG's were performed. Characteristics of PJRT on the postnatal ECG include an often incessant tachycardia at a rate of 120-250 beats per minute with inverted P waves in the inferior leads and a P-R interval shorter than the R-P interval. The definite diagnosis of PJRT was made by invasive electrophysiologic study (EPS) [15]. Follow-up, consisting of three to six

monthly out-patient visits with ECG and echocardiographic investigations, was obtained in all cases. Holter investigations were performed at least once in every patient.

Results

Case reports

Case 1

A mother presented with a fetus at 31 weeks of gestation with a sustained tachycardia at 240 bpm. Upon presentation no signs of congestive heart failure were encountered and treatment was initiated with oral maternal flecainide 75 mg 2 times per day, but had to be increased to 100 mg 3 times per day before the heart rate dropped to 150 bpm, 48 hours after the dosage increase. The conversion to sinus rhythm remained, which allowed a decrease in the dosage of flecainide to 100 mg 2 times per day until delivery. Tachycardia did not re-occur during the prenatal period and at 38+3 weeks of gestation, a healthy boy of 2530 gram was born with good Apgar scores. The postnatal ECG showed a regular sinus rhythm at 140 bpm and since no recurrences were noted, no antiarrhythmic prophylaxis was given. Follow-up including ECG's and echocardiography did not reveal any tachycardias and the patient was discharged from follow-up, at one year of age.

At 6 years of age, the patient presented with intermittent, long-standing periods of tachycardia for more than two weeks, with heart rates up to 150 bpm present in rest. The patient did not seem to notice these periods and did not show any symptoms or signs. The ECG showed a narrow QRS tachycardia, with long RP and shorter PR interval, periods of tachycardia ended abruptly and the QRS complex was not followed by a retrograde P wave. The echocardiogram showed a dilated left ventricle. Electrophysiologic study (EPS) showed decremental VA conduction via a posteroseptal pathway and ultimately confirmed the diagnosis of PJRT. The accessory pathway was ablated with radiofrequency ablation and the follow-up ECG showed a sinus rhythm of 72 bpm, with positive P waves in leads I and II and a normal PR interval. The left ventricular end diastolic diameter as percentage (LVEDD%) before the procedure was 48 (body weight of 26 kg ~ > p97), compared to 35.5, two weeks after the procedure, while the left ventricular fractional shortening as percentage (LVFS%) before the procedure, 23, improved to 39 at two weeks after the ablation. The patient remains without signs or

symptoms related to PJRT at 2 years of follow-up and no more periods of tachycardia were noted. Holter investigations in this period did not reveal any periods of tachycardia.

Case 2

A mother presented with a fetus at 36^{+1} weeks of gestation with a sustained SVT at 230 bpm and a VA/AV ratio of approximately 5. Upon presentation no signs of congestive heart failure were noted and treatment was initiated with sotalol 80 mg 3x/day. This resulted in only a minimal decrease in heart rate to 215 bpm and the dosage was increased to 160 mg 2x/day three days later without significant result. The fetus was delivered by caesarean section at a gestational age of 37 weeks. A healthy boy of 3340 gram was born with Apgar scores of 9/9. Postnatal ECG showed short runs and intermittent periods of tachycardia with heart rates jumping from 110 to 210 bpm (*Figure 2*). Despite the initiation of digoxin (7 mcg/kg /day 2x/day) and the addition of flecainide (5 mg 3x/day) to the treatment, short and longer lasting periods of tachycardia remained. Only after the addition of propranolol (1 mg 4x/day), the intermittent tachycardia was controlled thirteen days after delivery. The boy was discharged in sinus rhythm with medications consisting of digoxin 15 mcg 2x/day, flecainide 5 mg 3x/day and propranolol 1 mg 4x/day. Despite these medications tachycardia of 180 bpm was noted again at the age of 5 months. Moreover, echocardiographic evaluation showed dilated cardiomyopathy. Invasive EPS showed decremental VA conduction via a posteroseptal accessory pathway. Radiofrequency ablation was performed and although the patient showed a brief transient period of first degree AV block, the patient was discharged in sinus rhythm without medication. The LVEDD% before the procedure was 30 (body weight of 6 kg ~ >p97), compared to 20, one week after the procedure, while the LVFS%, before the procedure, 20%, improved to 45% at one week. Follow-up, consisting of clinical, holter and telemetry investigations at one week, six weeks, three months and subsequently every six months after ablation showed no signs or symptoms of recurring tachycardia. The patient is in sinus rhythm and doing well at 2,5 years of age.

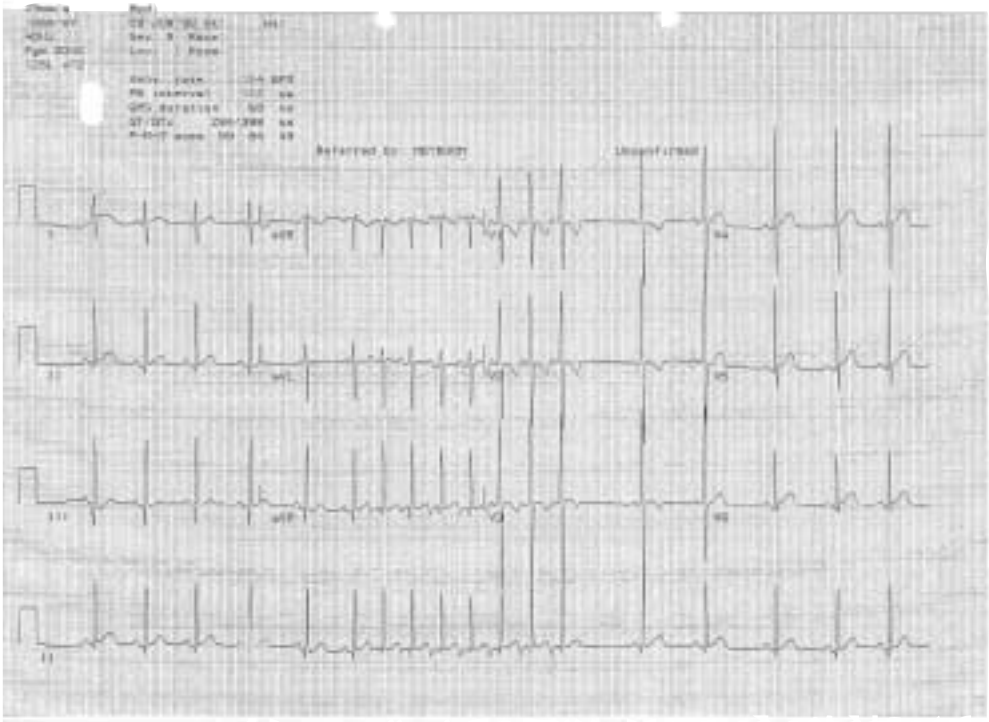

Figure 2.
An ECG performed on the first day of life. Sinus rhythm is interrupted by a short run of tachycardia. Negative P-waves are seen in aVF and a shorter PR than RP interval, consistent with PJRT.

Case 3
A mother with a fetus at 35^{+2} weeks of gestation presented with a sustained fetal SVT at 232 bpm and a VA/AV ratio of 1,25. There were signs of developing fetal hydrops, pleural and pericardial effusion were present. Sotalol was initiated at 80 mg 2x/day, though at 36 weeks G.A. tachycardia still remained. The maternal level of sotalol at that time was 0,9 mg/l (therapeutic range of 0,9 – 2,5 mg/l) and sotalol was increased to 160 mg 2x/day. At 37^{+3} weeks G.A. the fetus heart rate showed persisting normal sinus rhythm of 130-132 bpm. Signs of hydrops disappeared and the sotalol therapy was continued at 160 mg 2x/day. At the beginning of labour at 39^{+1} weeks gestation the cardiotocography recording showed a recurrence of the fetal tachycardia at 230 bpm, interrupted by periods with a sinus rhythm of 130 bpm. A boy

of 4270 gram was born with Apgar scores of 8/9. A postnatal ECG showed sinus rhythm of 130 bpm. During the first day of life the patient developed a tachycardia twice, with heart rates of 220 to 240 bpm, with PJRT characteristics on the surface ECG. These episodes were terminated by the diving reflex, induced by facial immersion in cold water, and oral digoxin (5 mcg/kg 2x/day) was initiated. Since no more periods of tachycardia were noted the patient was discharged on oral digoxin 5 mcg/kg 2x/day and remained in sinus rhythm, until the patient was readmitted with a sustained tachycardia at 240 bpm at 7 months of age. The patient regained sustained sinus rhythm after the addition of propranolol (5 mg 3x/day ~ 2 mg/kg/day). The patient is doing well on this combined treatment at the age of 1,5 year.

Case 4

A mother with a fetus at 31^{+2} weeks of gestation presented with sustained fetal tachycardia at 210 bpm, a VA/AV ratio of 3,33 (*figure 1*) and a small amount of pericardial effusion. Sotalol (160 mg 2x/day) was initiated and three days later the heart rate dropped to 186 bpm without pericardial effusion. Sotalol was increased to 160 mg po 3x per day and digoxin was added at 0,125 mg po 2x per day which resulted in sinus rhythm at 133 bpm. Sinus rhythm persisted on this medication until 35^{+5} weeks G.A, at which time the heart rate relapsed into tachycardia with a rate at 180 bpm. The maternal digoxin level at that time was 0,5 (therapeutic level 0,9-2,0) and the dosage of digoxin was increased to 0,125 mg 3x/day. Sinus rhythm at 164 bpm was achieved within one week on this medication. At 39 weeks G.A. a caesarean section was performed because of a breech presentation. A girl of 2735 gram was born with good Apgar scores of 9/10. Postnatal ECG showed a recurrent tachycardia with a long RP interval and a heart rate at 193 bpm. Intravenous adenosine terminated the tachycardia by antegrade block in the AV node, confirming the 1:1 AV relationship, and thereby excluding atrial ectopic tachycardia as a cause for the tachycardia. A re-entrant tachycardia with a slowly decrementally conducting accessory pathway lead therefore to the confirmation of a PJRT. Oral propranolol therapy (3 mg 3x/day ~ 3 mg/kg/day) was initiated and increased (4 mg 3x/day), but the tachycardia persisted at rates around 180-190 bpm at 41 days after delivery. The echocardiogram did not reveal any abnormalities in the first week of life and at day of life 20. At 41 days after delivery, however, the echocardiogram started to show a decreasing left ventricular function with a LVEDD of 23 mm (body weight of 3900 g ~ p97), compared to 19 mm two weeks in advance. Radiofrequency ablation was therefore considered until the patient

suddenly converted to sinus rhythm at 132 bpm for the first time postnatally. The patient remains in sinus rhythm on propranolol 10 mg 2x/day and is currently doing well at 1 year of age.

Discussion

PJRT is a type of tachycardia, that due to its incessant nature, is associated with tachycardia induced cardiomyopathy [2, 3, 16]. The literature reports that the tachycardia can be diagnosed in adults, children and usually can be recognized in early childhood [3, 17]. Our data show that PJRT can be diagnosed during the prenatal period but that therapeutic pharmacological intervention remains complicated.

Prenatal diagnosis of PJRT

In the absence of a reliable fetal ECG, M-mode echocardiography is the most commonly used method of diagnosis in fetal arrhythmias. The problem with this technique is that the exact nature of the arrhythmia remains unrevealed, although several methods have been proposed to increase the accuracy and reliability of M-mode echocardiography to diagnose fetal arrhythmias [4, 18]. These methods are of particular interest in differentiating re-entry SVT's through measuring the atrioventricular (AV) and ventriculoatrial (VA) interval. Dividing these intervals results in a VA/AV ratio, which is a measure of the conduction properties through eventual retrograde accessory pathways. The finding of a long VA interval can make the assumption of fetal PJRT, although atrial ectopic tachycardia can also show a long VA interval. Other types of supraventricular tachycardia may show a long RP interval, such as junctional ectopic tachycardia (JET), however, in JET there is no constant 1:1 AV association. Sinus tachycardia may also show a long RP interval, but is excluded in these cases with heart rates exceeding 200 bpm. The definite diagnosis of PJRT therefore requires additional assessment techniques, currently only available in the postnatal setting.
A small but persistent and difficult to treat group of fetal tachycardias, postnatally proven to be PJRT's, have been described in previous reports from our center by van Engelen et al. [9] and Oudijk et al. [10]. The above described technique has allowed us to define this group intra-uterine as probable PJRT's. Although this is a step in the right direction, future techniques such as fetal magnetocardiography, in which the magnetic field produced by electrical currents in the fetal heart is measured in a noninvasive way [19], may allow even further and more definitive deline-

ation of the fetal arrhythmic problems [20, 21]. This technique possibly provides a way to define the electrophysiologic mechanism of the tachycardia in a prenatal setting and is therefore of potential interest in the detailed diagnosis of fetal arrhythmias.

Characteristics of fetal PJRT

The mean peak fetal heart rates encountered in our PJRT cases, ranging from 210 –240 bpm, differ from the ones reported previously [9, 10], in which heart rates ranged from 200-300 bpm with a mean of 260 bpm. This is consistent with the slow conduction properties of the accessory pathway of PJRT.

Another characteristic observed in our cases of fetal PJRT is the incessant nature of the tachycardia. In all our cases, the tachycardia was sustained, whereas in SVT cases with a short VA interval or fetal atrial flutter, intermittent periods of sinus rhythm are more frequently observed as we have reported previously [9, 10].

The incessant nature of PJRT makes the heart vulnerable to congestive heart failure as can be found in children and adults [2, 3]. In half of the cases, signs of congestive heart failure were noted upon presentation in fetal life, consistent with a publication by Jaeggi et al [4]. Congestive heart failure disappeared in both cases after the administration of antiarrhythmics, although at this point intermittent periods of tachycardia were still noted, which may suggest a positive role of periods of sinus rhythm on the diminishment of heart failure.

Therapy and therapy resistance

Data from patients treated with antiarrhythmics in the postnatal period show a high therapy resistance of this type of SVT [3, 9]. Similarly, prenatal treatment of long VA SVT's is difficult [4, 11, 12]. In case 1 the fetus was successfully treated with oral maternal flecainide, however, after a report by Simpson et al. [7] on fetal death possibly caused by flecainide, we abandoned flecainide from early inclusion in our therapy protocol and replaced it by sotalol. As reported previously, in some cases, sotalol has also been associated with fetal demise. However, this was the case in SVT patients complicated by severe hydrops and we therefore decided to stay with our protocol with sotalol as drug of first choice, which has remained successful in most of our patients since our published results [10, 11]. Flecainide however, remains an option in patients with significant fetal hydrops.

The following three cases have shown limited success in fetal PJRT,

with sotalol as single therapy in two cases and additional digoxin in one case, reaching results ranging from a decrease in heart rate to achieving periods of sinus rhythm, although recurrence of intermittent periods of tachycardia occurred in all. Additional data from literature are scarce, since most centers do not differentiate between short and long VA SVT. Jaeggi et al. [4] treated three fetuses with long VA tachycardia with digoxin, which failed in all three; addition of sotalol resulted in a conversion into a sinus rhythm in two fetuses. One of the responders to sotalol died in utero as a result of severe secondary cardiomyopathy with generalized hydrops indicating the seriousness of longstanding VA tachycardia. The other two fetuses had postnatal confirmation of PJRT.

In summary, data from our cases and those from Jaeggi et al. show that 2 fetuses were treated with sotalol as a single therapy of whom one converted to sinus rhythm and 4 fetuses were treated with a combination of sotalol and digoxin of whom 3 converted to sinus rhythm. One case was treated successfully by flecainide, which makes one wonder if despite negative reports on this drug [7, 22] the treatment by flecainide in case of fetal PJRT should not be advocated, especially since congestive heart failure is frequently encountered in fetal PJRT. In cases not complicated by fetal hydrops, a combination of sotalol and digoxin might still be useful.

Postnatal period

All 4 patient reverted into the tachycardia after birth sooner or later and belong to the group of patients requiring significant (more than 1) postnatal medications. Congestive heart failure is more common at a younger age, possibly connected to the faster heart rate in PJRT noted at these ages compared to PJRT in older patients, according to Dorostkar et al [3]. Therefore, our center has opted for antiarrhythmic drug therapy (propranolol 3 mg/kg/day) in the first instance, but, in case of developing signs of congestive heart failure despite multiple antiarrhythmic medications, we consider these patients to be potential candidates for early ablation of the accessory pathway [16, 23].

Conclusions

The finding of a long VA interval in case of 1:1 AV association on M-mode echocardiography in the prenatal period is highly suggestive of fetal PJRT, however, fetal AET is also a possibility, though not observed at our center. Other characteristics of fetal PJRT observed in our cases

include a heart rate not exceeding 240 bpm, usually in a sustained manner, the frequent presence of congestive heart failure and therapy resistance. Therefore, we feel that in case fetal PJRT is suspected, a more aggressive approach as to treatment is necessary. It is our opinion that in the absence of congestive heart failure sotalol combined with digoxin might still be the treatment of choice, but especially in the presence of congestive heart failure, a more aggressive approach such as flecainide might be desirable. In the postnatal period, our center has opted for antiarrhythmic drug therapy (propranolol 3 mg/kg/day) in the first instance, but, in case of developing signs of congestive heart failure despite multiple antiarrhythmic medication, we consider these patients to be potential candidates for early ablation of the accessory pathway.

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Part 1
Fetal Tachycardia

Consequences of Fetal Tachycardia

Chapter 4

Neurological Outcome of children who were treated for fetal tachycardia complicated by hydrops

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Abstract

Background

Fetal tachycardia is a condition associated with congestive heart failure and development of fetal hydrops, which may result in neurological morbidity and mortality. Limited data exists on the long-term outcome of hydropic fetuses.

Methods

A retrospective study on cognitive and neurological functioning of 11 infants, aged 0,5 to 12 years, who experienced fetal tachycardia complicated by hydrops.

Results

Seven fetuses had supraventricular tachycardia, 3 had atrial flutter and 1 had ventricular tachycardia. Nine fetuses converted to sinus rhythm in a mean time of 7,9 days; resolution of hydrops was achieved in 6 of these patients in a mean time of 7,4 days.

Mean GA at birth was 35 weeks and 4 days. Neonatal cranial ultrasound was normal in 7 infants and all but one of these were normal at follow-up: one infant who initially had no abnormalities developed multiple cerebral lesions as a result of a malignant LQTS and died at the age of 2 years. The remaining 4 infants all had flaring on neonatal cranial ultrasound, one complicated by a pseudocyst and one by a porencephalic cyst. One of these infants was normal at follow-up, one died two days after birth and two infants had neurological abnormalities at follow-up, consisting of mild hemiplegia with normal cognitive function in one, and a cognitive developmental delay in the other.

Conclusions

Fetal tachycardia complicated by hydrops predisposes the unborn child to neurological damage. However, in this series 8 out of 11 infants were neurologically normal. Prognosis seems particularly good in case of successful treatment and delivery at term, and initiation of therapy should not be withheld or delayed on the assumption of poor neurological outcome.

Introduction

Fetal tachycardia is a serious condition in which the fetus is at risk for congestive heart failure and subsequent development of hydrops. This situation is associated with significant morbidity and mortality [1-3]. Neurological morbidity has been linked to fetal tachycardia in several reports and is probably the result of dysfunction of the cerebrovascular autoregulation in hemodynamically compromised fetuses [4-10]. This makes the prevention and management of fetal tachycardia complicated by hydrops most important. Intra uterine therapy is to be preferred over preterm delivery and postnatal treatment, in avoidance of neonatal complications of prematurity additional to the arrhythmia. Several management protocols have been proposed in the last years of which treatment with flecainide [11-13] or amiodarone and digoxin [14] seem to be the most successful in SVT, and sotalol the most successful in AF [15]. However, little is known on the neurological follow-up of these children. We present a retrospective study on 11 cases that were treated for fetal tachycardia complicated by hydrops, with special focus on neurological outcome.

Methods

All cases with fetal tachycardia complicated by hydrops and treated at our hospital from 1991 until 2002 were reviewed. Two of these patients have been described in a previous study [4].
Fetal tachycardia was defined as a ventricular heart rate exceeding 180 beats per minute (bpm). Supraventricular tachycardia (SVT) was defined by 1:1 atrioventricular conduction and atrial flutter (AF) was defined as an atrial rate > 250 bpm with a fixed or variable AV block, resulting in a variable ventricular response. Fetal hydrops was defined by clear fluid accumulation in 2 or more of the compartments in the fetal body, such as pericardial effusion, pleural effusion, ascites and skin edema.
Treatment differed between cases as a result of the time span of this study and due to the progressing insights on therapy.

Neurological follow-up

All records, both prenatal and postnatal, were reviewed. All 11 neonates had cranial ultrasounds performed shortly after birth. Neonates who were diagnosed to have neurological abnormalities were accurately documented and enrolled in the neurological follow-up. Neonates who

showed no signs of neurological damage, both at cranial ultrasound and during the neurological follow-up in the first year of life, were discharged from further neurological follow-up. Further development was noted at cardiological follow-up.
At the time of this follow-up study, the patients were invited at our out-patient clinic. They were asked for possible signs and symptoms of any disease, medication, level of education and participance in sports. A full standardized neurological investigation was performed by one neurologist (RHJMG). Normal neurological outcome was defined by adequate cognitive functioning, as defined by a normal level of education and no abnormalities at neurological investigation.
Statistical difference in GA at presentation and delivery between groups was made by the Mann-Whitney-U test. A p value of 0,05 was considered significant.

Results

Prenatal situation

Eleven hydropic patients were included in this study. The mean gestational age at the time of presentation was 30^{+3} weeks (range 24^{+4} – 38^{+4} weeks). Seven patients had SVT, 3 had AF and 1 patient had ventricular tachycardia (VT). Table 1 shows the patient characteristics. In nine patients, conversion to sustained sinus rhythm was achieved in a mean time of 7,9 days (SD 6,0). In 6 of these patients, resolution of hydrops was achieved in a mean time of 7,4 days (SD 3,8) after conversion to sinus rhythm. Of the remaining three patients that converted to sinus rhythm, two went into preterm labour before the hydrops was dissolved (case 9 and 10), and one was delivered at 39 weeks after several days of sinus rhythm (case 5), although still hydropic.

One case that converted to sinus rhytm without treatment was included in the group that converted to sinus rhythm (case 4). This was a twin pregnancy presenting at 31 weeks, with one fetus with SVT at 300 bpm and massive hydrops, and one unaffected twin. In view of the minimal cardiac output and expected poor neurological prognosis, it was decided in conjunction with the parents, not to initiate therapy. However, at follow-up at 32^{+4} weeks, the heart of the affected twin showed a normal sinus rhythm and signs of decreasing hydrops. Hydrops was completely resolved at 33^{+2} weeks and the biophysical profile was satisfying. At 35 weeks, relapse of the tachycardia occurred at 300 bpm, and at this point we decided to perform a caesarean section (S.C). Two healthy daughters

were born with good Apgar scores and birth weights of 2500 and 3000 gram.
Two patients did not convert to sinus rhythm. One patient had intermittent VT at 260-280 bpm , and was treated with sotalol and digoxin. As no conversion to sinus rhythm occurred and hydrops was progressing, it was decided to perform a S.C. at 31^{+1} weeks. A daughter was born with an Apgar score of 5/8 and a birth weight of 2180 gram. She was diagnosed to have long QT syndrome (LQTS) type 3 (case 7). The other patient not converting to sinus rhythm had AF at 300:150 bpm and intermittent 1:1 conduction at 300 bpm. Although not converted to sinus rhythm, on therapy, no 1:1 conduction was seen anymore. Hydrops resolved in 14 days (case 8). Six fetuses were delivered vaginally and 5 by caesarean section (S.C.) Indications for S.C. included breech presentation (n=2), therapy resistance (n=1), relapse (n=1) and emergency S.C. (decreased fetal movements and reduced FHR variability; n=1).

Case	GA (weeks)	Mechanism	Int/ continuous	FHR	Therapy	T to conv (days)	T to resolution (days)	Delivery	GA	Outcome
1	31+1	SVT	continuous	260	S+D	12	4	nvd	41^{+2}	Good
2	29+3	AF	int	360/180	S+D	8	6	nvd	32^{+6}	Hemiplegia
3	25+0	SVT	continuous	60-240	F (-), S (+)	14	7	CS	34^{+2}	Delay
4	31+0	SVT	continuous	300	None	11	16	CS	35	Good
5	38+4	SVT	int	170-200	F	2	-	CS	39	Good
6	24+4	SVT	int	250-260	S	9	6	nvd	36	Good
7	29+4	VT	int	260	S+D	-	-	CS	31^{+1}	Died at 2 years
8	28+0	AF, int. 1:1 conduction	continuous	300/150	F+D	-	14	nvd	37^{+1}	Good
9	33+1	AF	continuous	460/230	S	1	-	nvd	33^{+3}	Died at 2 days
10	31+0	SVT	continuous	250	F	1	14	nvd	40^{+1}	Good
11	27+4	SVT	continuous	290	F(-), amio+D	16	-	CS	31	Good

Table 1

Prenatal characteristics and outcome of all 11 patients. GA, gestational age. SVT, supraventricular tachycardia. AF, atrial flutter. Int, intermittent. FHR, fetal heart rate. S, sotalol. D, digoxin. F, flecainide. Amio, amiodarone. T to conv, time to conversion to sinus rhythm in days. T to resolution, time to resolution in days. Nvd, normal vaginal delivery. CS, caesarean section. Delay, cognitive developmental delay.

Postnatal situation

Mean G.A. at birth was 35+4 weeks (range 31 – 41+2). Neonatal cranial ultrasound was normal in 7 infants (group 1) and abnormal in 4 (group 2). The infants of group 1 had a mean GA at presentation of 30,5 weeks (SD 4,2), as compared to a mean GA of 28,8 weeks (SD 3,4) in group 2 (not significant). However, there was a significant difference between the groups in gestational age at delivery (mean 37, SD 3,5 vs mean 33, SD 1,4; p = 0,047).

The infants of group 2 were neurologically abnormal shortly after birth and another one became neurologically abnormal later on, due to ongoing cardiac problems. Two of these five infants died. All together there were 9 survivors, two of whom with neurological sequelae.
Six of the seven infants with a normal neonatal cranial ultrasound were normal at follow-up. One is at present 8 months old with normal neurological results and a normal MRI scan. The other 5 infants are 6 to 12 years old at present. The one patient from this group, who developed abnormally (case 7), had runs of polymorphic tachycardia shortly after birth and a QTc of 0,51 (prolonged) and she was diagnosed to have congenital LQTS. A ventricular pacemaker was implanted and propranolol therapy was initiated. Convulsions were present in the first two weeks of life and a repeated cranial ultrasound performed at two weeks of age showed a small infarction in the left thalamus. A MRI at two months of age showed a small cyst in the left-sided nucleus lentiformis. Neurological development however, was good up to one year of age. At this point in time, the cardiac condition was critical with several periods of ventricle fibrillation and need for resuscitation. A cardioverter defibrillator was implanted, but repeated shocks were required and signs of heart of failure developed. The neurological condition deteriorated and the infant died at 2 years of age of intractable ventricle fibrillation.

There were four infants with an abnormal neonatal cranial ultrasound. Two infants had severe flaring (case 3 and 9) and the other two had mild flaring, with a pseudocyst (case 11) and a porencephalic cyst (case 2). Only case 11 did well. This infant is at present 6 months old, has no abnormalities on repeated cranial scans and is also neurologically developing normal. The other 3 cases are discussed below.
Case 3 initially developed well, but proved to have psychomotor retardation at the age of 16 months when he was functioning conform the age of 9-10 months, determined with the Griffiths developmental assessment scale (63 out of 100). No subsequent follow-up could be

obtained as a result of emigration shortly after the last visit (described in a previous study 4).

Case 2 showed signs of dilatation of the left cerebral ventricle and a shift of the midline at two months of age. These findings were confirmed on MRI, and a ventriculoperitoneal drain was placed. At the time of this study, he is 7,5 years old, has a mild hemiplegia on the right side and requires physical therapy, although development is well and quality of life is not hampered by the mild hemiplegia. Cognitive functioning is normal (described in a previous study 4).

Case 9 was born preterm with massive hydrops at 33 weeks and 3 days of gestation, as a result of preterm contractions. In addition to the severe flaring, a precysteus periventricular leucomalacia was seen and convulsions occurred. In view of the poor prognosis it was decided to abstain from therapy. The infant died at the second day of life.

Discussion

Fetal tachycardia is a situation in which the fetus is predisposed to neurological abnormalities probably as a result of hemodynamical compromise. These abnormalities are only present in hydropic fetuses and therefore seem to be related to situations in which such a hemodynamical compromise is severe. Hemodynamic compromise as a result of a disturbance in rhythm predisposes the fetus to cerebral ischemia in periods of moderate hypotension and to intracranial hemorrhage in periods of moderate hypertension 4. The gestational age at presentation of the tachycardia has been proposed as a risk factor for neurological complications, but we could not demonstrate this in our study. A significant difference however, was present in GA at the time of delivery between infants with normal and abnormal neonatal brain scan, probably as a result of the severity of the condition (preterm delivery as a result of polyhydramnios in three cases and induced preterm delivery because of therapy resistance in one case).

Case reports have suggested an association between fetal hydrops due to tachycardia and neurological abnormalities 6-10, but the outcome of a consecutive series is not known. Three of the 11 patients of our study proved to have neurological complications related to the prenatal tachycardia, and in one of them these complications were severe enough, to decide to abstain from further treatment. One patient had

a marked mental retardation and one a mild hemiplegia with a good quality of life. One further case initially was neurologically normal, but deteriorated as a result of the critical cardiological condition. Outcome of the group as a whole was above our expectations and compares favorably with that of other causes of fetal hydrops. However, publications on outcome are mostly focused on mortality rates. In severe immune fetal hydrops a mortality rate of 45 % has been reported [16], even after intrauterine treatment. Outcome in non-immune fetal hydrops related to other causes is poor with perinatal mortality rates of 80 – 100 % [17, 18]. In one study, outcome of 126 surviving infants who had suffered from anemia prenatally, induced by red blood cell-alloimmunization, has been studied. In 21 % of infants who had been severely hydropic prenatally, visits to neurology and rehabilitation departments were reported, suggesting neurological abnormalities. A percentage of neurological impairment that is comparable to our findings. In addition, they reported a trend towards behavioural problems in the group with severe hydrops [19].

Our data indicate that the majority of fetuses apparently seem capable of handling fetal tachycardia at least for a certain amount of time, and adequate blood flow to the fetal brain must be assumed in these cases. Initiation of therapy should therefore never be withheld or delayed based only on the unfounded assumption of poor neurological outcome. Even in cases in which it might take several weeks to achieve a sinus rhythm and a subsequent resolution of hydrops, outcome is not necessarily poor (case 11). Only in situations in which obvious neurological lesions are detected in utero one may opt, in conjunction with the parents, to abstain from therapy. Our data do not provide a clue as to which hydropic fetus will develop favorably or otherwise.

Conclusions

Fetal tachycardia complicated by hydrops predisposes the unborn child to neurological damage. In our population of 11 fetuses, two deaths occurred, one shortly after birth as a result of the fetal tachycardia and its complications, and one at 2 years of age related to the arrhythmia. The neurological abnormalities encountered in this study, were mild hemiplegia with normal cognitive function in one patient and a cognitive developmental delay in the other. However, neurological outcome of the hydropic group as a whole was reasonably good with no neurological abnormalities in 73 % of cases. At long term follow-up, cognitive

function was normal in all surviving infants. Prognosis seems particularly excellent in case of successful treatment and delivery at term. Therefore, initiation of therapy should not be withheld or delayed based only on the assumption of poor neurological outcome.

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Part 1
Fetal Tachycardia

Transplacental Treatment of Fetal Tachycardia

Chapter 5

Drug Treatment of Fetal Tachycardias

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Abstract

Background

The pharmacological treatment of fetal tachycardia (FT) has been described in various publications. We present a study reviewing the necessity for treatment of FT, the regimens of drugs used in the last two decades and their mode of administration.

Methods

Review study of the literature regarding FT in the last two decades.

Results

The absence of reliable predictors of fetal hydrops (FH) has led most centers to initiate treatment as soon as the diagnosis of FT has been established, although a small minority advocate non-intervention. As the primary form of pharmacological intervention, oral maternal transplacental therapy is generally preferred. Digoxin is the most common drug used to treat FT; however, effectiveness remains a point of discussion. After digoxin, sotalol seems to be the most promising agent, specifically in atrial flutter (AF) and nonhydropic supraventricular tachycardia (SVT). Flecainide is a very successful drug in the treatment of fetal SVT, although concerns about possible pro-arrhythmic effects have limited its use. Amiodarone has been described favorably, but is frequently excluded due to its extensive side effects. Conclusions on other less frequent used drugs cannot be drawn.
In severely hydropic fetuses and/or therapy resistant FT direct fetal therapy is sometimes initiated. To minimize the number of invasive procedures, fetal intramuscular or intraperitoneal injections that provide a more sustained release are to be preferred.

Conclusions

Based on these data we propose a drug protocol of sotalol 160 mg twice daily orally, increased to a maximum of 480 mg daily. Whenever sinus rhythm is not achieved, the addition of digoxin 0,250 mg three times daily is recommended, increased to a maximum of 0,5 mg three times daily. Only in SVT complicated by FH, either maternal digoxin 1 to 2 mg IV in 24 hours and subsequently 0,5 to 1 mg/day IV or flecainide 200 to 400 mg/day orally is proposed. Initiating direct fetal therapy may follow failure of transplacental therapy.

Introduction

Fetal tachycardia is a condition that occurs in 0,4-0,6 % of all pregnancies[1].
With the development of Doppler and M-mode echocardiography, the knowledge on this rhythm disorder and its impact on the condition of the fetus has greatly improved [2-5]. In the last two decades a number of publications have highlighted views and experiences on the diagnosis and management of fetal tachycardia. Fetal tachycardia can hemodynamically compromise the fetus, presenting with signs as ventricular dysfunction and dilatation, secondary atrioventricular valve regurgitation and fetal hydrops, which may ultimately lead to fetal death.
Several treatment protocols have been developed, in which different modes of pharmacological intervention, indirect (transplacental, through oral or intravenous maternal therapy) or direct (intra-umbilical, intra-amniotic, intra-peritoneal and intra-muscular fetal therapy) have been proposed. Although prenatal treatment in advanced cases of fetal tachycardia is widely accepted, the necessity for treatment in milder cases is still a point of discussion [6, 7].
This review article will discuss the various regimens of drugs used in the treatment of fetal tachycardia over the past two decades, their mode of administration, necessity for treatment and future prospects.

Definition of Fetal Tachycardia

The normal fetal heart rate ranges are approximately 120-160 bpm at 30 weeks and 110-150 bpm at term [8, 9]. Frequencies up to 170 bpm are considered mildly abnormal, whereas overt tachycardia is usually defined as a heart rate exceeding 170 bpm [8] or 180 bpm [10]. Fetal tachycardia is subdivided in supraventricular tachycardia (SVT, defined by 1:1 atrioventricular conduction), of which permanent junctional reciprocating tachycardia (PJRT) is a particular therapy resistant type; atrial flutter (AF, with atrial rate >250 bpm with fixed or variable AV block, resulting in a variable ventricular response); ventricular tachycardia (VT, with AV dissociation, lack of a 1:1 relationship between atria and ventricles) and sinus tachycardia [10]. Further categorization can be made on the basis of the percentage of time that the tachycardia is present: sustained, >50% of time present or intermittent, < 50% of time.
This article focuses on fetal tachycardia as a primary condition, whereas its presentation as a secondary condition (cardiac structural malformation, infection, uterine contraction and fetal distress) might require in a different management protocol.

Diagnosis

Detection of fetal tachycardia often occurs at routine prenatal visits after which referral to a specialized center for fetal cardiology is arranged. Fetal electrocardiography is not of clinical significance in the diagnosis of FT because its signal-to-noise ratio is low, thereby precluding the demonstration of atrial activity. The diagnosis is made by M-mode and sometimes Doppler echocardiography, which enables a differentiation in types of rhythm. The two-dimensional image is used to exclude structural cardiac malformations and to position the M-mode sampling line to intercept both the atrial and ventricular walls. The relationship between atrial and ventricular contraction is sufficient to make a division in SVT, AF, VT and sinus tachycardia (see definitions), although the exact electrophysiologic mechanism of the tachycardia remains undisclosed. Fetal magnetocardiography allows a more complete evaluation of the type of arrhythmia but the technique is currently still in an experimental stage.

Drugs used

All drugs used in the treatment of fetal tachycardia are classified following the Vaughan-Williams classification of antiarrhythmics. *Table 1* provides a list of antiarrhythmic agents and their recommended use. *Table 2* contains a comparison of treatment protocols used in the larger studies published recently.

All information in paragraphs on pharmacokinetics and dose refer to maternal values and are obtained from women who are not pregnant, unless otherwise stated. Direct fetal treatment will be discussed in a separate chapter.

Digoxin

Pharmacodynamics

Digoxin, a digitalis glycoside exerting direct and indirect effects on the myocardium, conduction system and autonomic nervous system, has positive inotropic and negative chronotropic properties, resulting in an increase in cardiac output and a decrease in heart rate, respectively. In addition, digoxin prolongs the refractoriness of the AV-node, thereby delaying atrio-ventricular conduction and the ventricular rate in AF or SVT.

Drug	SVT, no hydrops	SVT, hydrops	AF, no hydrops	AF, hydrops	Administration schedule
Sotalol	+++	-	+++	+++	PO: 160 mg 2x/day, max. 480 mg/day
Digoxine	+++	+++	+	+	PO: 0,25 mg 2x/day, max. 1 mg/day, IV: 0,5-1 mg/day
Flecainide	-	+	-	-	PO: 200-400 mg/day
Amiodarone	-	+	-	+	PO: 800-1200 mg/day, gradually decrease
Procainamide	-	+	-	-	PO: 500 mg 8x/day, IV: 2-6 mg/min maintenance
Dofetilide	-	-	(+)	(+)	Individualize on creatinine clearance
Propranolol	-	-	-	-	PO: 30 mg 4x/day, max. 320 mg/day
Adenosine	-	-	-	- -	Intraumbilical: 0,1-0,2 mg/kg estimated fetal weight
Disopyramide	- -	- -	- -	- -	Not relevant
Quinidine	- -	- -	- -	- -	Not relevant
Verapamil	- -	- -	- -	- -	Not relevant

Table 1

Figure legends

- - contraindicated; - not recommended; (+) experimental use as drug of last resort; + may be used in case of therapy resistance to other drugs, ++ recommended, +++ strongly recommended

Study	# of patients	NFH	FH	SVT	AF	Digoxin	Flecainide	Sotalol	Dig + Fl	Dig + S	Multidrugs	IUD
Jaeggi et al. (30)	11	10	1	0	11	5+ / 4-				1-	1-	0
Sonesson et al. (95)	14	6	8	14	0					10+ / 4-		2
Allan et al.* (63)	14	0	14	12	2		12+		2+			1
Azancot group 1 (39)	9	5	4	4	5	2+					2+ / 5-	0
Azancot group 2 (40)	7	2	5	5	2	5+ (i.v. Dig)			2+ (i.v. Dig)			0
Oudijk et al. (90)	20	12	8	10	10			10+ / 3-		6+ / 1-		3
van Engelen et al. (27)	34	19	15	25	9	11+ / 4-	7+		2+		8+ / 2-	2
Frohn-Mulder et al. (28)	35	22	13	35	0	13+ / 6-	3+ / 4-		4+		5-	6
Simpson et al.* (29)	110	63	47	92	18	40+ / 11-	16+ / 5-		4+		23+ / 11-	15

* These studies may have included similar patients.

Table 2.
Comparison of treatment protocols larger studies.

NFH= No Fetal Hydrops, FH= Fetal Hydrops, SVT= Supraventricular Tachycardia, AF= Atrial Flutter, Dig + Fl= Digoxin and Flecainide combined treatment.
Dig + S= Digoxin and Sotalol combined treatment, Multidrugs= treatment with a combination of more than two drugs, IUD= intra uterine death.
i.v.Dig = maternal intra-venous Digoxin, + = successful treatment, - = unsuccessful treatment.

Pharmacokinetics

Orally administered digoxin is absorbed for 75 %. Elimination half-life of digoxin is 30 to 40 hours. Therapeutic serum concentration of digoxin is 1 to 2 mg/l. Digoxin has a small therapeutic range with a high incidence of toxicity. Approximately 57-80 % of the available digoxin is excreted unchanged in the urine. The rest is eliminated by non-renal routes: 6-8 % by biliary excretion, 3-5 % by fecal excretion and approximately 16 % is metabolized in the liver [11].

During pregnancy renal clearance and maternal blood volume increases, and this higher doses of digoxin are required to achieve adequate therapeutic levels in the fetus [12, 13] , although higher digoxin plasma concentrations in pregnant women due to increased absorption are reported [14].

Dose

Loading dose for orally administered digoxin, varies between 0,25 and 1,5 mg, followed by a maintenance dose of 0,125 to 0,5 mg daily. The relatively long elimination half-life of digoxin results in slower achieved steady-state plasma concentrations. Dosing should be individually adjusted by combining plasma concentration and clinical effects. Rapid achievement of adequate levels can be reached by intravenous administration of 1 to 2 mg digoxin given in multiple doses during the first 24 hours, followed by 0,5 to 1 mg daily for 7 days guided by maternal tolerance and fetal echocardiography [10].

Antiarrhythmic drugs like quinidine, amiodarone, propafenone, verapamil and flecainide increase the digoxin plasma concentration. Maternal plasma concentrations are therefore required to adjust the dosages in case of combined use of digoxin and these drugs [10, 15]. Dose adjustments based on combined maternal and fetal blood levels (by cordocentesis) are complicated by the fact that measurement of digoxin levels within the fetus is hampered by cross reactions with preexisting fetal digoxin-like immunoreactive substance [16]. Therefore, we recommend to adjust the dose solely on maternal blood levels.

Placental transfer

Reported fetal: maternal plasma concentration ratios vary between 0,4 and 0,9 [14, 17-19]. However, in the hydropic fetus this ratio is reduced, which may result in failure of treatment. This lower digoxin concentration may be caused by altered volume distribution, change in protein binding or other pharmacokinetic parameters in the hydropic fetus [20-24].

Adverse effects and precautions

Digoxin does not appear to be teratogenic [25]. Maternal adverse effects mainly concern overdosing. Signs of overdosing, such as anorexia, nausea, vomiting and headache have, however, also been reported at therapeutic plasma concentrations. Frequent cardiac adverse effects are arrhythmias (especially ventricular extrasystoles) and heart block; atrial tachycardia with an AV-block is characteristic. Digoxin is contraindicated in Wolff-Parkinson-White syndrome.

Dose adjustment is required in case of renal failure, maternal hypokalemia or concomitant administration of digoxin with other antiarrhythmics.

Clinical experience

Digoxin transplacental therapy has been the drug of choice in the treatment of fetal tachycardia since its complications are few and well known. Six large studies and a great number of small studies and case reports have been published. The large studies have shown that digoxin monotherapy is relatively effective in the treatment of fetal tachycardia not complicated by fetal hydrops with conversion rates ranging from 32 % to 71 % [26-29]. In contrast, disappointing conversion rates of 10 % to 20% have been reported with digoxin monotherapy in fetal tachycardia complicated by fetal hydrops, although Kleinman et al. reached a conversion rate of 43 % in these complicated cases [4]. A study by Jaeggi et al. on the use of digoxin in fetal atrial flutter showed a moderate success rate of 45 % [30]. Several other studies stress the relative inefficacy of orally administered digoxin in atrial flutter and fetal SVT complicated by hydrops due to the reduced transplacental transfer of this drug, with an overall success rate of approximately 50 % in nonhydropic fetuses compared to a disappointing rate of 15-20 % in hydropic cases [31-38]. Intravenous administration of digoxin may avoid problems related to poor absorption of digoxin, and consequently favors the transplacental transfer of the drug; with such a policy adequate therapeutic fetal plasma concentrations are rapidly achieved [39-41].

In conclusion, digoxin is a safe drug in the treatment of fetal tachycardia with the advantages of a positive inotropic effect. However, digoxin is known to act slowly and its therapeutic importance in hydropic fetuses is limited. The maternal intravenous administration of digoxin seems promising, however, logistically complicated. It should therefore be reserved for severe cases of tachycardia complicated by hydrops and possibly in combination with a second line drug as flecainide.

Quinidine

Pharmacodynamics

A class IA antiarrhythmic agent that delays conduction and prolongs the refractory period. An indirect parasympaticolytic effect neutralizes the delayed AV conduction and may even enhance conduction. It has a weak negative inotropic effect.

Pharmacokinetics

Peak plasma concentrations occur after 1-2 hours. Quinidine metabolizes partly in the liver and is eliminated through the urine. The elimination half-life is 6-8 hours. Therapeutic plasma levels are 2-6 mg/l.

Dose
The starting dose is 200 mg orally every 3 hours until the desired effect is reached. The maximum daily dose should not exceed 3 gram.

Placental transfer
Quinidine crosses the placenta, one case report shows a fetal: maternal plasma ratio of approximately 0,3 [42], and another report a ratio of 1,0 [43].

Adverse effects and precautions
Quinidine toxicity in the mother can lead to severe nausea and vomiting, diarrhea, light-headedness and tinnitus [42]. Cardiac adverse effects include hypotension, torsade de pointes tachycardia and sudden death. No reports linking the use of quinidine with congenital defects have been identified.
Neonatal thrombocytopenia has been reported after maternal use of quinidine.

Clinical experience
There is limited fetal experience with the use of quinidine in the treatment of fetal tachycardia. We could identify thirteen cases in the international literature. Five cases were treated successfully with a combination of digoxin and quinidine [15, 44], five cases did not revert to sinus rhythm on this combination [19, 45-47], while another case was therapy resistant to quinidine as a monotherapy [48]. Two fetuses required maternal oral quinidine as additional therapy to a fetal intramuscular injection of digoxin to sustain sinus rhythm [47].
In conclusion, the present data are too scarce to draw conclusions on the safety and efficacy of quinidine. Since it is thought to increase maternal mortality [10], it should not be used in the treatment of fetal tachycardia.

Procainamide

Pharmacodynamics
Procainamide is a class IA antiarrhythmic agent that delays conduction in the atria, AV node and ventricles with prolongation of the action potential and the effective refractory period. It does not have a negative inotropic effect. Its active metabolite N-acetylprocainamide has class III antiarrhythmic properties.

Pharmacokinetics
Procainamide is absorbed rapidly and almost completely, resulting in a bioavailability of 85 %. It metabolizes in the liver to the active N-acetylprocainamide and is excreted mainly by the kidneys. The elimination half-life is 3-4 hours. Therapeutic plasma concentrations are 4-8 mg/l.

Dose
Oral administration is hampered by the fast elimination of procainamide and it is thus mainly initiated intravenously, with a loading dose of 100 mg over 2 minutes followed by a maintenance dose of 2- 6 mg/min. If administered orally the recommended dose is 1 g followed by 500 mg 8x/day.

Transplacental transfer
Fetal: maternal ratios vary between 0,28 and 1,1 [49, 50]. Caution is required as procainamide could accumulate in the fetus [51].

Adverse effects and precautions
Prolongation of QT interval, hypotension, gastro intestinal symptoms and agranulocytosis have been reported. Procainamide interacts with amiodarone. Administration should be carefully monitored by ECG.

Clinical experience
There is limited fetal experience with procainamide and data is mostly confined to reports on its use as a second or third line drug. Frohn-Mulder et al. found it to be ineffective in 5 hydropic fetuses in a multidrug setting [28], and van Engelen et al. treated 4 hydropic fetuses with several drugs including procainamide [27]. Three of these four fetuses converted to sinus rhythm. Data from case reports is inconclusive, with 14 fetuses treated and conversion reached in 6, [52-56] . Moreover, most of these fetuses were treated with a multidrug regimen and the specific effect of procainamide cannot be determined. A problem encountered is the high frequency of the doses needed, if administered orally.

In conclusion, data are inconclusive on the efficacy of procainamide and moreover, the inconvenience of the high frequency of oral dosing is a major limitation to compliance. Procainamide should therefore not be considered for early inclusion in the treatment protocol.

Disopyramide

Pharmacodynamics

Disopyramide is a class IA type antiarrhythmic agent that delays the conduction throughout the myocardium and lengthens the refractory period. It has an indirect parasympathicolytic effect and, as a result, has virtually no effect on the sinus node frequency and conduction through the AV node. It has a negative inotropic effect.

Pharmacokinetics

Orally administered disopyramide has a bioavailability of approximately 45- 85 %. Peak plasma concentrations occur 1-2 hours after administration. Disopyramide is metabolized into the active N- monodesalkyl disopyramide and is excreted for 75 % by the kidney and the remainder through the faeces. The eliminition half-life is 4-9 hours.

Dose

The oral dosage is 100- 150 mg 4x/day. Intravenously, the loading dose consists of 2 mg/kg in 10 minutes under close ECG monitoring and is continued by 0,4 mg/kg/hour, up to a maximum of 800 mg/day. Therapeutic blood levels are 2- 4 mg/l.

Placental transfer

Measured fetal: maternal plasma concentration ratios vary from 0,26 to 0,39 [57, 58].

Adverse effects and precautions

Life threatening ventricular arrhythmias induced by prolongation of the QT interval have been reported, as well as induction of an AV block. Disopyramide may aggravate heart failure. In late pregnancy, disopyramide may stimulate uterine contractions, causing vaginal hemorrhage and induction of labor [59, 60].

Clinical experience

Data on the use of disopyramide in the treatment of fetal tachycardia are non existent. Due to its adverse effects and to its stimulating effect on the induction of labor in particular, it should not be used in the treatment of fetal tachycardia.

Flecainide

Pharmacodynamics

Flecainide is a class IC antiarrhythmic agent. Flecainide depresses conduction throughout the myocardium, with its greatest effects on the

His-Purkinje system, and a prolongation of atrial, AV nodal and ventricular refractory periods. Flecainide has been shown to produce negative inotropic effects and congestive heart failure has been reported.

Pharmacokinetics
The bioavailability of orally administered flecainide is 70 %- 90 %, with peak plasma concentrations occurring 1,5 to 6 hours after administration. Plasma protein binding occurs in approximately 40 %. Flecainide undergoes extensive biotransformation to 2 major metabolites and several minor metabolites, all of which are inactive. A mean of 86 % is excreted in the urine as flecainide and metabolites. In patients with normal renal function, the elimination half-life is 7 to 22 hours, with an average of 14 hours.

Dose
The recommended daily dose of oral flecainide varies from 200 to 400 mg, given twice to thrice daily without a loading dose. The daily dosage should not exceed 600 mg. It is recommended to initiate therapy in a small dose (100 mg 2x/day), and stepwise increase the dosage to obtain efficacy. Blood levels should not exceed 1 mg/l, as higher serum levels are associated with a higher incidence of proarrhythmic effects [61].

Placental transfer
Flecainide passes the placental barrier easily, with fetal: maternal plasma concentrations ranging from 0,5- 0,97 [39,61-64].

Adverse effects and precautions
Dizziness, headache, visual disturbances, paresthesia, tremors, flushing, nausea and vomiting have been reported. One report describes conjugated hyperbilirubinemia shortly after birth in an infant that was treated with flecainide prenatally for fetal SVT. An extensive evaluation did not disclose a cause and the authors attributed the condition as an adverse effect of flecainide [65]. Flecainide has negative inotropic effects and development of or worsening of congestive heart failure occurs in 2 % to 5 % of patients [66]. Flecainide does generally not prolong the QT segment [67], however, one report described marked QT segment anomalies in a newborn that was treated with flecainide prenatally [68].
Of concern is the increased mortality reported in the Cardiac Arrhythmia Suppression Trial (CAST) [69]. This placebo controlled trial, in which flecainide was initiated in patients with ventricular premature beats after myocardial infarction, was discontinued prematurely because of excess deaths in the flecainide group. The authors concluded that

flecainide should be reserved for use in patients with life threatening arrhythmias. Publications on the safety and efficacy in children conclude that flecainide appears to be safe and efficacious in children with SVT. Flecainide may not be safe for children who have structurally abnormal hearts and atrial flutter or ventricular arrhythmias [70, 71].

Proarrhythmia
Proarrhythmic effects tend to occur in 4 % to 8 % of patients, however, these effects are not always related to life-threatening ventricular arrhythmias.

Clinical experience
In 1988, the first report appeared in which flecainide was used to suppress fetal tachycardia after digoxin had failed [33]. Since then several successful (case) reports have been published in which flecainide was used as a second line drug [20, 34, 35, 39, 72]. In 1991, Allan et al. published an article in which flecainide was the drug of first choice in a population of 14 fetuses with tachycardia complicated by hydrops [63]. Twelve fetuses converted to sinus rhythm and two other fetuses converted to sinus rhythm after the addition of digoxin. The authors state that, though very successful, the use of flecainide should be confined to patients with SVT complicated by severe hydrops due to the risks of possible side effects. Another report published by the same group several years later showed that although flecainide proved to be successful in the greater part of patients, rate control was not always achieved and some intra uterine deaths still occurred [29]. Two other larger studies published success rates of 100% in nonhydropic fetuses and 50 %-80 % in hydropic fetuses [27, 28]. In the past years, numerous case reports have been published in which flecainide proved to be successful as a single therapy or in combination with digoxin [31, 32, 64, 72-76].

In conclusion, flecainide is a successful drug in the treatment of fetal SVT. Of concern are the possible adverse effects experienced in the CAST study, which could affect both mother and fetus [69]. However, most studies on flecainide in the treatment of fetal tachycardias did not show any adverse effects. Intra uterine deaths while on flecainide have been described, although these might have been the result of the seriousness of the presenting condition, as flecainide is mainly used in severely hydropic fetuses. Flecainide should not be used in fetal AF as it can increase the ventricular response and therefore increase heart rate [63].

Propranolol

Pharmacodynamics

Propranolol is a nonselective Bèta-adrenergic blocking agent, devoid of intrinsic sympathicomimetic activity. It causes a decrease in cardiac output and oxygen consumption and it increases AV-nodal refractoriness.

Pharmacokinetics

Propranolol is completely absorbed after oral administration. Protein binding in pregnancy is 80 %. Propranolol is metabolized by the liver with subsequent renal elimination of the polar metabolites thus produced. The elimination half-life of orally administered propranolol is 3-6 hours. Therapeutic serum concentrations vary between 0,02 and 1 mg/l. The pharmacokinetics of propranolol and its metabolites are not significantly altered by pregnancy.

Dose

The recommended oral dose ranges between 30 –320 mg/day divided in 3-4 doses as the therapeutic concentrations vary widely (0,02 mg/l to 1 mg/l).
Intravenously, 1-6 mg given slowly is recommended.

Placental transfer

Propranolol, with a high degree of liposolubility, readily crosses the placenta. Fetal: maternal plasma ratios varying between 0,2-1,3 have been reported [77-79]. Caution must be exercised when interpreting cord blood propranolol concentrations. Lower plasma protein binding of propranolol in the cord blood implies that the unbound concentration of propranolol is similar in the mother and the fetus, even when the total drug concentration in the fetal plasma is only 50 % of that in the maternal plasma [80].

Adverse effects and precautions

Maternal adverse effects have been reported as a result of the Bèta-blocking properties of propranolol such as bronchospasm, bradycardia, hypotension, dizziness, heart failure, cold and cyanotic extremities [81] The drug is apparently not teratogenic, but fetal and neonatal toxicity may occur [82]. The most consistent observation is intrauterine growth retardation [83]. This occurred in 50% of the 12 cases in the study by Pruyn et al. [84]. A plausible mechanism is a reduced umbilical blood flow and thus a decreased nutrition after long-term propranolol administration, as has been shown in the ewe [84]. Other perinatal adverse

effects described are birth apnea, bradycardia, hypoglycemia, polycythemia, hyperbilirubinemia, prolonged labor and even fetal death [79, 81-83]. Propranolol should never be given in combination with verapamil, because both drugs have negative inotropic properties, which may lead to poor myocardial contractility and function [5].

Clinical experience

In 1978 Teuscher et al. reported a successful cardioversion of fetal tachycardia with maternal administration of propranolol (160 mg/day) during the last 20 days of a diabetic pregnancy [77].
Since then a couple of case reports have been published, though the results are largely disappointing [5, 19, 85].
Dumesic et al. reported only partial improvement of supraventricular tachycardia after maternal administration of propranolol in combination with digoxin [49].
Ito et al. published a review article in 1994 in which they describe failure of maternal propranolol therapy in 14 of 16 patients [80].
In conclusion, propranolol does not seem to be effective in the treatment of fetal tachycardia, moreover, it has been associated with intra uterine growth retardation and other adverse effects. Therefore we advise not to use propranolol, unless there is no other alternative.

Sotalol

Sotalol hydrochloride is a noncardioselective Bèta-adrenergic-blocking agent devoid of intrinsic sympathomimetic and membrane-stabilizing actions. In addition, sotalol prolongs the duration of action potentials in cardiac tissue and increases the refractory period. Hence, besides the Bèta-blocking actions, it has additional class III anti arrhythmic properties. The net hemodynamic effects of sotalol are the result of a balance between its negative inotropic action caused by Bèta-adrenergic antagonism and its tendency to increase contractility by prolongation of the action potential duration [86].

Pharmacokinetics

Orally administered sotalol is virtually completely absorbed and does not undergo first-pass metabolism in the liver, resulting in an absolute bioavailability of 90-100 %. Peak plasma concentrations generally occur 2 to 4 hours after administration and a linear relation exists between the administered dose of sotalol and the plasma concentration. Sotalol is not bound to plasma proteins and not metabolized but excreted unchanged in urine. In patients with normal renal function, the mean (±SD) elimination half-life is 8±3 hours [86].

Dose
The recommended oral starting dose is 160 mg 2x/day and can be increased to a maximum of 160 mg per 3x/day.

Placental transfer
Sotalol passes the placental barrier rapidly and almost completely. Measured fetal: maternal plasma concentration ratios vary from 0,47 to 1,42 [61, 87-89] . Current investigations at our center suggest a ratio of 1:1, with an amniotic fluid level: maternal plasma concentration ratio of 3:1.

Adverse effects and precautions
Some Bèta-blockers may cause intra uterine growth retardation and reduce placental weight, however, these findings have not been demonstrated with sotalol.
Maternal adverse effects can result from the Bèta-blocking properties of sotalol and present as fatigue, dizziness, dyspnoea, chest pain, palpitations, asthenia, bradycardia, nausea and vomiting. In our series this occurred temporarily in 2/21 patients [90].

Proarrhythmia
Of more concern are the possible proarrhythmic effects of sotalol, both in the mother as well as in the fetus. The development of torsade de pointes tachycardia is always a point of concern with the use of class III antiarrhythmics and concerns approximately 2,4 % of patients [91]. In general, women are at increased risk for the development of torsade de pointes while using sotalol. However pregnant women are generally without heart disease and these complications are likely to be lower. Precaution should still be taken whenever sotalol therapy is initiated and a thorough maternal examination, consisting of the exclusion of preexisting arrhythmias or heart failure and an ECG recording to evaluate the QT interval, should be performed. Unfortunately, it is currently not possible to measure the fetal QT interval and the possible proarrhythmic effects on the immature fetal myocardium can not be minimized, although the development of fetal magnetocardiography may provide a solution to this problem in the near future (see discussion).

Clinical experience
The experience with sotalol in the treatment of fetal tachycardia, besides several successful case reports [92-94] confines to two studies. The study by Sonesson et al. [95] consists of patients with fetal SVT in which

digoxin as a monotherapy was not successful and sotalol was added to the treatment. Conversion to sinus rhythm after the addition of sotalol to the treatment was achieved in almost all fetuses, however, two severely hydropic fetuses died in utero. The authors conclude that sotalol might be considered as the drug of second choice in the treatment of fetal SVT. In our study of 21 patients, with both SVT and AF, sotalol was used as drug of first choice with the addition of digoxin in unsuccessful cases. The treatment protocol proved to be very successful in fetal AF with a conversion rate of 80-90 %. A moderate success rate of 60 % was achieved in fetal SVT. The mortality rate in this study was 19 % and consisted of 3 fetuses with SVT and 1 fetus with AF. We concluded that sotalol should be considered as the drug of first choice in fetal AF, but that in case of fetal SVT complicated by hydrops, the risks of sotalol may outweigh its benefits and might therefore be limited in the treatment of fetal SVT with hydrops [90].

Amiodarone

Pharmacodynamics

Amiodarone is a class III antiarrhythmic agent, with a content of 39 % iodine, that prolongs the repolarization of the myocardium, without influencing the rest potential. Additionally, it has Alpha- and Bèta-sympathicolytic and vasodilatating effects.

Pharmacokinetics

Orally administered amiodarone has a bioavailability of 30-80 %. As a result of tissue affinity, the drug accumulates in muscle and fat tissue in the first few days. This is followed by elimination, and after two months a steady state occurs between uptake and elimination. The iodine is split from amiodarone, the rest is partially metabolized in the liver. Iodine is eliminated through the urine and the rest of the molecule for 65-75 % through bile and faeces. The elimination half-life is 20-100 days.

Dose

The recommended oral starting dose is 800-1200 mg daily during 8-10 days. When the effect is achieved the dose can be lowered to a maintenance dose of 400- 800 mg daily.

Placental transfer

Amiodarone and its metabolite, desethylamiodarone, cross the placenta to the fetus. Fetal: maternal ratios vary between 0,10-0,28 [96, 97].

Adverse effects and precautions
Fetal or maternal hypo- or hyperthyroidism has been reported [98-102]. Neonates exposed to amiodarone in utero should have thyroid function studies performed because of the large proportion of iodine contained in each dose [103, 104]. Furthermore gastro-intestinal symptoms, rash, pruritis, corneal microdeposits, peripheral neuropathy, myopathy, extrapyramidal tremor, cerebellar ataxia, insomnia and nightmares are reported. Pulmonary toxicity and hepatic toxicity may occur. Neonates should have liver functions tested. Intra uterine growth retardation occurs frequently in infants exposed to amiodarone in utero [99, 104]. Rarely proarrhythmic adverse events such as torsade de pointes tachycardia related to prolonged QT interval occur. Bradycardia is also reported.

Clinical experience
Several case reports have been published on the use of amiodarone, mostly in the treatment of fetal SVT [26, 36, 100, 105, 106]. In most of these reports, amiodarone was initiated in combination with other drugs of which the combination with digoxin is most common. Although amiodarone did not succeed in establishing sinus rhythm in all cases, over one half of all case reports were successful, and one must bear in mind that it is mainly used in cases that are refractory to conventional treatment protocols. Direct fetal administration of amiodarone has been described in 7 cases [101], [105-107] of whom 6 proved to be successful, twice fetal bradycardia was noted and one fetus died on the second day postnatally due to renal failure, disseminated intravascular coagulation and intractable SVT [29]. Of major concern is the potential to cause hypothyroidism in the fetus and subsequent neurological abnormalities which has been described in several reports. Other adverse effects as intra uterine growth retardation, prematurity and fetal bradycardia are also reported [104].

In conclusion, amiodarone seems to be a very potent antiarrhythmic agent in the treatment of therapy resistant fetal tachycardia. However, amiodarone has been shown to produce substantial fetal adverse effects and is therefore excluded for early inclusion in the treatment protocol. It may be used as drug of last resort when other types of therapy fail to restore sinus rhythm. Full neonatal thyroid function tests are in that case recommended. If pathological, the thyroid function should be normalized and developmental follow-up is recommended.

Dofetilide

Pharmacodynamics

Dofetilide is a pure class III antiarrhythmic agent and therefore selectively prolongs repolarization without affecting conduction velocity.

Pharmacokinetics

The bioavailability of orally administered dofetilide approaches 100 % and peak serum levels occur within 2,5 hours of administration. It is metabolized partly in the liver and excreted in the urine and the elimination half-life is 7-8 hours [108].

Dose

Dosing of dofetilide should be individualized and depends on the QTc interval and calculated creatinine clearance (CrCl). In patients with a QTc greater than 440 milliseconds, dofetilide is contraindicated. If the CrCl > 60 milliliters/minute (mL/min) the recommended dose is 0,5 mg 2x/day. If CrCl is 40 to 60 mL/min, the oral dose is 0,25 mg 2x/day. Whenever the CrCl is 20 to 40 mL/min, the oral dose is 0,125 mg 2x/day. The drug is contraindicated in patients with a CrCl of < 20 mL/min. Patients are to be monitored for a minimum of 3 days.

Transplacental transfer

No data exists on the transplacental transfer of dofetilide.

Adverse effects and precautions

Dofetilide has been well tolerated, although headache, dizziness, and chest pain are reported [109]. It does not appear to have a negative inotropic effect. torsade de pointes occurs in approximately 0,8 %, associated with higher doses, usually shortly after initiation and in patients with electrolyte imbalances [110]. It is contraindicated in congenital or acquired long QT syndrome and patients with severe renal impairment. Concomitant use of dofetilide with cimetidine, ketoconazole or verapamil is contraindicated.

Clinical experience

No reports on the use of dofetilide in the treatment of fetal tachycardia have yet emerged. Our opinion is that dofetilide may prove to be useful in fetal atrial flutter resistant to conventional therapy.

Verapamil

Pharmacodynamics

Verapamil is a class IV antiarrhythmicum, a calcium channel blocking

agent that inhibits the slow influx of calcium-ions through the cell membrane of contractile and conducting cells in the heart and of smooth muscles of coronary and peripheral arteries. It decreases contraction and delays conduction in the sinus node and the AV-node. This results in an increased coronary blood flow and a decreased peripheral arterial resistance. The oxygen consumption of the myocardium decreases and the oxygen supply increases.

Pharmacokinetics
As a result of an extensive first-pass effect, bioavailability after oral administration is only 10-35 %. Peak plasma levels are achieved after 1-2 hours, and 4-8 hours after intake of retard tablets. The plasma protein binding is approximately 80 %. Verapamil is mostly excreted as metabolites through the urine and faeces. The elimination half-life is approximately 8 hours.
With repeated admission, accumulation of the active metabolite norverapamil is possible.

Dose
An intravenous loading dose of 5- 10 mg over 60 sec. is recommended. Oral maintenance dose should be 320- 480 mg daily divided in 3 to 4 doses. The daily dosage should not exceed 720 mg.

Placental transfer
Verapamil has been shown to pass the placenta. Fetal: maternal plasma ratios vary from 0,17- 0,26 [16].

Adverse effects and precautions
Hypotension, bradycardia, obstipation, headache, nausea, flushing and dizziness are reported.
Animal studies have shown verapamil to be embryocidal and cause retarded fetal growth and development. Hypotension has been observed in patients after rapid bolus [4], and reduced uterine blood flow with fetal hypoxia is a potential risk [111] . Verapamil should not be initiated in combination with propranolol as this could have severe negative inotropic effects and may induce high-grade AV block [4, 5].

Clinical experience
Verapamil is a drug that has been frequently used, particularly in the 1980's. Numerous case reports and several larger studies exist in the international literature in which verapamil was mostly initiated in combination with digoxin. Both successful and unsuccessful case

reports have emerged. One large study reports a conversion rate of 10/14 nonhydropic fetuses and 11/17 hydropic fetuses with a combination of digoxin and verapamil. However, one hydropic fetus was treated with an intraumbilical injection of 0,2 mg verapamil which immediately lead to asystoly from which the fetus could not be resuscitated [29]. Another report of 6 cases successfully treated with a combination of digoxin and verapamil warns for maternal adverse effects as verapamil caused second degree AV block in one mother [4]. One fetus that initially reverted to sinus rhythm on digoxin and verapamil died spontaneously in utero and the authors conclude that this could have been the result of side effects of the drug therapy [112]. In addition, verapamil has been shown to cause fetal bradycardia, heart block, depression of contractility and hypotension in the fetus [5, 35].

In conclusion, although verapamil, especially in combination with digoxin, seemed to be a potent drug in fetal tachycardia, major concerns have arisen on its adverse effects and possible increased mortality. In our opinion, verapamil should, therefore, not be used in the treatment of fetal tachycardia.

Adenosine

Pharmacodynamics

Adenosine, an endogenous purine-based nucleoside, is found in all cells of the body. It delays AV-nodal conduction which interrupts re-entry and restores normal sinus rhythm. Adenosine can be used to confirm the diagnosis of re-entrant tachycardia.

Pharmacokinetics

Erythrocytes or vascular endothelial cells eliminate adenosine by uptake from the plasma. Elimination half-life is very short (<10 sec).

Dose

Adenosine is used for direct treatment of the fetus by intravenous injection into the umbilical vein in a dose of 0,1-0,2 mg/kg estimated fetal weight [10].

Adverse effects and precautions

The short elimination half-life limits the maternal adverse effects of direct fetal treatment and a number of reports have described the safety of adenosine during all phases of gestation [113].

Clinical experience
A few case reports are described in which fetal administration was transiently successful [26, 29, 80]. However, tachycardia recurred in all fetuses and additional therapy was required. One fetus died, presumably of recurrence of the tachycardia or as a result of proarrhythmic effects of the drug regimen [114].

In conclusion, adenosine is a potent drug for direct fetal treatment of SVT with immediate but transient cardioversion, however, in all cases additional drug therapy is required. In our opinion, if one opts for direct fetal therapy, a drug with a longer lasting effect has the preference.

Discussion

Necessity for treatment
The decision to initiate pharmacological intervention in the case of fetal tachycardia depends on several factors and must be weighed against possible maternal and/or fetal adverse effects inherent to the use of antiarrhythmics (see drugs). The problems encountered with a premature delivery has lead to the decision of treatment in utero, although delivery by cesarean section in case of a gestational age of > 33 weeks may be an option in severe cases with therapy resistant tachycardia. The most important goal of initiation of treatment is the prevention or resolution of hemodynamic compromise with subsequent development of hydrops. Although conversion to a sinus rhythm is desirable [7], in case of atrial flutter, an AV-block with a significant decrease in ventricular rate is acceptable. In cases where signs of hemodynamic compromise is present, the fetus is at high risk of demise and should therefore be treated immediately [115]. However, the optimal treatment protocol of fetuses with isolated tachycardia (without signs of hemodynamic compromise) remains controversial [6]. The absence of reliable predictors of fetal hydrops and the difficulties in management of hydropic fetuses lead to the initiation of treatment as soon as the diagnosis of fetal tachycardia has been established in most centers [17, 116]. The reports on expectant management in fetal tachycardia [6, 7, 53] oppose this regimen and suggest that in cases with isolated fetal SVT, conservative management in the setting of close surveillance could prove to be a reasonable alternative, since spontaneous resolution of the tachycardia has been described [1, 6].
Determining the likelihood of the development of hydrops in a particular case may be a difficult or impossible task. However, if one contemplates to opt for conservative therapy, the following factors play a role:

- The percentage of time that the tachycardia is present. Sustained tachycardias are presumed to be at greater risk to develop hydrops although intermittent tachycardias can lead to hydrops as well [117].
- The ventricular rate may be a predictive factor in the development of hydrops [7]. However, several reports did not found a difference in ventricular rates between hydropic and nonhydropic fetuses [27, 90].
- The site of origin of the tachycardia may play a role in the risk of development of hydrops. When the atrial depolarization arises in the left atrium, the resulting reversal in the pressure gradient could result in a volume overload of the right atrium. This could be the first step in a rise in right atrial and systemic venous pressure [10].

Hemodynamic compromise may occur in less than 24 hours in these fetuses [4, 118] and the three factors described are not very sensitive. We therefore prefer to initiate therapy as soon as the diagnosis has been established. The more so since outcome in hydropic fetuses is poor with intra uterine death or neurological damage as possible consequences [119].

Place for Direct fetal treatment

Transplacental therapy should be the mode of therapy in nonhydropic fetuses and first choice in hydropic fetuses. However, when conversion to sinus rhythm is not achieved with several maternally administered antiarrhythmic drugs, one may opt for direct fetal therapy.

The relative therapy resistance to transplacental therapy in hydropic fetuses has lead some centers to pursue direct fetal therapy [21, 26, 29, 47, 105, 106, 114]. Several modes of direct fetal therapy have been described, including intra-umbilical, intra-amniotic, intra-peritoneal, intra-muscular and intra-cardiac injections. These reports however, show a significant mortality, but it is unclear if these deaths are attributable to the invasive measures or the severity of the underlying condition.

The routes of administration all have their specific characteristics. An intra-umbilical injection allows direct access to the fetal circulation and thereby the potential for a quick response to therapy [47] , a characteristic also observed with intra-cardiac injections. However, both of these invasive measures pose a significant risk to the fetus. Intra-peritoneal, intra-amniotic and intra-muscular injections (preferably in the buttock of the fetus), pose less risk to the fetus and provide a more sustained release of the medication.

Parilla et al. combined the use of transplacental and direct fetal intramuscular therapy with digoxin in 6 fetuses with SVT complicated by hydrops [47]. While some fetuses required additional transplacental

drugs, the authors saw a reduction in time to cardioversion and resolution of hydrops compared to a group that was solely treated with transplacental multi-drug therapy. Hansmann et al. treated fetuses with SVT complicated by hydrops with IV therapy via the umbilical vein after failed transplacental therapy [26]. A mean of seven injections (range 2 to 25) was required to achieve sustained sinus rhythm, but several fetuses died in utero. Simpson et al. reported in 1998 on 4 fetuses that were treated through direct fetal therapy [29]. One fetus died immediately after an intra-umbilical injection of 0,2 mg verapamil. Two fetuses were successfully converted with intra-umbilical amiodarone (dosage varying from 10 – 20 mg), while another fetus that was treated by intra-umbilical amiodarone died 2 days after birth due to multiple complications. Flack and colleagues took a different approach, a hydropic fetus with atrial flutter at 480 bpm with 2:1 AV-block that was refractory to transplacental sotalol and flecainide therapy, was treated by combined intra-umbilical, intra-peritoneal and transplacental amiodarone therapy [106]. While the intra-umbilical route (15 mg) provided a rapid therapeutic response, the intra-peritoneal injection of 15 mg provided a maintenance dosage. The oral maternal dosage of 200 mg 3x/day prevented the amiodarone from spreading from the fetal to the maternal compartment and may even have maintained a therapeutic level in the fetus. This combined therapy succeeded in controlling the tachycardia and resolving the hydrops, and maybe even more important, succeeded in minimizing the number of invasive procedures. Other case reports provide us with information that placental transfer of digoxin in hydropic fetuses is poor and intra-muscular fetal injections proved to be successful in reaching adequate therapeutic levels and conversion to sinus rhythm [16, 21]. Kohl et al. converted a hydropic fetus with SVT at 240-280 bpm with intra-umbilical adenosine injections (0,2 mg/kg); to maintain sinus rhythm, digoxin 0,05 mg/kg and flecainide 1,0 mg/kg was injected intra-umbilically [114]. One week later, the fetus had died in utero, presumably due to the recurrence of the pre-existent tachycardia or as a proarrhythmic result of the drug regimen. If one chooses to opt for direct fetal therapy, one must bear in mind that the antiarrhythmic drug will probably distribute to the maternal compartment, unless this compartment is primed with the drug. Therefore, direct fetal therapy should always be administered as an adjunct to maternal administration [80]. In addition, intra-muscular or intra-peritoneal injections that provide a more sustained release into the fetal circulation, as well as an antiarrhythmic drug with a long half-life are to be preferred as this will minimize the number of invasive procedures required [106].

Future prospects

Fetal magnetocardiography

The lack of the presence of a reliable fetal ECG has hampered our ability to define the exact electrophysiologic mechanism of the tachycardias encountered in utero. The development of fetal magnetocardiography, a method that measures in a noninvasive way the magnetic field produced by electrical currents in the fetal heart, provides a way to define the electrophysiologic mechanism of the tachycardia [120]. This has resulted in several publications on the diagnosis of the long QT syndrome in utero [121, 122].

Development of specific therapeutic protocols

Specific types of tachycardia (e.g. WPW syndrome, long QT syndrome), are sometimes treated with potentially harmful drugs. In addition, fetuses with a specific condition are probably not always treated with the optimal drug for that condition. Establishment of the exact electrophysiologic mechanism of the tachycardia as described in the previous paragraph enables the pharmacological intervention to be specific for the type of tachycardia. This may result in a more fitting approach to these specific types of tachycardia, and therefore may result in higher success rates and decrease the incidence of morbidity and mortality, possibly induced by contraindicated antiarrhythmic agents.

Development of new antiarrhythmics

Much is to be expected form the ongoing development of new drugs with specific clinical applications and with less adverse effects. A promising agent is dofetilide, a pure class III antiarrhythmic agent, which is specifically developed for the treatment of atrial flutter/fibrillation.

Optimal dosing regimen

Transplacental drug therapy requires an adequate dosing schedule as the antiarrhythmic agent will spread to two compartments with transplacental passage playing a crucial part in the eventual outcome. Currently a prospective study on the pharmacokinetics in transplacental therapy is performed at our center. The relationship between maternal, fetal, amniotic and neonatal plasma levels of antiarrhythmic drugs and the effects of drug therapy may eventually lead to an optimal dosing regimen.

MulticenterTrial

Most treatment protocols found in the international literature are

based on a combination of local clinical experience and retrospective studies. In view of the evidence based medicine, we and Simpson and Sharland [29] , consider there is a need for a prospective, multicenter, randomized trial to establish the optimum protocol for the management of fetal tachycardias.

Proposed drug protocol

Based on the literature and previous studies at our center in Utrecht we developed a drug protocol for fetal SVT (*figure 1*) and for fetal AF (*figure 2*).

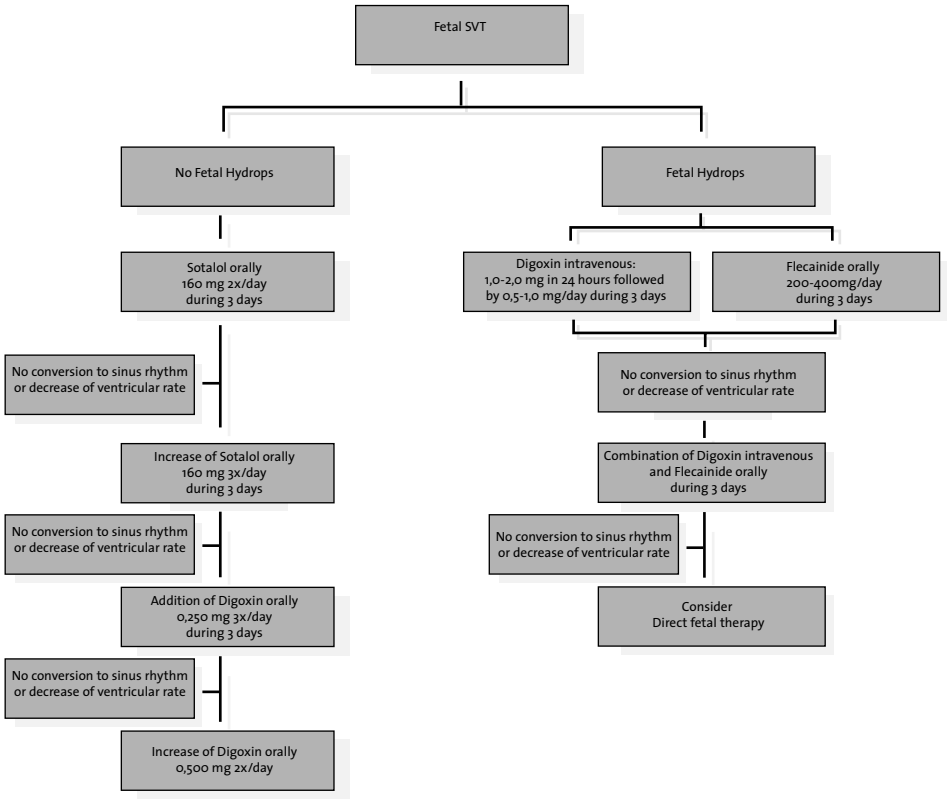

Figure 1

Utrecht protocol Fetal Supraventricular Tachycardia

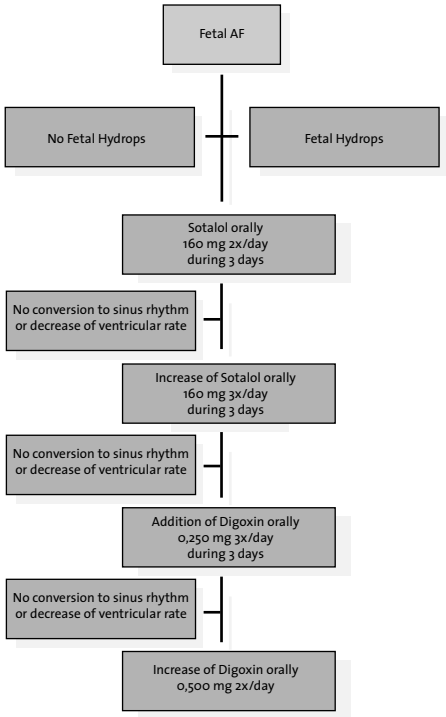

Figure 2

Utrecht protocol Fetal Atrial Flutter

In the treatment of fetal nonhydropic SVT we recommend sotalol as drug of first choice, followed by digoxin as drug of second choice. This protocol has reached conversion rates of around 60 % with sotalol as a single therapy, and a conversion rate of 71 % after the addition of digoxin. These results are comparable with the upper range of other treatment protocols.

In case of SVT complicated by hydrops we opt for a more aggressive approach with maternal IV digoxin or maternal oral flecainide. The second step is a combination of these drugs.

In fetal AF we prefer the use of sotalol above digoxin. Our center has been using this protocol for many years now, and has been satisfactory. We believe that sotalol is superior to digoxin in the treatment of fetal AF as written in our article [90], with a conversion rate as high as 80 %, nowhere to be found in the international literature in which conversion rates are mentioned of around 50 %. However, if sotalol as a single therapy fails to restore sinus rhythm within 6 days, we do add digoxin

to the treatment. We therefore do value the place of digoxin in the treatment of fetal AF. In our protocol there is no difference in treatment with regard to the hydropic state.

Conclusions

Fetal tachycardia can lead to fetal hydrops, neurological damage and fetal death. In the absence of reliable predictors of hemodynamic compromise, pharmacological intervention, as soon as the diagnosis has been established, has our preference. In fetuses with SVT not complicated by hydrops, or AF with/without fetal hydrops, oral maternal transplacental therapy is preferred. Sotalol is the drug of first choice, followed by digoxin as drug of second choice. Fetal SVT complicated by hydrops should be more aggressively treated, by digoxin administered intravenously. However, one can opt for oral flecainide therapy as it has proven to be very successful in hydropic fetuses. The second step in fetal SVT is a combination of IV digoxin and oral flecainide. In cases complicated by severe hydrops and/or in case of therapy resistance, direct fetal therapy may be initiated. Our preference would be to opt for an approach that will quickly achieve a therapeutic level in the fetus and thus hopefully conversion to sinus rhythm, for instance through the umbilical route. Secondly, a more sustained release of the antiarrhythmic agent into the fetal circulation is desirable and may be reached through an intramuscular or intraperitoneal fetal injection. Finally, direct fetal therapy should always be installed in conjunction with oral maternal therapy.

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Chapter 6

Treatment of Fetal Tachycardia with Sotalol: Transplacental Pharmacokinetics and Pharmacodynamics

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Abstract

Background

Maternally administered, intra uterine therapy of fetal tachycardia is dependent on the transplacental passage of the antiarrhythmic agent. In this study, the pharmacokinetics and -dynamics of sotalol and digoxin are therefore investigated.

Methods

A prospective study of patients treated for fetal tachycardia with sotalol and/or digoxin. Concentrations of sotalol and/or digoxin were determined in maternal, umbilical and neonatal blood and in amniotic fluid and the relationship between these concentrations and the occurrence of conversion to sinus rhythm, was investigated.

Results

Nineteen patients were studied, 10 with atrial flutter and 9 with supraventricular tachycardia. Fourteen were treated with sotalol; 13 converted to sinus rhythm, of whom 2 relapsed. There was one intra uterine death. Four patients were treated with sotalol and digoxin of whom 2 successfully. One patient was unsuccessfully treated with digoxin and flecainide. Mean birth weight was 3306 gram.The daily maternal sotalol dose was linearly related to the maternal plasma concentration. The mean fetal/maternal sotalol plasma concentration (F/M ratio) was 1,1 and the mean amniotic fluid/fetal blood ratio of sotalol was 3,2. The effectiveness of sotalol therapy could not be extrapolated from maternal blood levels. The sotalol T1/2 in neonates varied from 5,9 to 48 hours. Digoxin passes the placenta partially with a mean F/M ratio of 0,53.

Conclusions

Sotalol is a potent anti-arrhythmic agent in the treatment of fetal tachycardia. The placental transfer is excellent. Sotalol accumulates in amniotic fluid but not in the fetus itself. Therefore it seems that renal excretion in the fetus is efficient and greater than the oral absorption by fetal swallowing. The maternal blood level is not a reliable predictor of the chances of success of therapy. Sotalol is not associated with fetal growth restriction. Pharmacokinetics in the neonate show that the renal excretion in the neonate is adequate.

Introduction

Fetal tachycardia is a condition that occurs in approximately 0,4-0,6% of all pregnancies [1].

It is associated with congestive heart failure, fetal hydrops, neurological morbidity and intra-uterine death [2-5]. Most centers have therefore opted for prenatal intervention in the form of maternal pharmacological treatment [6-18]. Its success however, depends largely on the amount of drug that crosses the placenta, which is subject to the altered maternal pharmacokinetics and pharmacodynamics in pregnancy. Various physiologic changes during pregnancy influence maternal pharmacokinetics. In addition, the fetal plasma concentration is also influenced by changes in the fetus itself. Studies on the maternal-placental-fetal unit are limited for obvious ethical reasons, however, the treatment of fetal tachycardia provides us with a unique opportunity to investigate this matter. In the literature, data on the transplacental passage of sotalol is confined to two small studies and one case report [19-21].

We present a study in which we have prospectively investigated drug levels of the anti-arrhythmics sotalol and digoxin, in maternal blood, umbilical cord blood after delivery, amniotic fluid and neonatal blood. A correlation between the success or failure of treatment of maternal-fetal pharmacotherapy and blood concentrations in both mother and neonate is presented.

Methods and Materials

Definitions

Fetal tachycardia, defined as a fetal heart rate exceeding 180 bpm, was diagnosed by M-mode echocardiography and subdivided in supraventricular tachycardia (SVT; 1:1 atrioventricular conduction) and atrial flutter (AF; atrial rate >250 bpm with a fixed or variable atrioventricular block).

Congestive heart failure was diagnosed if fluid accumulation existed in the fetal body, such as pericardial effusion, pleural effusion, ascites or skin edema. Fetal hydrops was diagnosed if fluid accumulation existed in 2 or more of these compartments.

Patients

All mothers that were diagnosed with fetal tachycardia at the department of Obstetrics, University Medical Center, Utrecht, from 1999 until 2002 were given a detailed description of the study protocol and consented to enter this study. A maternal history was obtained to exclude preexisting arrhythmias, and a maternal ECG was made to exclude pro-

longed QT intervals. Therapy was installed according to a previously published protocol, consisting of sotalol 160 mg 2dd, increased to a maximum of 160 mg 3dd, and the addition of digoxin in case conversion to sinus rhythm did not occur [18, 22]. Patients were regularly scheduled (at least once a week) for control visits to evaluate the fetal heart rhythm and possible signs of congestive heart failure.
All deliveries took place at our institution and neonates were admitted immediately after birth for at least 48 hours for observation. Postnatal ECG's were performed in all neonates.

Blood sampling
At every prenatal visit, a 5 ml blood sample was drawn from a maternal peripheral vein to measure maternal drug levels. At the time of delivery 5 ml maternal blood, 5 ml blood from the umbilical artery and from the umbilical vein and whenever possible, 10 ml of amniotic fluid was collected. In three neonates, multiple blood samples of 1,5 ml were drawn to measure the elimination rate in the newborn.

Drug analysis
Digoxin in plasma was quantified using AxSYM Digoxin II Microparticle Enzyme Immunoassay (Abbott Laboratory, North Chicago, IL 60064, USA).
Sotalol concentrations in plasma and amniotic fluid were determined by a modified ionpair reversed-phase HPLC method, with ultraviolet detection at 226 nm described by Kärkkäinen [23]. The lower limit of quantification was 0,08 mg/L with an intra day coefficient of variation (CV) of 4,4% at 0,02 mg/L and an inter-day CV of 2,6% at 0,02 mg/L [24].

Approval
The study was approved by the Medical Ethics Review Committee of the UMCU, according to the Helsinki protocols.

Results

Nineteen women agreed to participate in this study. Details on diagnosis, treatment modalities and outcome are summarized in *Figure 1*. Out of 10 patients with AF, one fetus was hydropic; 2 out of 9 fetuses with a SVT had congestive heart failure. Fourteen patients received sotalol as single therapy. Of these fourteen patients, 10 converted to sustained sinus rhythm in a mean time to conversion of 46 hours (SD 32 h). In one additional patient two weeks were required to reach sustained sinus rhythm. Two patients, who initially converted to sinus rhythm within 48 hours, relapsed into tachycardia, after 1 and 5 weeks of sinus

rhythm, respectively. Since both patients had reached a gestational age of 37 + weeks at that time, we decided to perform a caesarean section (S.C.) rather than increasing the dosage or addition of another antiarrhythmic agent. One nonhydropic fetus with SVT died unexpectedly 3 days after initiation of therapy with sotalol 160 mg 2dd. Sinus rhythm had not been achieved. The maternal blood level of sotalol was 1,01 mg/L, which is within the normal range. Autopsy showed significant dilatation of the heart and minimal signs of hydrops. No structural abnormalities were present.

In four patients, digoxin was added to the sotalol treatment according to protocol, because of persistent fetal tachycardia. In two patients this was successful 24 h and 48 h after the addition of digoxin, respectively. One patient was delivered by S.C. at 35 weeks and 6 days after membranes had ruptured spontaneously and a prolapsed arm was diagnosed; sinus rhythm had not been achieved despite longstanding multiple drug therapy. The other patient was delivered by S.C. at 36 weeks and 6 days because of persistence of tachycardia despite 6 days of multiple drug treatment.

One patient with AF received both flecainide and digoxin. The addition of digoxin yielded a decrease in rhythm from 420/220 bpm to 300/150 bpm, however signs of fetal hydrops developed and maternal side effects consisting of nausea, vomiting and general malaise, probably due to extensive medication, increased. At 34 weeks and 1 day amniocentesis showed adequate fetal lung maturation (Lecithin/Sphingomyelin ratio > 2) and a S.C. was performed.

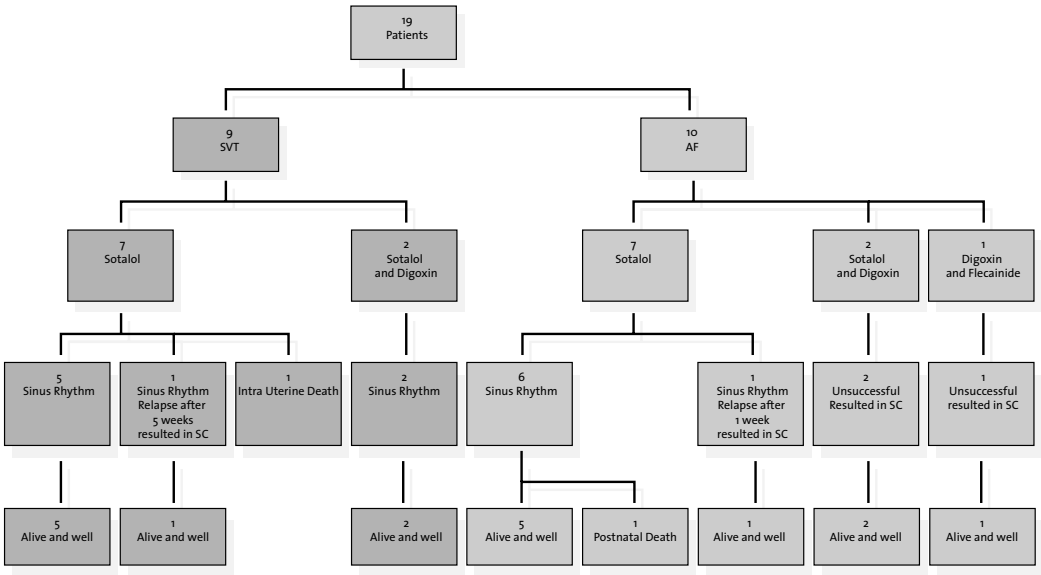

Figure 1

Details on diagnosis, treatment modalities and outcome of all cases. SVT, supraventricular tachycardia; AF, atrial flutter; SC, caesarean section.

Sotalol and digoxin levels

Maternal sotalol levels measured at the prenatal visits in all patients increased linearly with increasing dosis (*Figure 2*).

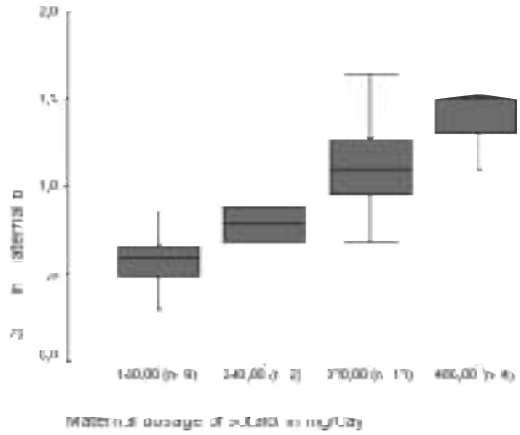

Figure 2
Mean interquartile range and overall range of maternal blood levels of sotalol per daily dosage. Number of women with observations are shown within brackets. A linear relationship between blood level and increasing dosage is shown.

Umbilical vein samples were obtained in 12 cases. The relationship between maternal sotalol dosage and umbilical vein concentration is shown in *Figure 3*.

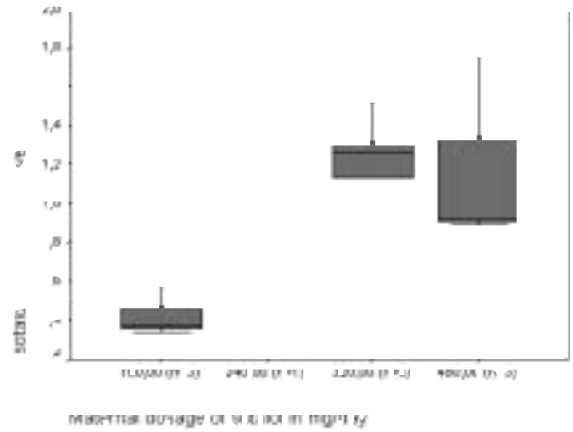

Figure 3
Mean interquartile range and overall range of umbilical blood level of sotalol per daily maternal dosage. Number of observations are shown within brackets.

Maternal and fetal blood levels were almost equal and the mean fetal/maternal sotalol ratio was 1,11 (SD 0,63), *Table 1*.
Data on digoxin dose and maternal and umbilical cord levels are shown in *Table 1*. The mean fetal/maternal digoxin ratio was 0,53 (SD 0,21).

Case #	F/M sotalol	F/M digoxin	Amn. fluid/F sotalol
1	0,83		
2	0,75	0,53	
3	0,75	0,77	4,0
4	1,79		3,15
5	1,02		
6	1,14	0,56	2,57
7	0,85		3,11
8	0,67		2,49
9	0,72		5,8
10	2,87		1,28
11		0,25	
12	0,82		
13	1,1		
Mean	1,11	0,53	3,2
SD	0,63	0,21	1,4

Table 1

The fetal/maternal ratio's at the time of delivery of sotalol and digoxin. Amn. fluid/F sotalol = ratio of sotalol in amniotic fluid/fetal blood.

Sotalol was measured in amniotic fluid in 7 cases. The concentration was higher in amniotic fluid than in fetal cord blood and maternal blood and the concentration ratio's were 3,2 and 2,94 respectively.

Correlation between maternal blood levels and success of therapy

In *figure 4* the maternal sotalol blood concentrations are shown in relation to the occurrence of conversion to sinus rhythm or otherwise. The levels at which the drug proved to be effective were only slightly higher than those that did not result in conversion, indicating a large difference in sensitivity to the drug. In the 3 individual patients in which sotalol initially was not effective, an increase in dose from 80 mg 2dd in two patients (blood levels 0,60 and 0,87 mg/L) to 160 mg

2dd (blood levels 1,27 and 1,63 mg/L) and from 160 mg 2dd in one patient (blood level of 0,77 mg/L) to 160 mg 3dd (blood level of 1,50 mg/L) was associated with conversion to sinus rhythm, whereas in one case a decrease in dose (from 160 mg 2dd to 80 mg 3dd) and blood level (1,75 mg/L to 0,6 mg/L) was associated with a relapse of AF.

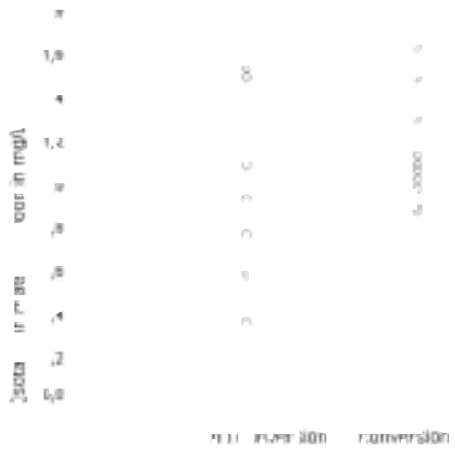

Figure 4

Maternal blood levels of sotalol in relation to the occurrence of conversion to sinus rhythm or persistence of tachycardia. No significant difference is noted.

Pharmacokinetics in the neonate

In 3 neonates, 2 to 3 blood samples were available for measurement of the elimination half-life of sotalol. The results are shown in *figure 5*. The $T_{1/2}$ varied from 5,9 hours to 48 hours, roughly comparable to the $T_{1/2}$ in adulthood (10-20 hrs).

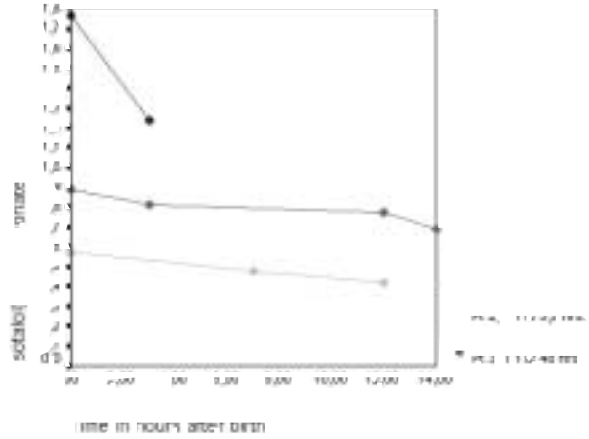

Figure 5

Blood samples of sotalol of 3 neonates. The calculated elimination half-life is shown on the right.

Postnatal outcome

One fetus died in utero and one infant with a massive hydrops, delivered at 33 weeks and 4 days, died two days after delivery. Follow-up is available for the other 17 infants, varying from 6 months to 30 months after birth. Eight infants (5 had AF and 3 had SVT) had no rhythm disturbances during the newborn period and no medication was initiated. None of these patients have developed episodes of tachycardia and are currently doing well. Four patients showed AF at birth (three therapy resistant cases and one relapse) and all required electrical cardioversion to reach sustained sinus rhythm. These four patients are currently doing well and require no medication. Five patients showed SVT postnatally, of whom 2 had WPW, 2 had PJRT, and 1 patient showed intermittent periods of SVT of unknown origin. All are doing well on antiarrhythmic therapy, consisting of digoxin in two patients, propranolol in one patient, and a combination of these two agents in two patients.

All surviving infants are in good neurological condition.

Birth weight

The mean birth weight was 3306 gram (SD 814). All infants were appropriate for dates with one exception. This baby was born at 33^{+4} weeks of G.A. with a birth weight of 960 gram, which is below 2,3 rd percentile [25]; this infant was only treated for 4 days and the low birth-

weight could therefore not be attributed to the Bèta blocking therapy.

Discussion

Success of therapy

In the patients treated with sotalol as a single agent, results were favorable, since 13/14 patients converted to sinus rhythm in a relatively short amount of time. Unfortunately, the one patient who went into premature labour did not profit long enough of sinus rhythm as this only lasted for three days and hydrops was still present at the time of delivery. The other 2 patients who went into relapse clearly profited from in utero therapy as they reached gestational maturity while on therapy. Our choice of delivery by S.C. at that time rather than the increase of dosage or the addition of a second antiarrhythmic agent was based on our opinion that the possible harmful effects of transplacental therapy (adverse effects of mother, and potential proarrhythmic effects for both mother and fetus) outweigh the benefits of further in utero maturation. In the case that was treated with both sotalol and digoxin in which no conversion was reached at 36^{+6} weeks, the decision to perform a S.C. was based on the same opinion.
The unexpected intra uterine death, possibly as a result of ventricle fibrillation raises the possibility of proarrhythmic effects of sotalol in the fetus. Although we have no evidence that this was indeed the cause of death, we think that this possible risk should be minimized. Intra uterine therapy should therefore always be weighed against possible adverse effects. As proarrhythmia of sotalol is known to be dose related [26], low initiation doses are preferable and dosage increases should be stepwise. Close monitoring, especially during the initiation phase is recommended. We therefore propose a new dosage scheme with an initiation dose of 80 mg 2dd, stepwise increased with 80 mg per 3 days to a maximum of 160 mg 3dd. Digoxin may be added as second line drug.

Dosage and maternal blood levels

Despite high oral sotalol dosages, all maternal blood levels remained below the 'toxic' level of 2,5 mg/L (at which marked QTc prolongation is noted). This is probably the result of the increased blood volume in pregnant women. This is important, as maternal adverse effects and the risk on torsade de pointes tachycardia (as a result of QTc prolongation) are dose-related. The F/M ratio of 1,11 shows that the fetus also stays below the 'toxic' level.

Fetal/maternal ratio of plasma concentration

Sotalol passes the placenta easily and completely as can be concluded from the mean F/M ratio of 1,11. This relates to the publication of O'Hare et al.[19], though differs from the lower ratio found in the study of Erkkola et al.[20]. This could be explained by the nature of the study in which only a single dose was administered 3 h before delivery. The ratio of 1,11 compares favorably with the F/M ratios of other commonly used drugs in fetal tachycardia. Apparently sotalol does not accumulate in the fetus, which implies that the excretion of sotalol by the fetal kidney is efficient close to term. The adequate renal excretion may explain the relatively high concentration of sotalol in amniotic fluid. The high amniotic fluid/umbilical venous blood ratio combined with an almost 1:1 relationship of fetal and maternal blood and the nature of swallowing of amniotic fluid by the fetus implies that the elimination rate of sotalol is greater than the oral reabsorption.
Digoxin passes the placental barrier, though not completely as is observed by the F/M ratio of 0,62. This is in agreement with other publications in which ratio's of 0,4 – 0,9 [27-30] have been found. Therefore high maternal dosages are required to achieve adequate fetal blood levels. This may induce maternal adverse effects as was observed by us in one case in which the pregnancy had to be terminated by 34 weeks and 1 day by S.C. because of these adverse effects and the impossibility to increase the dosage further.

Correlation of maternal blood level and success of therapy

Although in individual cases, the maternal dosage of sotalol was related to the success of therapy, statistically a strong relation between the maternal blood level and the success of therapy was not shown. The therapy resistant cases required either electrical cardioversion or multiple drug therapy, wich suggests that the success of therapy may be more related to the type of arrhythmia.
The maternal blood levels do however, strongly relate to the fetal blood level and could thus be valuable in preventing the fetus to be exposed to toxic levels.

Birth weight

Some Bèta blockers like propranolol, have been associated with intra uterine growth retardation [31]. All but one of our patients had birth weights within the normal range with one exception, even though in several cases this treatment was continued throughout the whole

third trimester. Therefore, it seems unlikely that sotalol induces fetal growth restriction.

Conclusions

We conclude that sotalol is a potent anti-arrhythmic agent in the treatment of fetal AF with or without hydrops as well as in SVT not complicated by hydrops. Sotalol passes the placenta quickly and reaches a steady state level almost identical to the maternal plasma level. Maternal blood levels can therefore be used as an indicator of the fetal blood levels. Sotalol accumulates in amniotic fluid but not in the fetus itself, indicating that renal excretion is efficient, and implying that the elimination rate of sotalol exceeds oral absorption in term fetuses. Maternal blood levels are not a reliable predictor of the chances of success of therapy. Sotalol is not associated with fetal growth restriction. Pharmacokinetics in the neonate show that the renal excretion in the neonate is adequate and comparable to the excretion in adults.

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Chapter 7

Sotalol in the treatment of Fetal Dysrhythmias

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Abstract

Background

Fetal tachycardia may cause hydrops fetalis and may lead to fetal death. No unanimity of opinion exists regarding the optimum treatment. This study evaluates our experience with transplacental sotalol therapy in the treatment of fetal tachycardias in terms of safety and efficacy.

Methods and Results

The charts of 21 patients who were treated with sotalol for fetal tachycardia were reviewed. Ten fetuses had atrial flutter (AF), 10 had supraventricular tachycardia (SVT) and 1 had ventricular tachycardia (VT). Hydrops fetalis was present in 9 fetuses. Drug treatment was successful in establishing sinus rhythm in 8 of 10 fetuses with AF and in 6 of 10 fetuses with SVT. The mortality rate in this study was 19% (4 of 21 fetuses, 3 had SVT, 1 had AF), 3 deaths occurred just days after initiation of sotalol therapy and 1 occurred after a dosage increase. At birth, tachycardia was present in 6 infants. Two patients who converted to sinus rhythm in utero were found to suffer from neurologic pathology postnatally.

Conclusions

Fetal tachycardia is a serious condition in which treatment should be initiated, especially in the presence of hydrops fetalis. The high success rate in fetuses with AF suggests that sotalol should be considered a drug of first choice in fetal AF. The low conversion rate and the fact that 3 of the 4 deaths in this study occurred in fetuses with SVT indicate that the risks of sotalol therapy outweigh the benefits in this group and that sotalol should, therefore, be limited in the treatment of fetal SVT.

Introduction

Fetal tachyarrhythmia may cause nonimmune fetal hydrops and lead to fetal morbidity and mortality [1-6]. Several protocols for pharmacological therapy to restore sinus rhythm have been proposed [7-18]. Digoxin and flecainide are the most commonly used agents in such therapies. Digoxin as a single therapy, however, is not successful in restoring sinus rhythm in all fetuses with atrial flutter (AF) or in hydropic fetuses [8, 11-13, 19-21]. The use of flecainide was called into question after a report regarding the potential proarrhythmic dangers of this drug [9]. These data have lead to a continued search for new and possibly better drugs.

Sotalol is a potent Bèta-blocking agent with additional class III antiarrhythmic properties and a mild or absent negative inotropic effect [22, 23], that has proven to be safe and efficacious in the treatment of tachycardia in adults [24-26] and infants [27-30]. Sotalol passes the placental barrier rapidly and almost completely [31]. On the basis of these findings, we hypothesized that sotalol would be a safe and effective antiarrhythmic agent for the treatment of various forms of tachycardia in fetuses. Little is known about the effect of sotalol on fetuses. We present a multicenter retrospective study reviewing our experience with the use of sotalol in the treatment of fetal tachycardia.

Methods

Patients

This retrospective study includes 21 fetal patients who were diagnosed with tachycardia between 1993 and 1999 at the University Hospitals of Utrecht and Nijmegen, the Netherlands and Yale-New Haven Children's Hospital, New Haven, CT, USA. The patients included in the study had either supraventricular tachycardia (SVT, defined by 1:1 atrioventricular (AV) conduction with a rate of > 180 beats per minute, bpm) or atrial flutter with a regular atrial rate of > 250 bpm with fixed or variable AV block. Ventricular tachycardia (VT) was encountered in 1 patient who will be described separately. Tachycardia was detected during routine prenatal visits, and the patients were subsequently referred for further evaluation. Associated cardiac structural abnormalities and possible definable causes for tachycardia, such as viral infections, were excluded. Hydrops fetalis, a sign of fetal cardiac failure, was diagnosed when two or more fluid collections existed in the fetal body, such as pericardial effusion, pleural effusion, ascites and skin edema, regardless of the

amount of effusion present. Fetuses were monitored for 30 minutes and treatment was initiated when during this whole period tachycardia was present or a combination of intermittent tachycardia and hydrops fetalis existed.

In Utero Management

Oral maternal drug therapy was chosen because of previous positive experience with this technique [11]. Patients received sotalol as their initial mode of therapy to achieve sinus rhythm or rate control due to partial AV block. Prior to the initiation of sotalol therapy, preexisting arrhythmias in the mother were excluded. Mothers were interviewed to reveal possible histories of arrhythmic events and ECG's were performed to evaluate QT-interval to minimize the potential for maternal proarrhythmic events.

Dosage

The starting dosage used was 80 to 160 mg of sotalol, given orally 2 times a day. The dosage was occasionally increased to a maximum of 160 mg 3 times per day if tachycardia persisted [32]. Digoxin was added to the treatment in patients in whom adequate control could not be achieved with sotalol as a single therapy.

Variables included in the study were the following: gestational age at recognition of the tachycardia, heart rate, mechanism of the tachycardia as noted on prenatal M-mode echocardiography, the presence of hydrops, possible structural malformations, in utero therapy and results, maternal adverse effects, gestational age at birth, mode of delivery, Apgar score, mechanism of the tachycardia as noted on postnatal electrocardiography, postnatal therapy and outcome of these newborns.

The statistical evaluation of the differences in heart rates and time to successful conversion was performed by Student t-test. A p-value of $< 0{,}05$ was considered significant.

Results

The 21 fetuses were divided into 3 groups according to their electrophysiologic mechanism as noted on prenatal M-mode echocardiography (*Figure 1*). SVT was present in 10 fetuses; they had heart rates of 200 to 300 bpm (mean, 237 bpm; mean peak fetal heart rate 260 bpm). AF existed in 10 fetuses; they had atrial rates of 283 to 550 bpm (mean, 383 bpm; mean peak fetal heart rate 403 bpm) and a variable degree of

AV block, which resulted in a slower ventricular heart rate (mean, 193 bpm). VT was seen in 1 fetus. A total of 9 fetuses were hydropic at the time of presentation: 5 had SVT, 3 had AF and 1 had VT. The mean gestational age at the time of presentation was 31 weeks (SEM, 0,96 weeks).

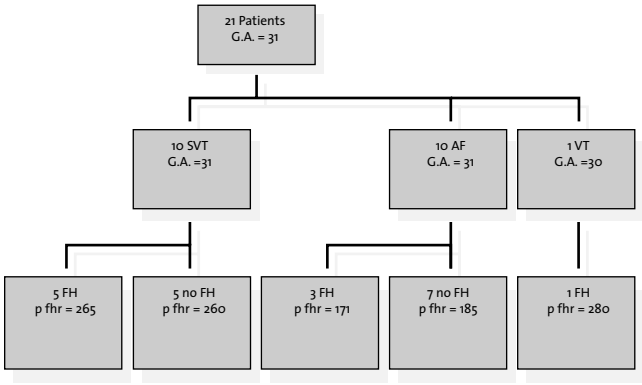

Figure 1.

Allocation of patients to three groups.

AF= atrial flutter, FH= fetal hydrops, G.A.= average gestational age (in weeks), phfr= average peak fetal heart rate (beats per minute), SVT= supraventricular tachycardia, VT= ventricular tachycardia.

In utero management

Figure 2 shows the mode of therapy and results. Regardless of the mechanism of tachycardia, all but 1 fetus were initially treated with sotalol.

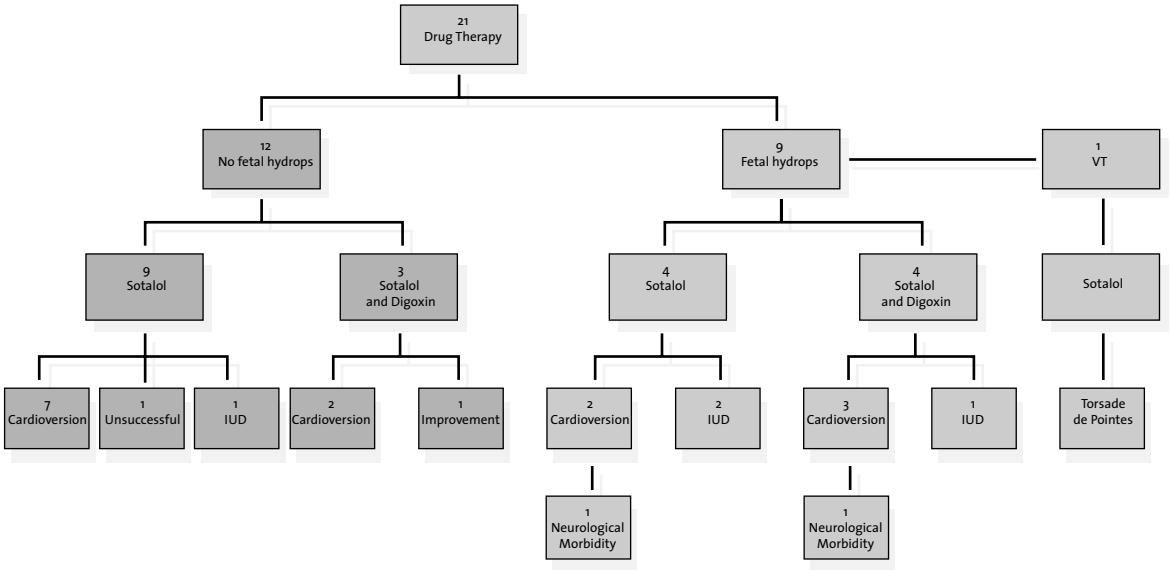

Figure 2.

Outcome of all fetuses, differentiated in the presence of hydrops and form of therapy.

IUD= intra uterine death.

Nonhydropic fetuses

Twelve fetuses showed no signs of hydrops at the time of presentation: 5 had SVT and 7 had AF. All 12 fetuses had a gestational age of 21 to 37 weeks and were started on sotalol as a single therapy; 7 converted to normal sinus rhythm and no further tachycardia was encountered.

Relapses

One patient (aged 21 weeks) who had AF at 300 bpm and 3:1 AV block converted to sinus rhythm on a sotalol dose of 160 mg 2 times per day, but the patient relapsed into flutter after the initial sotalol dosage was diminished to 80 mg 3 times per day. This prompted an increase in the sotalol dosage to 80 mg 4 times per day and the addition of digoxin to the drug regimen. Stable sinus rhythm was then achieved, and no

further relapses occurred. A second patient (aged 35 weeks) who had SVT at 300 bpm initially reverted to sinus rhythm for 2 weeks, after which a relapse occurred. The original dosage of sotalol had been decreased from 80 mg 3 times per day to 80 mg 2 times per day; it was subsequently increased to 160 mg 2 times per day. The fetus died in utero 1 day later. Autopsy did not establish a cause of death.

One patient with SVT at 240 bpm did not convert to sinus rhythm although the heart rate slowed to 210 bpm. Despite a dosage increase from 80 mg 3 times per day to 80 mg 4 times per day, SVT persisted at 210 bpm. After 1 week of unsuccessful treatment, a caesarean section was performed at 37 weeks of gestation. Shortly after birth the patient was diagnosed with a permanent junctional reciprocating tachycardia. Heart rate persisted at 195 bpm, and intravenous digoxin therapy was initiated. This was followed by conversion to normal sinus rhythm.
The remaining 2 nonhydropic fetuses, both with AF, did not convert to sinus rhythm and digoxin was added to their treatment. This combination succeeded in restoring sinus rhythm in 1 fetus. In the other patient, sinus rhythm was never achieved but an atrial rate of 220 bpm and a ventricular rate of 110 bpm was well tolerated. At birth the ECG showed AF and electrical cardioversion established a normal sinus rhythm of 130 bpm.
In summary, 75 % of nonhydropic fetuses were successfully converted to a normal sinus rhythm in a mean period of 7 days (1-28 days), in 1 patient only an adequate block was achieved. Mean gestational age at birth was 39 weeks.
One fetus with SVT at 300 bpm died suddenly after the dosage of sotalol had been increased to 160 mg 2 times per day.

Hydropic fetuses

Eight fetuses were hydropic at the time of presentation (gestational age ranged from 25 to 33 weeks), 5 had SVT and 3 had AF. Sotalol as a single therapy successfully converted cardiac rhythm to sinus rhythm and resolved the hydrops in 2 fetuses. One severely hydropic fetus with SVT at 240 bpm at 29 weeks of gestation was started on 160 mg of sotalol 3 times per day, but the fetus died in utero after 2 days of treatment. Autopsy showed signs of chronic anoxia, and an abnormal accessory myocardial AV connection was seen, suggesting a reentry tachycardia mechanism. Another fetus, who had SVT at 260 bpm at 25 weeks of gestation and signs of ascites was initially treated with multiple drug combinations, including digoxin, flecainide and propranolol, as well as direct fetal intra-umbilical therapy with adenosine, which was

transiently successful for 30 minutes. Tachycardia persisted and hydrops fetalis worsened, therefore, at 29 weeks of gestation, all previous medication was withdrawn and sotalol was started at a dosage of 120 mg 2 times per day. The heart rate slowed within 2 days to 210 bpm, with intermittent episodes of sinus rhythm. As hydrops fetalis persisted, the sotalol dosage was gradually increased to 160 mg 2 times per day. The fetus converted into sinus rhythm with short runs of tachycardia to 220 bpm. Six days after the initiation of sotalol therapy and 2 days after the dosage increase, an ultrasound showed no fetal movements and a fetal heart rate of 90 bpm. On prostaglandin, the mother went into labour and gave birth to a stillborn infant. The retrospective nature of this study made it impossible for us to elucidate why induction of labour was preferred above an emercency caesarean section in this case. Autopsy was not performed.
In 3 of the remaining 4 fetuses, rhythm control was achieved after the addition of digoxin, with subsequent resolution of hydrops fetalis. The fourth fetus had an AF rate of 440 bpm with 2:1 AV-block. Sotalol was initiated at 80 mg 3 times per day. As rhythm control was not achieved, digoxin was added to treatment and the sotalol dosage was increased to 80 mg 4 times per day. Shortly after this change in treatment, the fetus died in utero at 39 weeks of gestation. Autopsy showed severe fetal hydrops, stenosis of the venous duct and a hypoplastic placenta.
In the hydropic group, 62,5 % of fetuses were successfully converted to normal sinus rhythm in a mean period of 7 days and hydrops resolved in all of these cases in a period ranging from 2 to 21 days (mean 14 days). The time to successful conversion to sinus rhythm was equal to that in the nonhydropic group (p=0,921). Mean gestational age at birth was 35 weeks. Three deaths occurred in the hydropic group, all of which occurred in a period ranging from 2 to 6 days after the initiation of sotalol.

Ventricular tachycardia

In 1 hydropic fetus, an intermittent tachycardia with a rate of 260 to 280 bpm was diagnosed at the gestational age of 30 weeks. This was erroneously interpreted as SVT and sotalol therapy was initiated. On this therapy the tachycardia worsened and became persistent. The echocardiographic appearance of the heart showed a strange peristaltic-like movement suggesting a torsade de pointes mechanism. Sotalol therapy was withdrawn and replaced by digoxin, which remained unsuccessful. After birth by caesarean section at 31 weeks, this patient proved to have prolonged QT syndrome and uncontrollable periods of ventricular, torsade de pointes tachycardia. Despite extensive and mul-

tiform therapy, which eventually included a defibrillation pacemaker, this patient died at 2 years of age of uncontrollable VT and secondary myocardiopathy.

Adverse effects

In 2 cases, maternal adverse effects were encountered. They were only temporary. One mother experienced nausea, and the other, dizziness and fatigue.

Unfortunately, we did not recognize fetal VT in 1 patient, and the worsening of the fetal tachycardia was probably because of provocation of torsade de pointes in this patient.

Supraventricular tachycardia versus atrial flutter

Sotalol therapy was successful in 6 of 10 fetuses with SVT and in 8 of 10 fetuses with AF. Treatment was partially effective in 2 fetuses, 1 with AF and 1 with SVT. Drug therapy was effective in 60% of cases of SVT and in 80 % of cases of AF. Three deaths in the SVT group and 1 in the AF group were encountered.

Management and outcome after birth

Follow-up was possible in 17 cases as there were 4 intra uterine deaths. No rhythm disturbances were seen in 11 of the 17 surviving patients with fetal tachyarrhythmias (65 %). Prophylactic drug therapy was administered for 9 months to 1 year in 5 of these 11 patients; 2 patients received sotalol, and the other 3 patients received digoxin. None of these patients have shown recurrent signs of tachycardia and are currently doing well.

A relapse of tachycardia was seen in 6 of the 17 cases (35 %). Two patients had AF and 3 patients had SVT. The child with VT had recurrent VT after birth. Two patients were successfully treated with sotalol, 1 patient was treated with digoxin and 1 patient received a combination of sotalol and digoxin. The fifth patient had AF and was electrically cardioverted to restore sinus rhythm and sotalol was administered. All newborns were treated till the age of one year.

Morbidity

Two patients with fetal hydrops had significant neurological morbidity immediately after birth. One had SVT and was treated with sotalol, the second had AF and was treated with sotalol and digoxin. Before conversion to persistent sinus rhythm was achieved, these patients experienced intermittent episodes of tachycardia with long-lasting periods of normal sinus rhythm. These episodes lasted 10 and 21 days, respecti-

vely, at gestational ages of 29 and 25 weeks, respectively. Although control of the tachycardia was achieved and these babies were born with good Apgar scores, their postnatal evaluation showed neurologic pathology; this was due to intracranial hemorrhage in one and cerebral hypoxic ischemia in the other [33].

Discussion

Fetal tachycardia can lead to fetal heart failure and death. This has led us to treat tachycardic fetuses prenatally, although others have been reluctant to treat certain forms of tachycardia [34]. The patients described in this study were treated on the basis of the existence of longstanding or sustained tachycardia with or without fetal hydrops.

Choice of drugs

Sotalol was drug of first choice in this study. Although previously used agents such as digoxin and flecainide have proven to be successful in most patients, various reports led us to search for alternative and hopefully better drugs. High maternal serum digoxin levels are required to reach therapeutic levels in the fetus, because this drug has slow and only partial transplacental transfer in the presence of hydrops fetalis [19-21]. Digoxin as a single therapy has had limited success in the treatment of AF [8, 13]. The use of flecainide remains controversial due to the report by Allan et al. [9] of a fetal death that was possibly induced by flecainide; however Frohn-Mulder et al. [12] remain very positive on the use of this drug.

The safety and efficacy of sotalol has been well established in adults, children and infants [22-30]. A negative inotropic effect, which might be expected, has not been found in isolated cardiac tissue. On the contrary, sotalol may even increase contractility slightly because its class III antiarrhythmic properties, which prolong the action potential, may increase time for calcium influx [22, 23]. The use of digoxin as second-line drug was motivated by the fact that digoxin, besides its antiarrhythmic properties, may have a positive inotropic effect on the compromised function of the fetal heart.

Recently, however, a study was published in which the risk of proarrhythmic events seemed to be higher in the pediatric age group than in adults and close monitoring by ECG was recommended during the initiation of sotalol therapy in children [27]. The most serious potential adverse effect of sotalol, the development of maternal torsade de pointes/ventricular fibrillation, deserves serious consideration. To mini-

mize this risk, the possible presence of prolonged maternal QT interval must be excluded prior to the initiation of sotalol therapy. In addition, a thorough and in-depth maternal history should be performed to detect previously existing arrhythmias. While on therapy, the maternal ECG should be regularly evaluated for changes in QT interval.

Mechanism of tachycardia

The efficacy of sotalol as single therapy was 40 % in the SVT group; in the AF group, 50 % reverted to sinus rhythm. After the addition of digoxin another 20 % in the SVT group and 30 % in the AF group reverted to sinus rhythm. The fact that this study was performed retrospectively hampered our ability to elucidate the relationship between the action mechanism of sotalol and the success rates. Perhaps this would have been possible in a prospective, randomized study.

The conversion rate in the SVT group (60 %) is dissatisfying when compared with the rates of other studies, which are as high as 88% [11]. The relatively low conversion rate in this study suggests that sotalol is probably not the optimal drug of first choice for the treatment of fetal SVT. Moreover, the fact that 3 of the 4 fetal deaths occurred in fetuses with SVT indicates that the use of sotalol should be restricted to those cases in which other treatment options have failed.

The rate of success in the AF group (80 %) compares favorably with previous studies, which have shown success rates ranging from 50 % to 66 % [11, 13]. One of 10 fetuses with AF died in utero, probably due to a combination of severe congestive heart failure, stenosis of the venous duct and a hypoplastic placenta. The low postnatal recurrence rate (10 %) also favors sotalol therapy. The high success rate and the low recurrence rate indicate that sotalol could, in our opinion, be considered a drug of first choice in the treatment of fetal AF, possibly with digoxin as second-line drug.

Hydropic versus nonhydropic fetuses

Hydropic fetuses carry a higher risk of an adverse outcome than nonhydropic fetuses [5, 8, 33]. Although our results suggest that hydropic fetuses can be treated successfully by the maternal administration of sotalol and/or digoxin, they also indicate, in accordance with other reports [35], that there is a high mortality risk (3 of 8 hydropic fetuses, 37,5%). In those cases in which conversion to sinus rhythm was achieved (5 of 8 hydropic fetuses, 62,5%), the hydrops resolved in a period ranging from 2 to 21 days (mean 14 days), which is a shorter period than that of previous reports [36].

The time to the successful restoration of sinus rhythm was equal in

both groups (nonhydropic and. hydropic, p=0,921) of fetuses treated with sotalol, which underscores the drug's effectiveness, especially in the hydropic fetus.

Postpartum medication

No unanimity of opinion exists regarding the need for neonatal prophylaxis in patients who do not have persistent or recurrent arrhythmias. Although 11 live-born patients showed no signs of postpartum relapse of the tachycardia, only 7 did not receive any further therapy and are currently doing well, suggesting that postnatal prophylactic medication might not be necessary. A relapse of tachycardia occurred in 6 patients; they received sotalol and/or digoxin prophylaxis for a year, after which it was discontinued without recurrence of symptoms. Remarkably, 2 of these relapsing patients showed neurological damage (described under morbidity) which suggests the presence of a therapy-resistant tachycardia. The patient who had torsade the pointes VT died after two years of unsuccessful therapy.

Morbidity

Fetal tachycardia has a good prognosis when conversion to sinus rhythm has been attained in utero: 82 % of all live-born children in this study are alive and well. However, 2 of our hydropic patients suffered from neurologic pathology postnatally. In both of these patients, the time from actual conversion to persistent normal sinus rhythm was longer than average (10 and 21 days compared to 7 days average). It seems likely that in the periods in which the patients reverted back and forth from tachycardia into sinus rhythm, neurological damage occurred. These results underline the necessity to initiate drug therapy as soon as possible in hydropic fetuses.

Mortality

Table 1 shows the mortality rates of studies performed throughout the past 13 years [4, 9, 11-13, 15, 37-39]. Mortality in this study was 4 of 21 fetuses, which is high compared to these previous studies. As autopsy did not establish a cause of death in any of our patients, there is a possibility that proarrhythmic events at higher sotalol doses may have caused these deaths. All intra uterine deaths occurred within 1 week after the initiation of sotalol therapy or a dosage increase to a daily dosage of more than 320 mg/day. It is in these periods that sotalol may cause proarrhythmic events [23, 24, 27, 30]. The incidence of proarrhythmic side effects of sotalol in the treatment of pediatric patients varies from 0 % to 22 % [27-30], but the proarrhythmic impact of sotalol may be more pro-

nounced in the immature fetal heart than it is in adult hearts. The study of Houyel et al. showed that sotalol causes a significantly greater prolongation of the corrected QT interval in the neonatal heart than in adult hearts [40]. In our fetus with VT, torsade de pointes was confirmed by ECG after birth. This fetus provided evidence that sotalol can cause proarrhythmic events in the immature fetal heart. Therefore, if one opts for sotalol treatment, low initiation doses of 80 mg 2 times per day are preferable and dosage increases should be stepwise and weighed against possible adverse effects. Close monitoring during the initiation of therapy and dosage increases is recommended.

Study	# of patients	Mechanism of tachycardia			Treatment				IUD	Mortality %
		SVT	AF	VT	Digoxin	Digoxin+...	Flecainide	Flecainide+...		
Bergmans et al. (4)	9	9	-	-	5	4	-	-	0	0%
Allan et al. (9)	14	12	2	-	-	-	12	2	1	7%
Engelhardt et al. (39)	9	9	-	-	4	5	-	-	0	0%
van Engelen et al. (11)	34	25	9	-	15	9	7	3	3	9%
Frohn-Mulder et al. (12)	35	35	-	-	19	9	7	-	6	17%
Naumberg et al. (38)	15								0	0%
Zielinsky et al. (37)	17	17	-	-	17	-	-	-	3	18%
Jaeggi et al. (13)	11	-	11	-	11	-	-	-	0	0%
Sonesson et al. (15)*	14	14	-	-	-	14	-	-	2	14%
Simpson et al. (35)	127	105	22	-					18	14%
Experience at Yale University 1994-1998	159	117	34	8					8	5%

Table 1.

Mortality rates of studies done over the past 13 years. * In this study, sotalol was added to digoxin.

IUD= intra uterine death, SVT= supraventricular tachycardia, AF= atrial flutter, VT= ventricular tachycardia.

Conclusions

Fetal arrhythmias present serious conditions in which treatment is necessary, especially in the presence of hydrops. Sotalol and the combination of sotalol and digoxin were very successful in the AF group, with a conversion rate as high as 80 % and the advantage of a low recurrence rate. Therefore, sotalol should be considered as a valuable treatment option for fetal AF.

The low conversion rate and the fact that 3 out of 4 deaths occurred in fetuses with SVT indicate that the use of sotalol in the treatment of fetal SVT may be limited. Sotalol can cause proarrhythmic events in the fetus and although there is no proof, sotalol may have contributed to the mortality rate. This calls into question whether sotalol should be used as a first-line drug to treat fetal SVT, because several other antiarrhythmic protocols have shown variable success rates without comparable mortality rates. The evidently present risks should be weighed against the limited benefits of sotalol therapy for fetal SVT. It is our belief that the use of sotalol should be restricted to cases with fetal AF and those cases of fetal SVT in which other treatment options have failed to be successful.

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Chapter 8

Protocollen voor de behandeling van supraventriculaire tachycardieën bij de foetus

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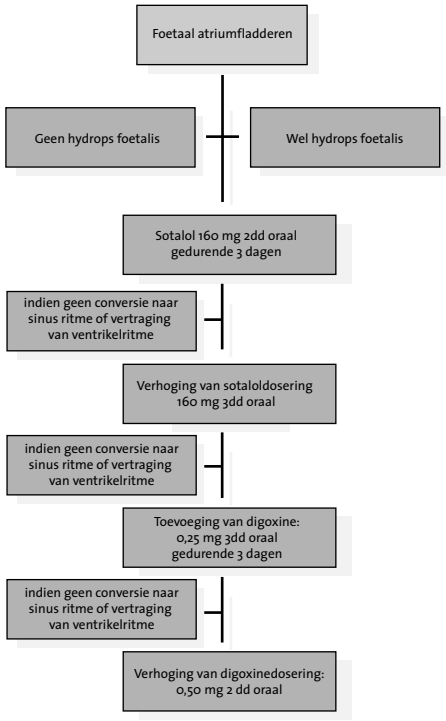
Abstract

Protocols for the treatment of supraventricular tachycardias in the fetus

The protocols mentioned are used by Utrecht University Hospital for the treatment of fetal supraventricular tachycardias (SVT). In case of atrial flutters the pregnant woman is treated with sotalol administered orally and, if no sinus rhythm is obtained nor a reduced ventricular rhythm occurs, subsequently with digoxin. If there is no hydrops fetalis, the same treatment regimen is used for other forms of fetal SVT. In the case of hydrops fetalis the treatment is more aggressive: digoxin intravenously or flecainide orally. If the rhythm does not convert into a sinus rhythm nor a reduced ventricular rhythm occurs then both of these medications are administered; if that also proves to be insufficient then direct fetal therapy can be considered.

Foetaal atriumfladderen reageert in de regel matig tot slecht op orale maternale digoxine, met name indien er sprake is van foetale hydrops [1, 2]. Een studie naar het orale gebruik van sotalol als middel van eerste keus, met toevoeging van digoxine in tweede instantie, liet echter een hoog succespercentage van 80-90 % zien [3]. Zowel in de groep foetussen met atriumfladderen zonder hydrops, als in de groep met hydrops gaf dit een goed resultaat.
De groep foetussen met supraventriculaire tachycardie van andere oorsprong dan atriumfladderen, die op het moment van de start van de therapie niet hydropisch was, reageerde ook goed op de behandeling volgens het ontworpen protocol (*Figuur 1*).

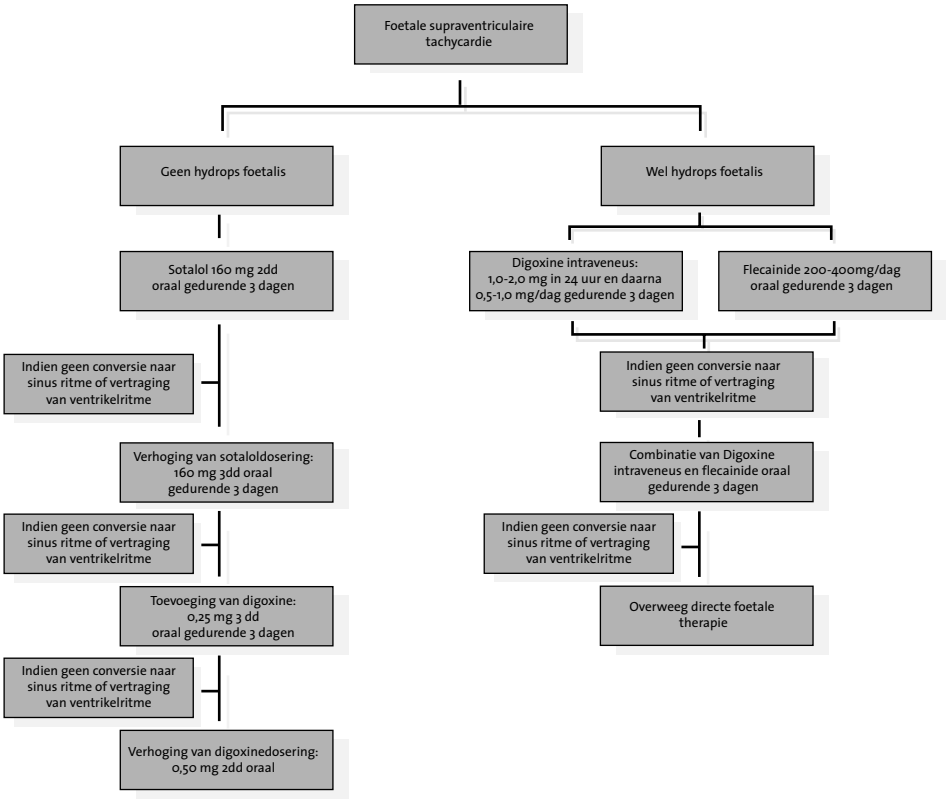


Figuur 1

Protocol voor de behandeling van een zwangere bij foetaal atriumfladderen, dat in het Universitair Medisch Centrum Utrecht wordt gehanteerd

De groep foetussen met supraventriculaire tachycardie met hydrops is een groep met een hoge morbiditeit en mortaliteit. Een agressievere therapeutische opstelling is dan ook noodzakelijk. Indien mogelijk verdient het de voorkeur de zwangere in de klinische situatie intraveneus

te behandelen met digoxine om zodoende een snelle en adequate therapeutische digoxinespiegel bij de foetus te verkrijgen. Een tweede optie, indien een klinische opname niet mogelijk is, is het gebruik van flecainide per os door de moeder. Bij onvoldoende effect is een combinatie van deze twee opties mogelijk (*Figuur 2*).



Figuur 2

Protocol voor de behandeling van een zwangere bij foetale supraventtriculaire tachycardie, anders dan atriumfladderen, dat in het Universitair Medisch Centrum Utrecht wordt gehanteerd

Mocht er zich in die situatie nog steeds geen verbetering van de tachycardie hebben voorgedaan, dan bestaat er een zeer ernstige en gelukkig weinig voorkomende situatie. Het zou dan te overwegen zijn de foetus direct te gaan behandelen middels intra-umbilicale, intra-musculaire, intra-peritoneale of intra-amniotische injecties, al bestaat daar in het perinatologisch centrum te Utrecht weinig ervaring mee.

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Part 2
Fetal ECG in labour, aspects of the intrapartum QT interval

Chapter 9

Changes in the Fetal QT Interval in Asphyxia

Martijn A. Oudijk
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Erik J. Meijboom
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Karl G. Rosén

Abstract

Background

The morphology of the fetal ECG complex may provide information on the fetal condition during labour, such as the ST segment and T wave configuration. The QT interval is known to react to situations of stress and exercise and we hypothesized that the fetal QT interval would react to acute asphyxia and could thus provide information on the fetal myocardial adaptation.

Methods

The hypothesis was tested on four cases, consisting of prolonged cord occlusion in three fetal sheep experiments and one human fetus exposed to severe hypoxia during labour as a result of placental abruption. The QT interval was measured on the fetal ECG displayed by the STAN® fetal heart monitor. The QTc was calculated using Bazett's formula: $QT/\sqrt{RR}$.

Results

A shortening of the QT and QTc intervals occurred during the initial phase of asphyxia. The shortening was associated with a rise in T/QRS ratio and increase of blood pressure, indicating a maintained cardiovascular function. Persisting asphyxia was associated with a return of the QT interval to pre-asphyxic values.

Conclusions

A marked shortening of the QT and QTc intervals occurs shortly after the onset of asphyxia. Probably this is the result of a surge in epinephrine and Bèta-adrenoceptor activation. These parameters may be of additional value in intrapartum fetal monitoring.

Introduction

Fetal ECG analysis has formed the basis for electronic fetal monitoring for decades. So far the FECG assessment has been limited to RR interval measurements only. Among other time constants, the relationship between PR and RR has also been extensively investigated. The PR shortening with RR lengthening during fetal heart rate (FHR) decelerations and bradycardia [1] and experimental hypoxia [2], has provided relevant information on fetal cardiac adaptation. Clinically, these measurements are not of additional value [3]. However, the morphology of the FECG including the ST segment and T wave configuration has been shown to provide specific and clinically useful information of fetal cardiovascular adaptation to experimental hypoxia and as an adjunct to standard FHR monitoring in labour [4] .

The QT interval has been the focus of many studies in the neonate and adult, as a prolonged QT interval, either genetic or acquired, predisposes to ventricular tachycardia and sudden death [5-8]. Many studies have shown changes in its properties in situations of exercise, stress and infection among others, [9-15]. We hypothesized that the QT interval on the FECG, representive of repolarization, could provide information on the physiology of the fetal myocardium and on the fetal myocardial adaptation to the ultimate stress of being born [16]. Hitherto, no data has been published on the dynamics of the QT interval in labour as the technology was not available until recently. The development of the STAN® technology, originally designed to perform analysis on the fetal ST waveform to improve fetal surveillance [4, 17] has provided us with the means of evaluation of specific features on the fetal ECG, including the QT interval.

The current report presents the pattern of QT changes noted in three premature sheep fetuses and one human fetus at term all being exposed to acute asphyxia.

Methods

The hypothesis was tested on four cases obtained from the STAN® database, consisting of prolonged cord occlusion in three fetal sheep experiments and a human fetus with severe hypoxia during labour, all monitored by the STAN® device (STAN S 21 recorder, Neoventa Medical, Gothenburg, Sweden).

Fetal sheep

In the three fetal sheep experiments, aseptic surgery was performed at 90 days of gestation. The fetuses were instrumented with polyvinyl catheters in each brachial artery, in the left brachial vein and in the amniotic cavity. ECG electrodes were placed subcutaneously over each shoulder (the right electrode was used as reference) and one over the apex of the heart. Antibiotics (garamycin, 5 mg/kg, i.v.) were administered daily to the ewe during the time span of the study. Asphyxia was induced 48 hours after placement of the electrodes by inflation of a vascular occluder (In Vivo Metric, Healdsburg, CA), that was placed around the umbilical cord. Continuous fetal arterial blood pressure was recorded on a Grass polygraph. The fetal ECG was continuously monitored by the STAN fetal heart monitor and QT intervals were measured off-line. The QT data was obtained from FECG recordings originating from studies approved by the Animal Ethical Committee of the University of Gothenburg.

The human fetus was monitored throughout labour with the STAN fetal heart monitor as part of normal fetal surveillance. The fetal ECG was recorded using a single helix scalp electrode and a maternal skin electrode, resulting in a unipolar fetal ECG lead.

Fetal ECG and measurement of intervals

The fetal ECG and QT interval was reviewed retrospectively from stored data using a special software application (STAN Viewer, NM Gbg Sweden). The FECG data was stored digitally at 500 Hz resolution. The STAN Viewer displayed the fetal ECG on the computer screen which is an average ECG consisting of 30 high quality FECG complexes. The T/QRS ratio and appearance of biphasic ST segments are displayed automatically. In cases 2 and 4, only trends in QT interval changes could be obtained, as these were recorded with an older version of STAN. To allow for more accurate measurements of QT in case 1 and 3, the software was updated. A specialized tool was developed for the assessment of FECG time intervals in which markers have to be placed manually on visual assessment of onset of the P-wave, onset and end of QRS complex and end of T-wave. The computer calculated the intervals in milliseconds (ms). An example of the fetal ECG and measurements is presented in *Figure 1*.

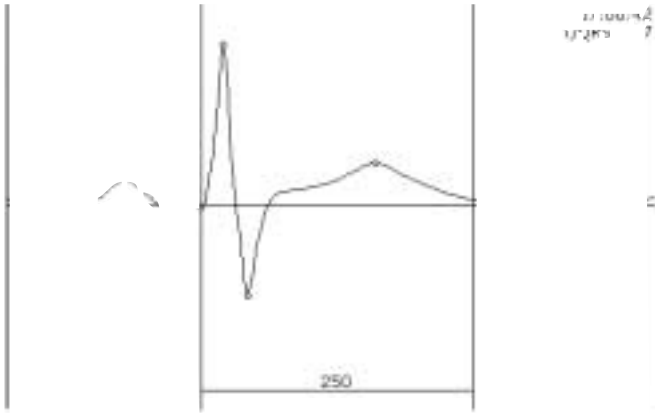


Figure 1
An example of measurement of the QT interval. The markers (vertical lines) are placed manually on visual assessment of the onset of the Q wave and end of the T wave. The computer automatically calculates the interval in ms, being 250 ms in this case.

The QTc was calculated using Bazett's formula: QT/√RR.

Results

All 4 cases are presented separately and illustrated with FHR changes and changes in T/QRS ratio.

Case 1

Sheep experiment, gestational age of 12 weeks and 6 days.
Fetal sheep experiment with cord occlusion at 05.57, lasting 25 minutes (*Figure 2*).

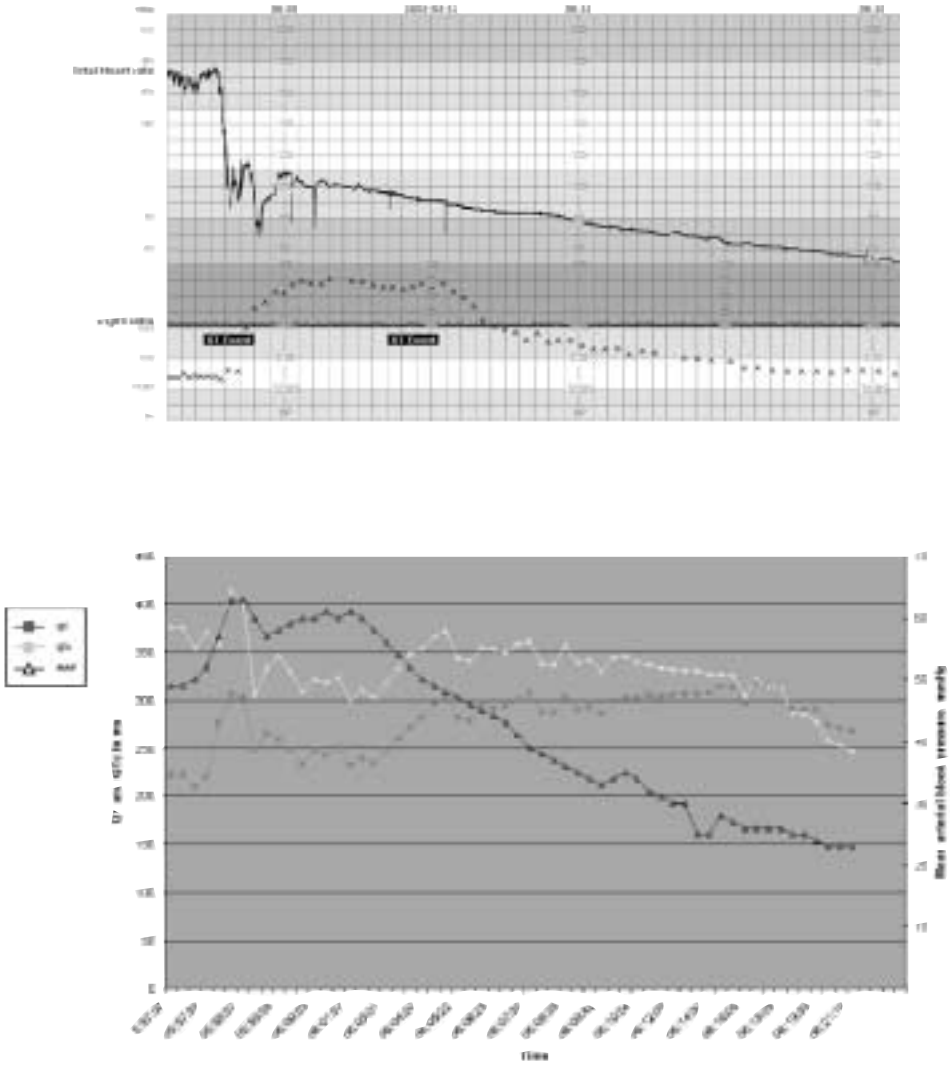


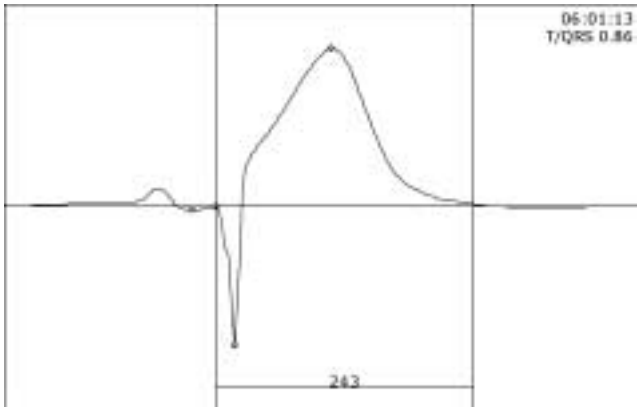
Figure 2

Illustration of the FHR (bpm) + T/QRS ratio recording (1 cm/min) in relation with mean arterial blood pressure (mmHg) and QT and QTc interval (ms) measurements at the time of cord occlusion.

After occlusion of the cord an immediate fall in fetal heart rate and a subsequent rise in T/QRS ratio occurred. An initial rise in mean arterial blood pressure is followed by a decrease. Measurements of the QT and QTc interval show an initial lengthening, followed by a 4 minute shor-

tening followed by a second lengthening.

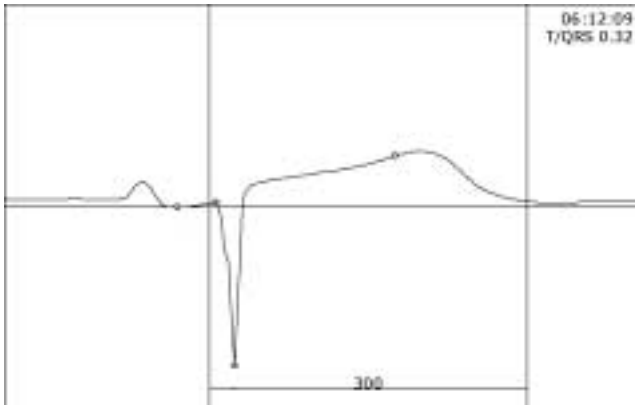
These ECG samples (*Figure 3 and 4*) show the QT interval shortly after the start of asphyxia (243 ms) coinciding with a rise in T/QRS ratio (0,86; *Figure 3*),



QT interval

figure 3

and several minutes later when the T wave decreases (T/QRS 0,32) at which point the QT is lengthening (300 ms; *Figure 4*).



QT interval

figure 4

Case 2

Sheep experiment, gestational age of 12 weeks and 6 days.
Second fetal sheep experiment with cord occlusion at 10:38 *(Figure 5*).

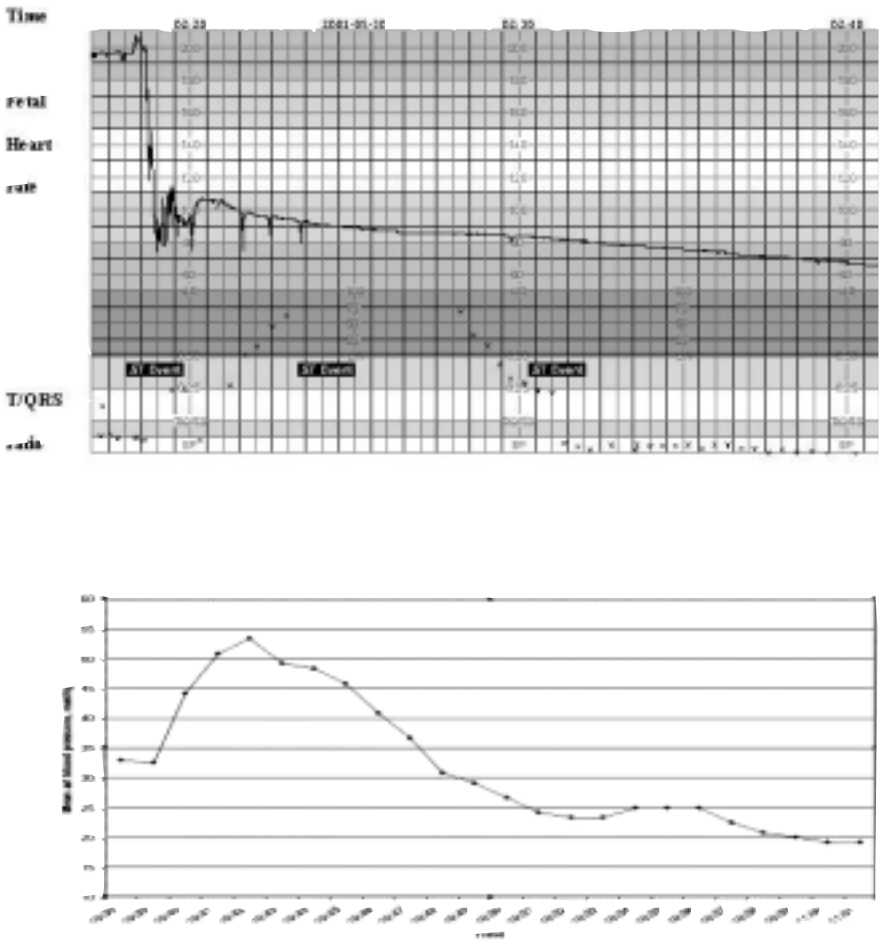


Figure 5

Illustration of the FHR (bpm) + T/QRS ratio recording (1 cm/min) in relation with mean arterial blood pressure (mmHg) measurements at the time of cord occlusion.

After occlusion of the cord an immediate drop in fetal heart rate and a subsequent rise in T/QRS ratio occurred. An initial rise in mean arterial blood pressure is followed by a decrease.

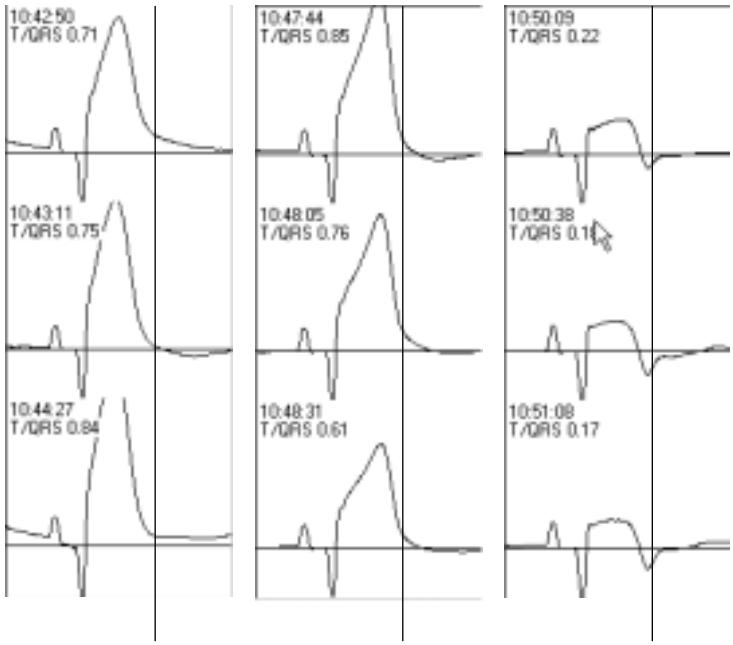


Figure 6

Illustration of consecutive fetal ECG's recorded after cord occlusion. The vertical line is placed at the end of the shortest T wave in the ECG at time 10:44:27.

Figure 6 shows a QT shortening during the first 2 minutes. This coincided with an increase of the T wave and an increase in blood pressure. Three minutes later, the QT interval is lengthening and in the last three ECG's, the T wave develops a negative segment, and the QT interval is markedly lengthening.

Case 3

Sheep experiment, gestational age of 12 weeks and 6 days.
Third fetal sheep experiment with cord occlusion at 4.54 (*Figure 7*).

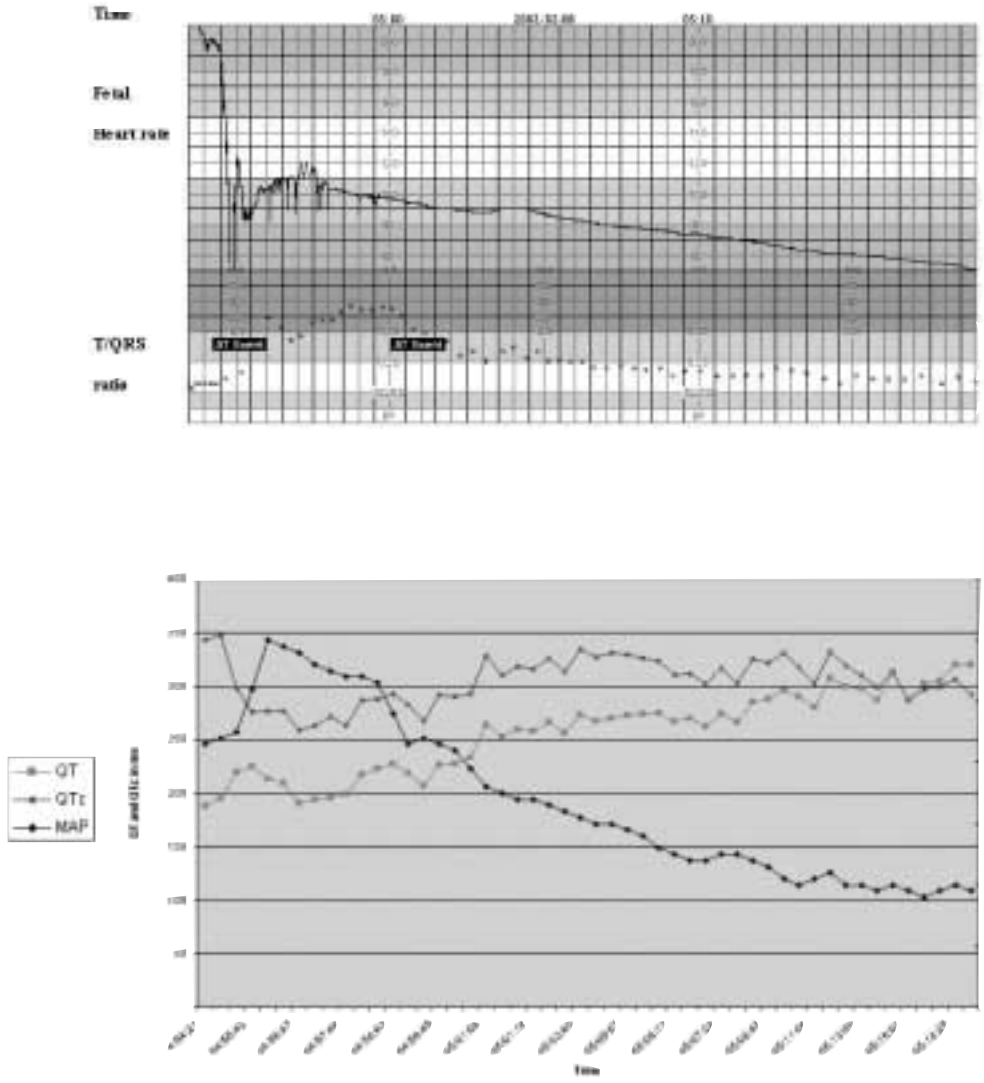
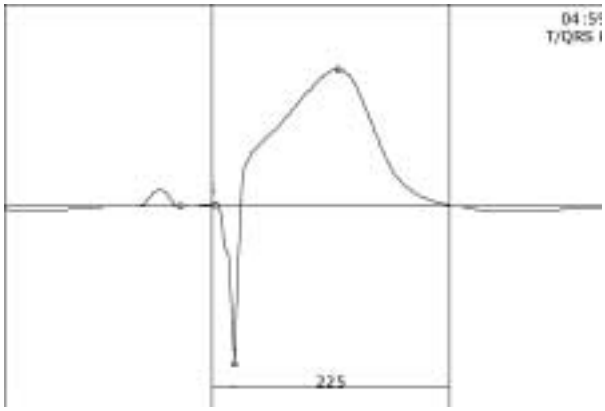


Figure 7
Illustration of the FHR (bpm) + T/QRS ratio recording (1 cm/min) in relation with mean arterial blood pressure (mmHg) and QT and QTc interval (ms) measurements at the time of cord occlusion.

After occlusion of the cord an immediate drop in fetal heart rate and a subsequent rise in T/QRS ratio occurred. An initial rise in mean arterial blood pressure is followed by a decrease. Measurements of the QT interval show an initial lengthening, followed by a shortening, until the T/QRS ratio decreased, at which point the QT is lengthening again. The QTc interval shows an immediate shortening, lasting until the T/QRS ratio is decreasing.

These ECG samples show the measurement of the QT interval shortly after the start of asphyxia (225 ms) coinciding with a rise in T/QRS ratio (0,68; *Figure 8*),



QT interval

Figure 8

and several minutes later when the T wave comes down (T/QRS 0,34) at which point the QT is lengthening (272 ms; *Figure 9*)

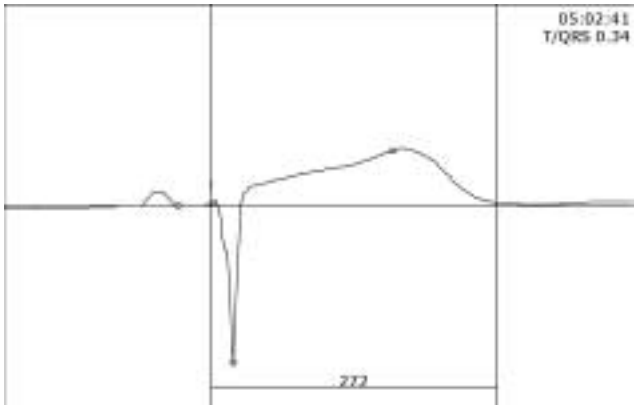


Figure 9 QT interval

Case 4

Human data

A term fetus was monitored with the STAN fetal heart monitor throughout labour and displayed a normal reactive heart rate pattern with a baseline of approximately 150 bpm. In the second stage of labour however, a sudden drop in heart rate and subsequent increase in T/QRS ratio was noted (*Figure 10*) and an emergency vacuum extraction was performed. A placental abruption was the reason for the sudden drop in heart rate and T/QRS rise.

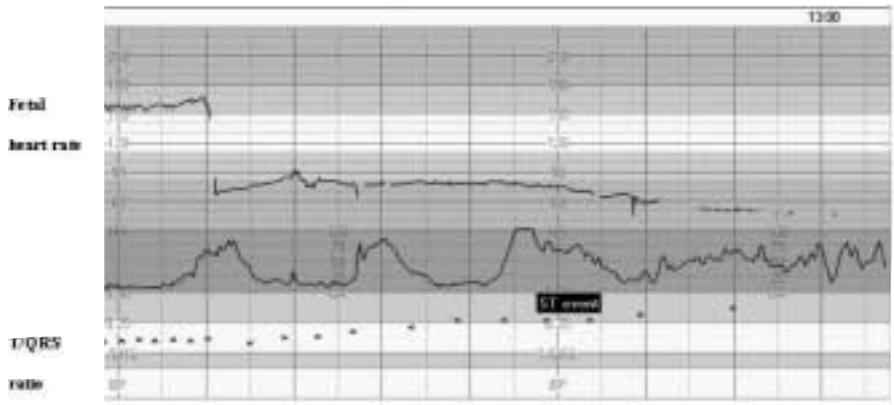


Figure 10

Illustration of FHR (bpm) and T/QRS ratio recording (2 cm/min) at the time of placental abruption.

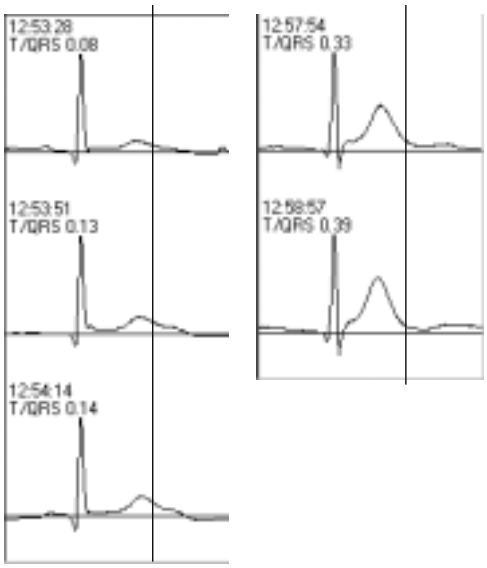


Figure 11

Illustration of consecutive fetal ECG's recorded at the time of placental abruption. The vertical line is placed at the end of the T waves shortly after the abruption.

In *Figure 11* a simultaneous progressive rise in T wave amplitude and shortening of the QT interval can be clearly seen in the last two ECG's.

Discussion

In a situation of hypoxia when the energy balance within the myocardial cell threatens to become negative, the fetus reacts with a surge in epinephrine [18], Bèta-adrenoceptor activation [19] and myocardial glycogenolysis [20]. This alarm reaction is characterized by an increase in amplitude of the T wave. The rate of T wave rise is directly related to the rate of glycogenolysis.

In these four cases, the following observations were made with regard to QT changes:

- A shortening of the QT and QTc intervals occurring during the initial phase of a rise in T/QRS during asphyxia.
- An association between the shortening of the QT and QTc intervals and

an increase in blood pressure (in the three mid-gestational fetal lambs).
- Signs of a subsequent return in QT interval in the sheep experiments with decreasing T/QRS ratio in association with a decrease in blood pressure.

The QT interval is a dynamic function of the fetal ECG and is influenced by asphyxia. It is known that exogenous catecholamines shorten the QT interval [11, 21] and that Bèta blockers prolong the QT interval [22]. The QT shortening in association with an increase in T/QRS ratio and maintained cardiovascular function might therefore be the effect of a surge in epinephrine and Bèta-adrenoceptor activation enhancing cAMP activity and ion channel pumping. The shortening of the QT interval during asphyxia provides us with additional information on the condition of the fetal myocardium, which is trying to respond to the stressful situation it is exposed to.
The decreasing T wave, finally progressing in a negative T wave component during prolonged asphyxia, is the result of a myocardium that has used its reserves and is not capable anymore of maintaining its function, as can also be seen from the decrease in blood pressure. Our observations indicate that in case of a failing myocardium, the QT interval is lengthening and returns to prehypoxic values, which is consistent with observations in children and adults with heart failure [13, 23-25].
Individuals suffering from the Long QT syndrome are at increased risk for life threatening arrhythmias in periods of physical or psychological stress [26, 27]. They are known to respond differently to catecholamines as compared to control subjects [28-29]. We speculate that in fetuses with the LQTS, the shortening of QT in the first phase of hypoxia/asphyxia, possibly as a sign of enhanced ion channel activity being part of a normal response to hypoxic stress, may not be present.

This study has shown that with a specialized tool it was feasible to accurately assess changes in QT interval. Such changes may provide additional information on the condition of the fetus.

Conclusions

A marked shortening of the QT interval, with an increase in T wave amplitude and an increase in blood pressure was noted during the onset of asphyxia. As asphyxia continued in the fetal sheep, the QT returned to pre-asphyxic values. These cases show that the QT interval

is subject to changes during acute asphyxia and that QT shortening seems to be related to the ability of the cardiovascular system to respond with an increase in blood pressure. Intrapartum measurements of the QT interval may therefore provide additional information on the condition of the fetus, in particular when combining QT shortening with T/QRS increase. The data also show that QT shortening may be observed in conjunction with acute intrapartum hypoxia due to placental abruption.

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Chapter 10

The effects of Intrapartum Hypoxia on the Fetal QT Interval

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Erik J. Meijboom
Karl G. Rosén

Abstract

Background

The morphology of the fetal ECG complex may provide information on the fetal condition during labour, such as the ST segment and T wave configuration. We hypothesized that the intrapartum fetal QT interval may provide additional information on the condition of the fetus, as it is known that the QT interval is known to react to situations of stress and exercise.

Methods

The intrapartum QT interval was measured in 68 fetuses who were acidemic at birth (pH < 7,05 and BDecf > 12 mmol/l) and in a control group of similar size. All of these cases were monitored by STAN. Measurements were performed at start of the recording at baseline heart rate, during variable decelerations and at the end of the recording. The QTc was calculated using Bazett's formula: QT/√RR. The intervals were compared using the Wilcoxon signed ranks test.

Results

In the acidemic fetuses, there was a significant shortening of the QTc interval at the end of the recording compared to the start of the recording (397 at the end vs 359,3 at start; p < 0,001), also, heart rate was significantly lower (136,3 vs 110,9 bpm, p < 0,001). Measurements of QT and QTc during variable decelerations at start and end of the recording, also showed a shortening of the QT interval (301,9 vs 273,3 ms, p < 0,001) and QTc interval (381,6 vs 340,3, p < 0,001), and this was not dependent on heart rate. In the control cases, no differences in FHR, QT and QTc intervals were present.

Conclusions

In severe intrapartum hypoxia, resulting in metabolic acidosis, a significant shortening of the fetal QT and QTc is present, irrespective of changes in heart rate. In control cases, this shortening does not occur. The intrapartum fetal QT interval may therefore provide additional information on the condition of the fetus.

Introduction

A prolonged QT interval, either genetic or acquired, predisposes to ventricular tachycardia and sudden death [1-4]. Changes in the QT interval have also been shown during exercise, stress, infection and heart failure [5-11]. Delivery is a stressful event for both the fetus and the mother and fetal hypoxia is a well known complication causing the fetus to respond forcefully with signs of cardiovascular and metabolic adaptation.
In an observational study in three preterm fetal lambs exposed to acute cord occlusion and in one term human fetus who became acutely asphyxiated due to placental abruption, we found that the fetal ECG QT interval, provides information on the electro-physiological changes of the fetal myocardium. A QT shortening was noticed in conjunction with an increase in T wave amplitude. It seemed logical to assume that the QT shortening would depend on the ability of the fetal myocardium to enhance its performance in response to the catecholamine surge and Bèta receptor activation known to elicit the rise in T wave amplitude.

The STAN® technology and clinical database, originally designed to perform analysis on the fetal ST waveform to improve fetal surveillance [12-14], provided us with the means of taking this observation further by evaluating QT interval changes in association with signs of intrapartum hypoxia.

Methods

Data were collected using the STAN® database which was created during the European community multi-center trial [12] and Swedish randomized controlled trial [13]. All cases with metabolic acidosis as defined by a cord artery pH < 7,05 and BDecf > 12,0 mmol/l were considered for inclusion.
The technique of measurement of the intrapartum QT interval is described in chapter 9.
As it was anticipated that these intervals may change with the dynamic heart rate a healthy fetus will display, measurements were obtained from at least 5 different points in time at baseline and at least 2 different points during accelerations and decelerations.
The QTc interval was calculated using Bazett's formula: $QT/\sqrt{RR}$.

Inclusion criteria

Cases were included if there was a minimal recording time of 30 minutes of good quality during which ECG's were recorded > 90 % of time and during which assessment of the end of the T-wave was feasible. The end of the recording had to be within 20 minutes of delivery to ensure that metabolic acidosis was indeed very likely at the time of recording the FECG.

QT measurement in cases with metabolic acidosis

All cases with metabolic acidosis present in the database and fulfilling the inclusion criteria were reviewed by one of the authors (MAO). Two sets of data were collected in these cases: PQ, QRS and QT intervals at baseline heart rate at the start of the recording and in the last 5 minutes of the recording when metabolic acidosis was likely to be present. As a second part of this study QT intervals were measured during variable decelerations at onset of the recording and during decelerations or bradycardia at the end of the recording when metabolic acidosis was present. Measurements were required to be at least one hour apart to ensure a difference in fetal condition. Cases that did not fulfil these requirements were excluded from the second part of the study. The fetal heart rate (FHR), QT and QTc intervals were compared using the Wilcoxon signed ranks test. Statistical significance was defined by a p value of < 0,05.

QT measurement in control cases

One control case for each metabolic acidosis case was randomly selected from the database. General inclusion criteria had to be met and all had a cord artery pH > 7,05 and BDecf < 12,0 mmol/l. The measurements performed were identical to those described in the cases with metabolic acidosis.

Results

QT measurement in cases with metabolic acidosis

A total of 68 cases with metabolic acidosis were included in the first part. The mean and SD of the PQ, QRS and QT interval and FHR at baseline heart rate at the start and end of the recording are shown in *Table 1*.

		N	Mean	SD	SE of mean
FHR	At start	68	136,3	12,2	1,5
	At end	68	110,9*	29,9	3,6
QT interval	At start	68	265,2	26,5	3,2
	At end	68	269,2	37,8	4,6
QTc interval	At start	68	397,0	33,6	4,1
	At end	68	359,3*	49,6	6,0
PQ interval	At start	68	113,7	13,2	1,6
	At end	68	96,8*	13,8	1,7
QRS interval	At start	68	60,8	7,1	0,9
	At end	68	61,7	8,6	1,1

Table 1

Mean, SD and SE values of FHR (fetal heart rate in bpm), PQ, QRS and QT intervals (in ms) recorded during baseline heart rate at the start and end of the recording in cases born with metabolic acidosis. * p value < 0,001.

There was a significant decrease in heart rate (136,3 vs. 110,9 bpm, p <0,001) and in QTc (397 vs. 359,3, p < 0,001) between the start and end of the recordings. Data on QTc are also shown in *Figure 1*. The PQ interval also showed a shortening (113,7 vs. 96,8 ms, p < 0,001). The mean QT intervals remained the same.

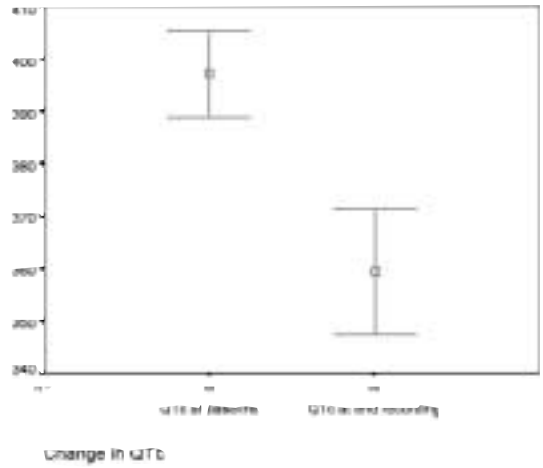

Figure 1

Mean and 95% confidence intervals of QTc at the start of the recording at baseline heart rate and at the end of the recording in cases with metabolic acidosis (n=68).

Cases with metabolic acidosis and variable decelerations

A total of 55 cases were included in the second part of the study. Outcome measures are shown in *Table 2*.

		N	Mean	SD	SE of mean
FHR	At start	55	97,0	15,1	2,0
	At end	55	94,5	22,6	3,0
QT interval	At start	55	301,9	38,3	5,2
	At end	55	273,3*	34,9	4,7
QTc interval	At start	55	381,6	50,1	6,8
	At end	55	340,3*	50,3	6,8

Table 2

Mean, SD and SE of FHR, QT and QTc during variable decelerations at the start of the recording (before the development of metabolic acidosis) and during decelerations or bradycardia during metabolic acidosis at the end of the recording. * p value < 0,001.

In these cases, no difference in FHR was present between the measurements at the start and end of the recordings (97 vs. 94,5 bpm, p = 0,504). However, both QT and QTc were statistically shortened in the period with metabolic acidosis present (QT, 301,9 vs. 273,3 ms, p < 0,001 ; QTc, 381,6 vs. 340,3, p < 0,001). The difference in QTc is shown in *Figure 2*.

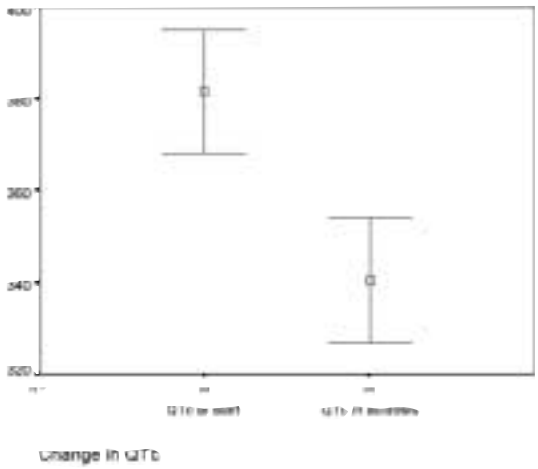

Figure 2

Mean and 95% confidence intervals of QTc recorded during variable decelerations or bradycardia at the start and at the end of the recording in cases who developed metabolic acidosis (n= 55).

Control cases

A total of 55 control cases were included. All had measurements on QT interval during variable decelerations at the start of the recording and during variable decelerations or bradycardia at the end of the recording. Outcome measures are shown in *Table 3*.

		N	Mean	SD	SE of mean
FHR	At start	55	88,5	11,0	1,5
	At end	55	92,5	16,7	2,3
QT interval	At start	55	303,0	31,5	4,2
	At end	55	300,1	28,7	3,9
QTc interval	At start	55	366,9	41,6	5,6
	At end	55	370,3	40,7	5,5

Table 3

Mean, SD and SE of FHR, QT and QTc during variable decelerations at start and during decelerations or bradycardia at end of recording (n= 55).

There were no differences in the measured variables between the start and end of the recording. Data on the QTc are also shown in *Figure 3*.

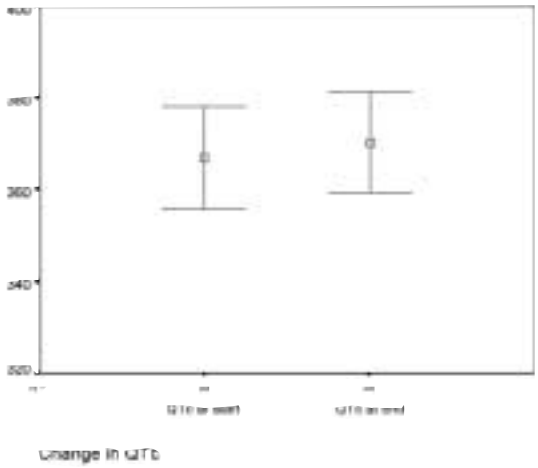

Figure 3

Mean and 95% confidence intervals of QTc during decelerations at the start and during decelerations or bradycardia at the end of the recording in 55 control cases without metabolic acidosis.

Discussion

This study has demonstrated that the QT interval is shortened during intrapartum hypoxia as quantified by umbilical artery metabolic acidosis. The observation was generally applicable in cases of metabolic acidosis comparing onset and end of labour. Furthermore, a significant shortening occurred during variable decelerations recorded during the final part of labour in cases with metabolic acidosis. The data also show that the QT shortening is not FHR dependent nor related to the general stress of labour as fetuses without metabolic acidosis did not show a QT shortening despite FHR changes indicative of such events. A QT shortening therefore seems to provide similar information as that noted with a rise in T wave amplitude and T/QRS ratio. These findings of a marked shortening of the QT interval during marked hypoxia are consistent with the observations made previously in three fetal sheep in which asphyxia/acidosis was induced by cord occlusion and in one human fetus after occurrence of a placental abruption (chapter 9). During hypoxia the energy balance within the myocardial cell threatens to become negative. The fetus reacts to this with a surge in epinephrine [15], Bèta-adrenoceptor activation [16] and myocardial glycogenolysis [17]. A responsive fetal myocardium reacts to these changes with an increase in T/QRS ratio [15]. Exogenous catecholamines shorten the QT interval [7] and Bèta blockers prolong the QT interval [18]. The QT shortening as described in this paper and the association with an increase in T/QRS ratio are therefore likely to be mediated through a catecholamine surge. The observation of a shortening QT interval during hypoxia provides us with additional information on the condition of the fetal myocardium that is trying to respond to the stressful situation it is exposed to.
Measurements of the intrapartum QT interval may therefore be useful in providing additional information on the ability of the myocardium to adapt to intrapartum hypoxia and thus may serve to inform about the condition of the fetus.

Conclusions

During severe intrapartum hypoxia and metabolic acidosis, there is a significant shortening of the QT interval. The intrapartum QT interval may therefore provide additional information on the condition of the fetus.

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Chapter 11

Summary and Discussion

Samenvatting en nabeschouwing

Acknowledgements

list of publications

Curriculum Vitae

The evaluation of the fetal heart rate provides the obstetrician with important information on the condition of the fetus. As the primary goal of obstetric care is the delivery of a healthy newborn, in conjunction with minimal risks for the mother [1], accurate interpretation of the fetal heart rhythm and detection of possible arrhytmias is of vital importance.
This thesis focuses on the diagnosis and treatment of fetal tachyarrhythmias. The second part deals with the evaluation of the QT interval of the fetal ECG during labour and on its possible value with respect to fetal monitoring.

Part I: Fetal tachyarrhythmias

Diagnosis

Fetal tachycardia may be a life threatening disorder and its occurrence should be regarded as a serious condition warranting specialized evaluation. In **chapter 2**, methods of diagnosis of fetal tachycardia are described, including Doppler and M-mode echocardiography, as well as the latest addition to the diagnostic armamentarium, fetal magnetocardiography (FMCG). Characteristics of specific types of tachycardia are described with examples of the images detected on M-mode and FMCG. Decisions regarding treatment and different treatment options are discussed.
M-mode echocardiography remains a valuable tool to classify the tachyarrhythmias into subgroups depending on the site of origin of the arrhythmia. A subdivision in supraventricular tachycardia (SVT), atrial flutter (AF), and ventricular tachycardia (VT) can be derived from this documentation but is not sufficient enough for differentiation according to the electrophysiologic mechanism. A more detailed diagnosis of the type of tachycardia enables the physician to develop a specific treatment. Therefore, several studies have been performed to enhance the accuracy of M-mode echocardiography [2, 3]. The study presented in **chapter 3** describes a method for further delineation in the classification of fetal SVT in short and long VA tachyarrhythmias. The relationship of peak excursions of atrial and ventricular wall motions allows for this division, which, in case of a re-entry tachycardia, is a measure of the conduction velocity of the accessory pathway. Usually, conduction through the accessory pathway is fast, as in the Wolff-Parkinson-White syndrome (WPW), but in some cases, slow conduction is observed, as in persistent junctional reciprocating tachycardia (PJRT).

In **chapter 3**, four fetuses are described in whom a long VA interval was noted on M-mode echocardiography and in whom the definite diagnosis of PJRT was made postnatally. The tachycardia in these fetuses differed in nature from our observations in cases with a short VA tachycardia. Characteristics of a long VA tachycardia include a sustained tachycardia at heart rates not exceeding 240 bpm and with frequent presence of congestive heart failure and therapy resistence. Postnatal treatment is complicated and requires either multiple drug therapy or radiofrequency ablation of the accessory pathway early in infancy.
An even more detailed examination of the electrophysiological properties of the fetal myocardium has become possible with the use of fetal magnetocardiography (FMCG) [4, 5]. Observations presented in **chapter 2** provide evidence that specific time intervals can be measured and that the electrophysiological nature of tachyarrhythmias can be revealed prenatally using FMCG. Images are presented of premature atrial contractions, AF, atrioventricular re-entry tachycardia and a prolonged QT interval. The application of this method to all cases of fetal arrhythmias may ultimately result in a specialized treatment protocol for all different types of arrhythmias.

Consequences

Tachyarrhythmia is a situation in which there is an increased demand of the fetal myocardium to maintain adequate cardiovascular function. Several factors may play a role in the development of congestive heart failure and consequent development of fetal hydrops as outlined in **chapter 4 and 5**. Predisposing factors for the development of hydrops seem to be the percentage of time that the tachycardia is present, the gestational age at which the tachycardia occurs [6], the ventricular rate [7] and the site of origin of the tachycardia [8]. However, statistical significance of these factors could not be obtained in our series. In case of fetal tachyarrhythmias complicated by fetal hydrops, the fetus is at risk for neurological morbidity probably as a result of hemodynamical compromise [9-11]. The cerebrovascular autoregulation that ensures adequate cerebral perfusion during infancy and adulthood, does not function adequately in the distressed newborn and most probably also not in the distressed fetus. A disturbance in rhythm resulting in hemodynamic compromise predisposes the fetus to cerebral ischemia during periods of hypotension and to intracranial hemorrhage during periods of hypertension [12]. Case reports have suggested that the prognosis of individuals with fetal hydrops is generally poor. Therefore, in **chapter 4,** we have investigated the outcome of the total group of 11 fetuses with

hydrops as a result of tachyarrhythmia.

In this group, two deaths occurred, one shortly after birth due to the tachycardia and its complications, and one at 2 years of age as a result of the arrhythmia. Seven of the 9 survivors are doing neurologically well; 1 infant suffers from a mild hemiplegia with a normal cognitive function, and one infant has a cognitive developmental delay. Cognitive function is normal in the 5 infants who have been followed up to 12 years of age. In case of fetal hydrops, initiation of therapy should therefore not be withheld or delayed based only on the assumption of poor neurological outcome.

Polyhydramnios is also a well known complication in case of a hydropic fetus, and may induce preterm uterine contractions. Tocolysis may lead to further in utero maturation and corticosteriods to enhance fetal lung development can be administered. However, most tocolytic drugs have cardiovascular adverse effects that may harm the fetal cardiovascular system. In our opinion, if one opts for tocolysis, the oxytocin antagonist atosiban is to be preferred above other tocolytica, as this drug does not have any cardiovascular adverse effects.

Necessity for treatment

The decision to initiate pharmacological intervention in case of fetal tachycardia depends on several factors and must be weighed against possible maternal and/or fetal adverse effects inherent to the use of antiarrhythmics. First, the seriousness of the fetal condition must be assessed. In the **chapters 3, 4, 6 and 7**, it is outlined that there is a significant predisposition to congestive heart failure, subsequent development of fetal hydrops and even sudden cardiac death. Secondly, the sensitivity of predictors of congestive heart failure mentioned in **chapter 5** is low, and these predictors are therefore clinically not very useful. In addition, hemodynamic compromise may occur in less than 24 - 48 hours as has been shown in the fetal lamb [13] and in tachycardic fetuses [14, 15]. On the other hand, spontaneous resolution of the tachycardia has also been described [16]. Thirdly, transplacental management of fetuses with congestive heart failure or fetal hydrops is difficult [17, 18], probably as a result of limited transplacental transfer of the antiarrhythmic drug [19, 20]. In case of fetal hydrops, conversion rates are decreased and time to conversion is increased [21]. In our opion, treatment is therefore to be preferred above expectant management, although some centers oppose this regimen and suggest that in cases with

(intermittent) fetal SVT not complicated by congestive heart failure or fetal hydrops, conservative management and close surveillance might be a reasonable alternative [22-24].
The most important goal of initiation of treatment is the prevention or resolution of hemodynamic compromise and therefore the prevention of fetal hydrops. In case of treatment the question remains whether to treat prenatally or postnatally, in the latter case after artificial preterm delivery. Several factors play a role in this decision. In case of transplacental treatment, the fetus will be able to thrive in its natural environment and the problems encountered with a preterm delivery will be avoided. One may oppose however, that, with elective preterm delivery and postnatal treatment, monitoring of the infant might be easier. In case of an emergency situation, for instance ventricle fibrillation, physicians may be able to react instantly. But, there is no guarantee of a favourable outcome of this situation in the postnatal setting. This view seems to result in a redirection of the problem in responsibility between different specialties and predisposes the neonate to additional complications of prematurity [25, 26]. In addition, an induced preterm delivery, is likely to result in a caesarean section with increased maternal risks and possible effects on subsequent pregnancies [27-29].
The decision as to prenatal or postnatal start of treatment mainly depends on gestational age and it is obvious that at an early gestation prenatal treatment is the only reasonable choice. At term, physicians may differ in opinion whether to treat pre- or postnatally. However, transplacental treatment has proven to be both safe and effective, and serious maternal adverse effects, although theoretically possible, have not been described in literature. It seems therefore logical to treat the fetus in its natural environment through transplacental treatment.
The issue of direct fetal therapy is described in **chapter 5**. In the international literature, several modes of administration, intra-umbilical, intra-amniotic, intra-peritoneal, intra-muscular and intra-cardiac, have been described. These ways of administration show a significant mortality, but it is unclear if these deaths are attributable to the invasive nature of the treatment or to the severity of the underlying condition [17, 30]. Such approaches should only be used in cases of fetal tachycardia complicated by hydrops with resistance to transplacental multidrug therapy.

Treatment

In **chapter 5**, a review of the literature on the various regimens of drugs used in the transplacental treatment of fetal tachycardia is presented. Numerous drugs have been proposed in the treatment of fetal tachy-

cardia, although only several have proven to be clinically useful. Digoxin has been the drug of first choice in most centers, with success rates of approximately 50 % in nonhydropic SVT and of 45% in AF [31-34]. In tachycardia complicated by hydrops, disappointing conversion rates of 15-20 % have been reported [35], probably as a result of reduced placental transfer [20]. Few adverse effects of digoxin are present in this population. Flecainide has been proposed as an effective drug in the treatment of SVT with hydrops either as drug of first choice or in combination with digoxin, with conversion rates ranging from 75 – 92 % [36-38]. Another drug of second choice, amiodarone, had received some attention in the past [39-41], but has gained much popularity lately [24], since treatment with digoxin and amiodarone proved to be effective in 15 hydropic fetuses with AVRT, and in 2 with VT and JET respectively [42]. In AF, a conversion rate of 50 % (3 out of 6 fetuses) was achieved. The adverse effects of amiodarone are of possible concern: in 5 of the 23 fetuses a mild transient biochemical hypothyroidism was detected, which required treatment in only 1 neonate who received amiodarone for a prolonged period after birth. In one mother, treatment had to be stopped because of the development of a photosensitive skin rash and thrombocytopenia.

In **chapter 6 and 7** we present the results of two studies on the treatment of fetal tachycardia with sotalol. This antiarrhythmic drug has both Bèta-adrenergic blocking properties as class III antiarrhythmic properties and it was hypothesized that this drug may be of value in the treatment of fetal tachycardia. **Chapter 6** describes the pharmacokinetics and dynamics of sotalol in pregnancy. In 19 patients, levels of sotalol were prospectively studied in maternal, umbilical and neonatal blood and in amniotic fluid. The maternal blood level of sotalol was linearly related to the daily maternal dosage, and strongly related to the fetal blood level as measured in the umbilical cord. The transplacental transfer of sotalol proved to be excellent with a mean fetal/maternal ratio of 1,11. Sotalol accumulates in amniotic fluid with a mean amniotic fluid/fetal cord blood ratio of 3,2, but not in the fetus itself. The maternal blood level can therefore be used as an indicator of the fetal blood level, although it did not prove to be a reliable predictor of the chances of success of therapy. Sotalol was not associated with intra uterine growth restriction. The overall success rate of sotalol as a single therapy in the treatment of atrial flutter in the studies presented in **chapters 6 and 7**, was 63 %, and reached 79 % after the addition of digoxin. This compares favorably with other reports [34] and it is concluded that sotalol is a superior drug in the treatment of AF. The success rate in fetal SVT was 53 % with sotalol as a single drug and

reached 74 % after the addition of digoxin. These results are comparable with other proposed treatment protocols. In the SVT group, there were however, four deaths. Two of these fetuses had a severe hydrops and the occurrence of an intra-uterine death in such a case may be expected. But in two of these deaths, no hydrops was present and no cause of death could be established at autopsy. Therefore the question of proarrhythmia was raised, since ventricle fibrillation might have been the cause of death. Although we have no evidence that this was indeed the cause of these deaths, it is proposed that this risk should be minimized by a low initiation dosage and stepwise dosage increase. In addition, close monitoring, especially during the initiation phase is recommended.

Protocol in the treatment of fetal tachycardia

In **chapter 8**, a preliminary treatment protocol is presented for the two main subgroups of fetal tachycardia, atrial flutter (AF) and supraventricular tachycardia (SVT). They differ in nature and course and therefore require different therapy. In fetal AF, the results of the study presented in **chapters 6 and 7** are superior to those published in the international literature and sotalol, with digoxin as a second line drug, should therefore be the treatment of choice, both in isolated AF as in the presence of fetal hydrops (*Figure 1*).

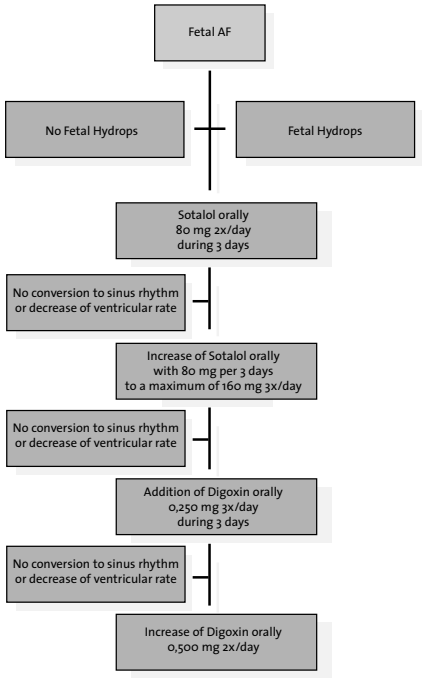

Figure 1

Treatment protocol Fetal Atrial Flutter

In nonhydropic fetal SVT, the optimal treatment regimen is more complicated. The success rates of the treatment protocol presented in **chapters 6 and 7** is comparable to that of other treatment protocols, however, there was a relatively high mortality rate in our series. In *table 1*, our results are compared to the results in other studies on nonhydropic fetuses, treated with different protocols. The differences in mortality, as measured by the Fischer's exact test were not statistically significant (P=0,261). The choice for sotalol was based on the electrophysiologic properties of this agent, but a definite clinical advantage could not be proved. This is the reason that the treatment protocol (*figure 2*) shows 2 options without a documented preference for either.

Study	Drugs used	IUD	Total # of patients	Mortality percentage
Oudijk et al.	S, D	2	20	10%
Simpson et al.	D, F, V	2	75	2,7%
Ebenroth et al.	D, F	0	30	0%
Frohn-Mulder et al.	D, F	0	22	0%
Jaeggi et al.	D	0	15	0%
van Engelen et al.	D, F	0	19	0%

Table 1

Mortality rates of nonhydropic tachycardic fetuses.

S = sotalol, D = digoxin, F = flecainide, V = verapamil, IUD = intra uterine death

In fetal SVT complicated by hydrops, a more aggressive approach with more potent drugs is required. Two options are proposed: flecainide, or a combination of intravenous digoxin and amiodarone, both of which have proven to be effective in this serious condition (*Figure 3*).
In conclusion, as a result of the studies of this thesis and of the latest international literature, new treatment protocols are proposed and presented (*figure 1-3*). As discussed in the beginning of this summary and discussion, a detailed diagnosis of the specific type of tachycardia may result in a more specific treatment. Hopefully this will result in a further reduction of morbidity and mortality in the field of fetal tachycardia.

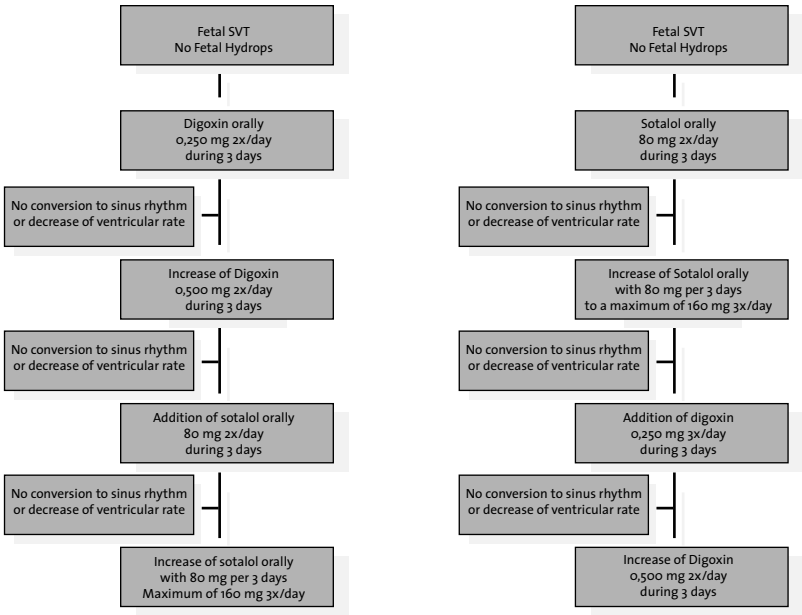

Figure 2

Treatment protocol options Fetal SVT not complicated by hydrops

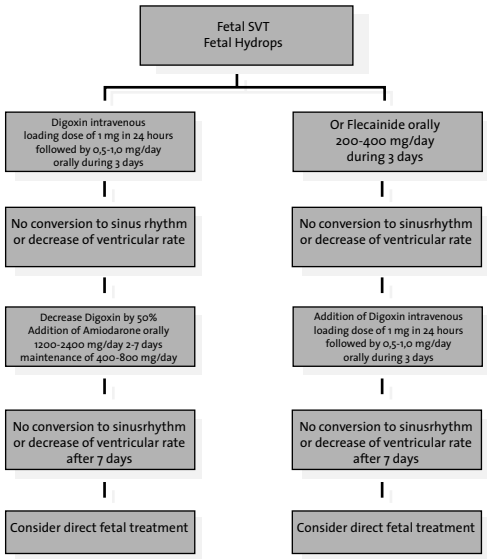

Figure 3

Treatment ptotocol options Fetal SVT complicated by hydrops

Part II: Fetal ECG in labour, aspects of the intrapartum QT interval

The Fetal ECG (FECG) has provided clinicians with useful information in electronic fetal monitoring for decades. The most extensively studied part of the FECG is the RR interval. Although a normal fetal heart rate pattern is reassuring with respect to the fetal condition, the predictive value of an abnormal pattern is low [43, 44]. In addition, it increases the rate of caesarean section [45], without a clear improvement of outcome [46, 47]. Other time constants, as the relationship between PR and RR intervals, have also been extensively investigated, but no clinically useful information could be obtained [48]. The morphology of the FECG including the ST segment and T wave configuration has, however, been shown to provide specific and clinically useful information of fetal cardiovascular adaptation to experimental hypoxia and as an adjunct to standard FHR monitoring in labour [49-51].

In part II of this thesis, a specific part of the fetal ECG, the QT interval, during labour is investigated. A prolonged QT interval, a measure for delayed ventricular repolarization, predisposes to episodes of ventricular tachycardia leading to recurrent (pre-) syncope and sudden cardiac death [52, 53]. As it is of the utmost importance that infants with a prolonged QT interval are identified at the earliest possible stage, the FECG in labour may prove to be of value in the detection of children at risk. Therefore, we conducted a study, in which the properties of the QT interval during labour are investigated. The QT interval has been shown to change in response to different (stressful) situations, catecholamine exposure, exercise, infections and heart failure [54-58], and in our study, interesting observations were made on the effects of hypoxia on the QT interval.

In **chapter 9**, observations on the intrapartum QT interval in three premature sheep fetuses and one human fetus at term, all being exposed to acute and severe asphyxia, are presented. A shortening of the QT interval is present, shortly after the fetus is exposed to asphyxia, in association with a rise in T/QRS ratio and an increase in blood pressure. In prolonged asphyxia, the QT interval lengthens again in association with a decrease in T/QRS ratio and decrease in blood pressure. In **chapter 10**, these observations were taken further by evaluating changes in the QT interval in 68 fetuses with signs of intrapartum hypoxia quantified by umbilical artery metabolic acidosis. The QT interval was measured at the start of the recording at baseline heart rate and during variable decelerations in a situation without acidosis and at the

end of the recording at which point metabolic acidosis was likely to be present. A significant shortening of the QT interval was present at the end of the recording in comparison with the start of the recording, consistent with the observations made in c**hapter 9**.
In a situation of hypoxia or asphyxia, when the energy balance within the myocardial cell threatens to become negative, the fetus reacts with a surge in epinephrine [59], Bèta-adrenoceptor activation [60] and myocardial glycogenolysis [61]. This alarm reaction of the fetus is characterized by an increase in T wave amplitude with the rate of T wave rise being directly related to the rate of glycogenolysis and maintained cardiovascular function. The QT shortening as described in this paper is associated with an increase in T/QRS ratio and these findings are therefore likely to be mediated through the same mechanism of catecholamine surge. We speculate that children suffering from the Long QT syndrome may not be able to react to hypoxia with the same changes as the cases displayed in **chapters 9 and 10**, as it is known they respond differently to exogenous catecholamines [62, 63]. Studies on the relation between a long QT interval during labour and the association with LQTS are ongoing.

In conclusion, the observation of an intrapartum shortening of the QT interval is a sign of developing metabolic acidosis and may therefore provide additional information on the condition of the fetus in labour.

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Samenvatting en nabeschouwing

De foetale hartslag is een belangrijke parameter voor het verkrijgen van inzicht in de conditie van de foetus. Aangezien het, het doel van verloskundige zorg is om ieder kind zo gezond mogelijk geboren laten worden met zo min mogelijk schade aan de moeder [1], is adequate interpretatie van het foetale hartslagpatroon en detectie van eventuele hartritmestoornissen van groot belang.

In dit proefschrift concentreren wij ons op de diagnose en behandeling van foetale tachycardieën. Een tweede gedeelte behandelt het foetale QT interval durante partu en de mogelijke bruikbaarheid van deze parameter bij de foetale bewaking.

Deel I: Foetale tachycardieën

Diagnose

Foetale tachycardie is een aandoening met een reëel risico op complicaties, en de bevinding rechtvaardigt nader onderzoek in een daartoe gespecialiseerd centrum. In **hoofdstuk 2** worden verschillende methoden van diagnose van foetale tachycardie beschreven, zoals Doppler en M-mode echocardiografie, alsook de nog in ontwikkeling zijnde foetale magnetocardiografie (FMCG). De kenmerken van de verschillende typen tachycardie worden beschreven met karakteristieke echo- en FMCG beelden.

Met behulp van M-mode echocardiografie is het mogelijk de tachycardieën in subgroepen in te delen. Een classificatie in supraventriculaire tachycardie (SVT), atrium flutter (AF) en ventriculaire tachycardie (VT) is echter niet voldoende om te differentiëren volgens het elektrofysiologische mechanisme van de tachycardie. Een meer nauwkeurige diagnose van het type tachycardie stelt de behandelaar in staat een specifieke behandeling in te stellen. Verschillende onderzoekers hebben daarom getracht de mogelijkheden van M-mode echocardiografie uit te breiden [2, 3]. In **hoofdstuk 3** wordt beschreven hoe foetale SVT kan worden onderverdeeld op basis van de relatie tussen het atrioventriculaire (AV) en ventriculoatriale (VA) interval, in korte en lange VA SVT tachycardieën. Deze relatie is in geval van een re-entry tachycardie een maat voor de snelheid van de geleiding over de accessoire bundel. Normaal gesproken is deze geleiding snel, zoals bij het Wolff-Parkinson-White syndroom. Echter bij enkele aandoeningen is de gelei-

ding door de accessoire bundel langzaam, zoals bij Persistent Junctional Reciprocating Tachycardia (PJRT). In **hoofdstuk 3** worden vier foetussen beschreven bij wie een lang VA interval werd gemeten met M-mode echocardiografie en de diagnose PJRT postnataal werd bevestigd. Het verloop van deze tachycardie bleek anders dan die waarbij sprake was van een kort VA interval. In geval van een tachycardie met een lang VA interval was prenataal sprake van een therapieresistente persisterende tachycardie waarbij de hartfrequentie niet boven de 240 slagen per minuut uitkwam en er een sterke associatie met decompensatio bleek te bestaan. De behandeling postnataal was eveneens gecompliceerd en vereiste diverse anti-arrhythmica combinaties danwel ablatie van de accessoire bundel op vroege kinderleeftijd.
Meer gedetailleerde informatie over de electrofysiologie van het foetale hart kan worden verkregen met behulp van FMCG [4, 5]. In **hoofdstuk 2** worden de FMCG beelden van premature atriale contracties, AF, atrioventriculaire re-entry tachycardie en een verlengd QT interval getoond. Deze beelden laten zien dat specifieke intervallen van het foetale ECG nauwkeurig kunnen worden gemeten en dat de tachycardieën ook prenataal kunnen worden gedifferentieerd op basis van de electrofysiologische achtergrond. Het toepassen van deze techniek bij alle gevallen van tachycardie zou uiteindelijk kunnen leiden tot een gespecialiseerd protocol voor de verschillende typen tachycardie.

Consequenties

Handhaving van een adequatefoetale circulatie loopt bij hoge hartfrequenties gevaar als gevolg van het Frank Starling effect. Dit betekent dat er bij foetale hartfrequenties boven de 180 slagen per minuut decompensatie, zich uitend in foetale hydrops, kan optreden. In **hoofdstuk 4 en 5** worden de factoren beschreven die een rol spelen in de ontwikkeling van decompensatio cordis en foetale hydrops, in geval van een tachycardie. Predisponerende factoren zijn onder andere: de tijd die de tachycardie aanwezig is, de amenorroeduur ten tijde van het optreden van de tachycardie [6], de ventriculaire frequentie [7] en de achterliggende oorzaak van de tachycardie [8]. Echter in ons onderzoek bereikten geen van deze veronderstelde factoren statistische significantie. Bij een foetale tachycardie die gecompliceerd wordt door hydrops, is er een verhoogde kans op neurologische morbiditeit, waarschijnlijk ten gevolge van de gecompromitteerde hemodynamiek [9-11]. De cerebrovasculaire autoregulatie die de cerebrale perfusie reguleert bij kinderen en volwassenen, werkt nog niet voldoende bij aan stress blootgestelde pasgeborenen, en zeer waarschijnlijk ook niet bij een dergelijke situatie vóór de geboorte. Grote veranderingen in hartritme

kunnen resulteren in een inadequate output van het hart, met een verhoogde kans op cerebrale ischaemie tijdens perioden van (milde) hypotensie en een verhoogde kans op intracraniele bloedingen tijdens perioden van (milde) hypertensie [12]. Enkele casuïstische mededelingen hebben gesuggereerd dat de prognose van foetussen met hydrops slecht zou zijn. In **hoofdstuk 4** hebben wij daarom de uitkomst onderzocht van 11 foetussen die in ons centrum bekend waren met hydrops op basis van een tachycardie.

Van deze groep zijn twee patiënten overleden, één vlak na de geboorte ten gevolge van de tachycardie en de daaruit voortvloeiende complicaties, en één op de leeftijd van twee jaar ten gevolge van een ernstige arrhythmie. Zeven van de 9 overlevende kinderen zijn gezond; 1 kind is bekend met een milde hemiplegie met normale cognitieve functie en 1 kind heeft op een leeftijd van 1,5 jaar een ontwikkelingsachterstand van enkele maanden. Wij concluderen dat in geval van foetale hydrops ten gevolge van een tachycardie, het instellen van therapie niet mag worden weerhouden of vertraagd op basis van een veronderstelde slechte prognose.

Ernstige hydrops met polydramnion gaat vaak gepaard met preterme uteriene contracties. Remming van weeën maakt het mogelijk om corticosteroiden ter longrijping in te laten werken. Echter de meeste tocolytica hebben cardiovasculaire bijwerkingen die potentieel gevaarlijk zijn voor de niet optimaal functionerende foetale circulatie. In geval voor weeënremming wordt gekozen, gaat onze voorkeur uit naar atosiban, een oxytocine antagonist, aangezien cardiovasculaire bijwerkingen niet zijn beschreven bij dit medicament.

De noodzaak van behandeling

De beslissing om te interveniëren met anti-arrhythmica in geval van een foetale tachycardie hangt af van verschillende factoren en interventie moet altijd worden afgewogen tegen mogelijke maternale en foetale bijwerkingen, die inherent zijn aan het gebruik van anti-arrhythmica. Bij de afweging al dan niet te behandelen is het van belang de risico's van de tachycardie te kennen. In de **hoofdstukken 3, 4, 6 en 7** wordt uiteengezet dat er bij foetale tachycardie een significant verhoogde kans is op congestief hartfalen, de ontwikkeling van foetale hydrops en zelfs op plotselinge hartdood. De sensitiviteit van de in **hoofdstuk 5** genoemde 'voorspellende' parameters voor hartfalen is helaas laag, en daarom zijn deze in de praktijk niet bruikbaar.
Uit dierexperimenteel onderzoek [13] en uit observaties bij de mens is

bekend [14, 15], dat tachycardie bij de foetus binnen 24 tot 48 uur kan leiden tot hydrops. Daar tegenover staat dat spontane resolutie van foetale tachycardie ook is beschreven [16]. De vraag of en wanneer er met de behandeling van de foetus moet worden begonnen wordt hierdoor dus niet opgelost. Een punt ten gunste voor het starten van een vroege behandeling wordt geleverd door het feit dat behandeling van de tachycarde foetus met hydrops middels transplacentaire therapie gecompliceerder is dan bij ontbreken van hydrops [17, 18], waarschijnlijk ten gevolge van de verminderde passage van het anti-arrhythmicum over de placenta [19, 20]. Ook is in geval van hydrops het percentage foetussen dat succesvol wordt behandeld lager, en indien toch conversie optreedt, dan is de tijd tot conversie langer dan bij nonhydropische foetussen [21]. De combinatie van deze gegevens leiden ons ertoe te stellen dat behandeling van de tachycardie te prefereren is boven het aannemen van een afwachtende houding. Echter enkele centra zijn hierop tegen en propageren in geval van (intermitterende) SVT zonder congestief hartfalen of hydrops, geen medicatie te starten, maar de foetus met zeer frequent echografische controles te bewaken [22-24].
Het belangrijkste doel van behandeling is de preventie danwel resolutie van hartfalen en daarmee de preventie van hydrops. In de keuze tussen prenatale of postnatale (na een iatrogene vroeggeboorte) behandeling spelen meerdere factoren een rol. In het geval van prenatale behandeling door middel van transplacentaire therapie, wordt de foetus in staat gesteld zich te ontwikkelen in zijn natuurlijke omgeving en worden de problemen van een premature partus voorkomen. Aan de andere kant echter zou men kunnen stellen dat, in geval van een geïnduceerde premature partus en postnatale behandeling, de vitale functies van het kind na de geboorte beter kunnen worden bewaakt. In geval van een noodsituatie zoals ventrikelfibrilleren, zou men dan direct kunnen reageren. Echter ook in een dergelijke situatie er is geen garantie op een goede uitkomst. Het lijkt dan ook eerder een verschuiving van het probleem te zijn van de ene naar de andere medische discipline met als gevolg de risico's van iatrogene prematuriteit [25, 26]. Tevens zal een geïnduceerde preterme partus vaker resulteren in een keizersnede, met kans op maternale schade en op mogelijke gevolgen bij een volgende graviditeit [27-29]. Deze beslissing hangt grotendeels af van de zwangerschapsduur en vroeg in de zwangerschap is het duidelijk dat prenatale behandeling de enige optie is en alleen in geval van een à terme zwangerschap is neonatale behandeling een reële optie. Transplacentaire behandeling is een veilige en effectieve therapie vorm, en ernstige maternale bijwerkingen, alhoewel in theorie aanwezig, zijn niet in de literatuur beschreven. Het verdient ons inziens dan

ook de voorkeur om de foetus in zijn natuurlijke omgeving te behandelen.

Directe foetale therapie wordt beschreven in **hoofdstuk 5**. In de internationale literatuur worden verschillende methoden, intra-umbilicaal, intra-amniotisch, intra-peritoneaal en intra-cardiaal, beschreven. In deze studies wordt een significante mortaliteit beschreven. Hierbij is het echter niet duidelijk of deze het gevolg is van de invasieve behandeling, of van de ernst van de conditie van de foetussen [17, 30]. Wij zijn van mening dat invasieve behandeling uitsluitend geïndiceerd is in geval van foetale hydrops waarbij geen reactie optreedt na transplacentaire therapie met meerdere medicamenten.

Behandeling

In **hoofdstuk 5** worden de verschillende farmacotherapeutische opties beschreven, die gebruikt worden bij de behandeling van foetale ritmestoornissen. Talloze medicamenten zijn in de loop der jaren gebruikt, maar slechts enkele zijn in de praktijk bruikbaar gebleken. Digoxine is in vele centra het middel van eerste keuze, met een succespercentage van ongeveer 50 % in geval van een nonhydropische SVT en van 45 % in geval van AF [31-34]. Bij tachycardieën gecompliceerd door hydrops zijn de succespercentages lager en in de orde van 15-20 % [35], waarschijnlijk ten gevolge van verminderde passage van digoxine door de placenta [20]. Een voordeel van digoxine is het lage percentage bijwerkingen. Flecainide wordt meer en meer beschreven als middel van eerste keuze in geval van SVT met hydrops, al of niet gecombineerd met digoxine. Het succespercentage van een dergelijke behandeling ligt in de orde van 75-92 % [36-38]. Amiodarone, een middel van tweede keuze dat vroeger sporadisch werd gebruikt [39-41], lijkt naar aanleiding van nieuwe resultaten meer aandacht te verdienen [42]. Behandeling met digoxine en amiodarone bleek effectief te zijn bij 15 hydropische foetussen met atrioventriculaire re-entry tachycardie en in twee gevallen met VT en JET [43]. Een dergelijke behandeling was ook effectief bij 3 van de 6 foetussen AF. Dit middel heeft echter een ongewenst effect op de foetale schildklier en bij 5 van de 23 behandelde patiënten werd na de geboorte een milde biochemische hypothyreoidie gevonden, die bij één kind behandeling vereiste (mogelijk omdat de behandeling neonataal werd voortgezet). Maternaal was er éénmaal sprake van een lichtgevoelige huiduitslag en trombocytopenie.

In **hoofdstuk 6 en 7** worden de resultaten gepresenteerd van twee studies over de behandeling van foetale tachycardieën met sotalol. Dit

anti-arrhythmicum is een Bèta blokker met additionele klasse III anti-arrhythmische eigenschappen en het was de veronderstelling dat dit middel van betekenis zou kunnen zijn bij de behandeling van foetale tachycardieën. In **hoofdstuk 6** worden de farmacokinetische en farmacodynamische eigenschappen van sotalol in de graviditeit beschreven. De bloedspiegels van sotalol werden bij 19 patiënten prospectief onderzocht in maternaal, navelstreng en neonataal bloed, alsook in het vruchtwater. De maternale bloedspiegel van sotalol was lineair gecorreleerd aan de dagelijkse dosis en er was sprake van een sterke relatie met de foetale spiegel in navelstrengbloed. De passage van sotalol door de placenta was uitstekend met een gemiddelde foetale/maternale ratio van 1,1. Sotalol blijkt zich op te hopen in het vruchtwater met een gemiddelde vruchtwater/foetaal bloed ratio van 3,2. De maternale bloedspiegel geeft dus een adequate indicatie van de foetale bloedspiegel, maar bleek geen goede voorspeller van het succes van behandeling te zijn. Bèta-blokkers zijn geassocieerd met intra uteriene groeiretardatie, maar daar vonden wij met betrekking tot sotalol geen aanwijzingen voor. Drieënzestig procent van de foetussen met AF werden met succes behandeld met sotalol en dit percentage steeg naar 79 % na toevoeging van digoxine (**hoofdstukken 6 en 7**). Deze percentages zijn hoger dan bij andere behandelmodaliteiten [34] en wij concluderen dan ook dat sotalol superieur is bij de behandeling van foetale AF. In geval van SVT bleek het succespercentage van sotalol 53 % te bedragen, en na toevoeging van digoxine 74 %. Deze resultaten zijn vergelijkbaar met andere behandelmodaliteiten. In ons onderzoek was echter viermaal sprake van een uteriene vruchtdood. Bij twee van deze foetussen kan dit verklaard worden door de ernstige hydrops. Echter bij de andere twee patiënten was geen sprake van hydrops en kon bij obductie geen oorzaak voor de sterfte gevonden worden. De mogelijkheid van een pro-arrhythmische bijwerking met als gevolg ventrikelfibrilleren kan dan ook niet uitgesloten worden. Alhoewel wij geen harde aanwijzingen hebben voor deze hypothese, zijn wij wel van mening dat een dergelijk risico geminimaliseerd moet worden en adviseren daarom met een lage dosis te beginnen met een stapsgewijze verhoging. Regelmatige controles zijn aangewezen, vooral in de initiatie fase.

Protocollen bij de behandeling van foetale tachycardieën

In **hoofdstuk 8** wordt een voorlopig behandelprotocol gepresenteerd voor de twee belangrijkste groepen foetale tachycardie, de AF en de SVT. De oorzaak en gevolgen van deze tachycardieën zijn verschillend en zij vereisen daarom een aparte behandeling. In het geval van AF zijn wij van mening dat de resultaten van ons onderzoek gepresenteerd in

de **hoofdstukken 6 en 7**, superieur zijn aan die van andere behandelmodaliteiten. Sotalol, met digoxine als middel van tweede keus, is daarom bij AF te prefereren als middel van eerste keus; dit geldt zowel voor de geïsoleerde AF als voor de hydrops (*Figure 1, summary and discussion, blz 187*).

Bij nonhydropische SVT, is de keuze meer gecompliceerd. De succespercentages van sotalol zijn vergelijkbaar met die van andere middelen; echter in ons onderzoek was sprake van een vrij hoge mortaliteit. In *Tabel 1* (*Table 1, summary and discussion, blz 188*) wordt het percentage intra uteriene vruchtdoden vergeleken met die van andere onderzoeken waarin aanzienlijke groepen nonhydropische foetussen met SVT werden behandeld met andere middelen. De verschillen tussen deze middelen, bepaald met behulp van de Fisher's exact test, bleken statistisch niet significant (p= 0,261). Er lijkt echter geen duidelijk klinisch voordeel van de behandeling van sotalol bij nonhydropische SVT te bestaan, en om deze reden zijn dan ook twee protocolopties opgenomen in deze samenvatting (*Figure 2, summary and discussion, blz 189*).

In SVT gecompliceerd door hydrops, is een agressievere behandeling vereist. Op basis van eigen ervaringen en op die gepubliceerd door anderen, worden twee behandelopties gegeven: flecainide, of een combinatie van intraveneuze digoxine en amiodarone. Beide opties bleken zeer effectief bij de behandeling van deze ernstige aandoening (*Figuur 3, summary and discussion, blz 189*).

Naar aanleiding van de resultaten van de studies beschreven in dit proefschrift en de meest recente publicaties in de literatuur worden nieuwe behandelprotocollen voorgesteld (*Figuur 1-3*). Zoals beschreven aan het begin van deze samenvatting en nabeschouwing zou een meer gedetailleerde diagnose kunnen leiden tot een meer specifieke behandeling voor de verschillende typen van tachycardie. Hopelijk zal dit uiteindelijk leiden tot een reductie van morbiditeit en mortaliteit.

Deel II: Foetale ECG durante partu; aspecten van het intrapartum QT interval

Het foetale ECG (FECG) bevat relevante informatie en wordt sinds tientallen jaren gebruikt voor foetale bewaking. Het meest bestudeerde deel van het FECG is het RR interval en het daaruit voorkomende hart-

slagpatroon. Een normaal hartslagpatroon is geruststellend omtrent de conditie van de foetus. De voorspellende waarde van een abnormaal patroon is echter laag [44, 45]. Tevens is aangetoond dat het aantal keizersneden na introductie van cardiotocografie is toegenomen, zonder een duidelijk gunstig effect op de uitkomst [46, 47]. De relatie tussen het PR en RR interval is ook onderzocht, maar hieruit kon geen klinisch relevante informatie worden verkregen [48]. Het ST segment en de configuratie van de T top blijken klinisch wel relevant en bevatten naast de standaard hartslagbewaking durante partu additionele informatie omtrent het cardiovasculaire aanpassingsvermogen van de foetus [49-51].

In het tweede gedeelte van dit proefschrift onderzoeken wij een ander specifiek interval van het FECG: het QT interval. Een verlengd QT interval is een maat voor vertraagde ventriculaire depolarisatie en predisponeert tot perioden van ventriculaire tachycardie die kunnen leiden tot wegrakingen en plotselinge hartdood [52, 53]. Het is daarom van groot belang om kinderen met een verlengd QT interval in een zo vroeg mogelijk stadium te identificeren. Mogelijk kan het FECG gebruikt worden om kinderen met een verhoogd risico reeds tijdens de partus op te sporen. Het QT interval blijkt te reageren op verschillende fysiologische processen, zoals stress, verhoogde catecholamine belasting, inspanning, infecties en hartfalen [54-58]. Wij hebben de effecten van hypoxie op het QT interval bestudeerd.

In hoofdstuk 9, worden de resultaten gepresenteerd van het verloop van het QT interval bij 3 premature schapenfoetussen en bij één humane foetus, die allen blootgesteld waren aan acute asfyxie.
Kort nadat de foetussen werden blootgesteld aan asfyxie trad een verkorting van het QT interval op, tegelijkertijd met een stijging van de T/QRS ratio en van de bloeddruk. Tijdens het aanhouden van asfyxie was na verloop van tijd sprake van een verlenging van het QT interval, tegelijk met een daling van de T/QRS ratio en van de bloeddruk. Naar aanleiding van deze observaties werd in **hoofdstuk 10** het QT interval van 68 foetussen met tekenen van hypoxie onderzocht. Bij al deze foetussen was na de geboorte sprake van metabole acidose in navelstrengbloed. Het QT interval werd gemeten aan het begin van de registratie bij een normale hartfrequentie, tijdens variabele decelaraties in afwezigheid van acidose en aan het einde van de registratie, in aanwezigheid van metabole acidose. Acidose bleek te leiden tot een significante verkorting van het QT interval, vergelijkbaar met de observaties beschreven in **hoofdstuk 9**.

In een situatie van hypoxie, wanneer de energiebalans in het foetale myocardium negatief dreigt te worden, reageert de foetus met een plotselinge toename van adrenaline [54] , activatie van bètareceptoren [55] en glycogenolyse in het myocardium [56]. Deze 'alarm reactie' gaat gepaard met een toename van de amplitude van de T-top, gerelateerd aan de bij glycogenolyse vrijkomende kalium ionen. Hierbij wordt de cardiovasculaire functie gehandhaafd. De verkorting van het QT interval zoals beschreven in dit proefschrift vindt plaats in samenhang met de toename van de T/QRS ratio en is waarschijnlijk gerelateerd aan hetzelfde mechanisme. Kinderen met het lange QT syndroom zijn mogelijk niet in staat om op hypoxie durante partu te reageren volgens het patroon zoals beschreven in **hoofdstuk 9 en 10**, aangezien zij anders reageren op exogene catecholamines [57, 58]. Onderzoek naar de relatie tussen een lang QT interval tijdens de bevalling en het 'lange QT syndroom' na de geboorte is nog gaande.

Wij concluderen dat een verkorting van het QT interval tijdens de partus een teken is van metabole acidose en dat dit mogelijk van additionele betekenis is met betrekking tot diagnostiek naar de conditie van de foetus tijdens de bevalling.

Referenties

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List of publications

Drs. M.A. Oudijk

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1 **'Sotalol in the Treatment of Fetal Dysrhythmias'**
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Curriculum Vitae

Martijn Alexander Oudijk zag het eerste levenslicht op zaterdag 31 juli1976 `s morgens om 08.07 uur na een hele vlotte bevalling in het Bleuland ziekenhuis te Gouda. In 1994 behaalde hij aan het Christelijk Lyceum te Gouda zijn Atheneum diploma. In datzelfde jaar begon hij met de studie Geneeskunde aan de Universiteit Utrecht. Zijn wetenschappelijke stage startte hij in 1998 in het oude Wilhelmina Kinderziekenhuis bij Dr. E.J. Meijboom. Het onderzoek naar foetale ritmestoornissen zette hij voort aan Yale University in New Haven, U.S.A. onder leiding van Prof. Dr. C.S. Kleinman. In 1999 behaalde hij het doctoraal examen. Tijdens zijn co-assistentschappen vertrok hij in 2000 voor het Gynaecologie en Obstetrie co-schap naar Zimbabwe, en keerde na 1 jaar weer terug naar het Murambinda Mission Hospital te Zimbabwe voor zijn keuze co-schap. Na zijn artsexamen op 31 augustus 2001 begon hij als arts-assistent op de afdeling Gynaecologie en Obstetrie in het UMCU. Gedurende deze jaren vervolgde hij tevens zijn promotieonderzoek naar foetale tachycardieën onder leiding van Dr. E.J. Meijboom en Prof. Dr. G.H.A. Visser. In het najaar van 2002 vertrok hij naar Göteborg, Zweden om zijn promotieonderzoek af te ronden bij Prof. Dr. K.G. Rosén. In augustus 2003 zal hij starten met de opleiding Gynaecologie en Obstetrie binnen het Utrechtse opleidingscluster in het Anthonius Ziekenhuis te Nieuwegein.