Cardiac pathology:

Prenatal diagnosis, management and outcome

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Cardiac pathology:

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Prenatale diagnostiek, behandeling en resultaten
(met een samenvatting in het Nederlands)

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P.M. Verheijen was the main author responsible for chapters 2, 3, 4, 7 and 10.
L.A. Lisowski was the main author responsible for chapters 5, 6, 8 and 9.

Chapter 1

General introduction

General Introduction

Congenital heart disease (CHD) has become a leading cause of neonatal death since improved perinatal care has minimized other causes of neonatal mortality.[1] In an effort to improve the outcome of the treatment of these patients prenatal diagnosis of heart disease plays an increasing role. Until the nineteen eighties physicians were confronted with undiagnosed newborns with CHD. These neonates were often severely ill and in need of urgent care. The development of sophisticated ultrasound equipment allowed that situation to change. The first description by Wang and Xiao almost 40 years ago formed the start of the development of fetal echocardiography.[2]

Initially, the discussion on fetal echocardiography was focused on the safety of the use of ultrasound before birth but this issue has gradually subsided. Ultrasound for clinical diagnosis uses sound waves of high frequency (2 to 10 mHz) and low energy, and has proven to be harmless to human tissues.[3] In the meantime the image quality has improved dramatically and the current generation of ultrasound equipment used for fetal echocardiography allows physicians to detect the majority of congenital heart anomalies during fetal life. This provides an accurate definition of the fetal cardiac structures as early as 16 weeks gestation.

Screening of the fetal heart has focused on the four-chamber view. Identification of this view is relatively easy and 80% of patients with CHD show abnormalities in the four-chamber view.[4] Abnormal findings in this view should initiate a thorough assessment by a specialized team of physicians, since the four-chamber view by itself, is not sufficient to detect all possible cardiac and associated abnormalities. A comprehensive cardiovascular examination should therefore entail a segmental assessment of the arrangement of the thoraco-abdominal organs and the entire fetal heart and great vessels. Besides the four-chamber view, this evaluation of the fetal heart should include views of the right and left ventricular outflow tracts, the three-vessel view and the aortic arch view. The additional use of M-mode and Doppler ultrasound extends the diagnostic yield beyond morphological forms of fetal heart diseases. This allows the evaluation of functional anomalies, such as arrhythmias and heart failure.
Prenatal diagnosis of a structural cardiac anomaly may yield important consequences for the management of both mother and fetus. It requires extensive counseling for the parents of the possible options, effects and risks of the potential strategies. Once these implications are outlined and understood a multi-disciplinary team including the obstetrician/perinato-

logist, neonatologist, pediatric cardiologist and cardiac surgeon should be involved in the elected management strategy. The broad spectrum of specific expertise of the participating physicians allows the team to provide comprehensive parental counseling and planning of the pre- and postnatal management of the patient.

It is very important to realize that despite all efforts to achieve the contrary, a significant number of pregnancies may end in spontaneous intrauterine death. Furthermore the presence of incurable heart disease, or heart disease which can preclude a reasonable quality of life for the patient, may lead parents to opt for termination of pregnancy.

The most significant salutary effect of a prenatal diagnosis of congenital heart malformations however is situated in those patients requiring immediate surgical intervention postnatally. In these cases a prenatal diagnosis of congenital heart disease should optimize perinatal care, guaranteeing the best possible preoperative condition of the newborn patient by prevention of postnatal deterioration. To achieve this goal, prenatal detection of heart disease should result in a planned delivery in a tertiary level perinatal and cardiac center. In these centers rapid sequence of life sustaining interventions are available. The importance of this strategy is that the majority of the prenatally diagnosed severe forms of congenital heart disease are dependent on a patent ductus arteriosus to guarantee the maintenance of an adequate circulation and oxygen transport. During fetal life the ductus arteriosus is a large channel with a diameter similar to that of the descending aorta. Patency of the ductus in utero is maintained by prostaglandins from the utero-placental site. The ductus arteriosus constricts rapidly after birth and in most mature infants is functionally closed within 10 to 15 hours. This mechanism is life threatening for the ductal-dependent forms of congenital heart disease and these patients therefore benefit from a timely infusion of prostaglandin E1 to maintain ductal patency.[5] Respiratory suppression however is an important side effect of the administration of prostaglandin E1 and its therapeutic use frequently provokes the need for immediate intubation and initiation of ventilatory support in these patients.

Preoperative care is aimed at the maintenance of an adequate circulation to facilitate oxygen transport, resulting in sufficient blood gas control and prevention of acidosis. The importance of avoidance of severe metabolic acidosis to prevent brain damage has been suggested in previous reports.[6,7] Enhanced acidosis may exaggerate ischemic glial and vascular cell damage, since it accelerates delocalization of protein-bound iron, with an ensuing

free-radical damage to membrane lipids and proteins. Reports in the literature show that in the surviving patient group of neonates operated on for congenital heart disease, a broad spectrum of developmental disorders is found.[8-11] This might to some extend be prevented by avoiding severe acidosis in the preoperative period.

Better surgical outcome in specific heart anomalies by the prevention of metabolic acidosis, has been reported in prenatally diagnosed patients with transposition of the great arteries[12], hypoplastic left heart syndrome[13] and coarctation of the aorta.[14] This thesis outlines the impact of prenatal diagnosis on the preoperative condition and outcome in a group of neonates with severe congenital heart disease. In a step by step approach, first the impact of prenatal diagnosis on acidosis in general is evaluated in a large multi-center study, then the study focuses on a smaller group in which the impact of prenatal diagnosis on serum lactates is highlighted and finally the relationship between preoperative lactate and neurophysiological outcome is studied.

The next chapters deal with two specific cardiac anomalies namely the hypoplastic left heart syndrome and Ebstein's anomaly, representing both extremes of the spectrum of prenatally diagnosed types of congenital heart disease. Although both types of congenital heart disease are increasingly surgically palliated, the longterm outcome and quality of life remain doubtful. Early prenatal diagnosis in those cases frequently leads to termination of pregnancy.

Ultrasound screening for congenital malformations is currently not yet performed on all pregnant women, and referral is primarily based on fetal and maternal risk factors. The fetal risk factors include fetal arrhythmias, fetal hydrops and/or hydramnion, chromosomal and structural anomalies and more recently an increased nuchal translucency. Maternal risk factors include congenital heart disease in mother or sibling, teratogenic exposure and maternal diseases such as Sjögren's syndrome, SLE and preexisting (type-1 or type-2) diabetes.

This last group, maternal diabetes, forms one of the largest referred group of patients. These patients carry an increased risk of congenital abnormalities in their offspring of which cardiac abnormalities form a large part. While improved maternal care has reduced the incidence of perinatal loss, infants of diabetic women remain at risk of developing congenital anomalies. Major congenital malformations occur 2 to 4 times more frequently in insulin dependent diabetic pregnancies than in infants born to nondiabetic

women.[15-19] Clinical observations indicate that poor control of maternal diabetes during the first trimester, the key period for fetal organogenesis, may cause congenital anomalies. The increased risk of diabetic women having children with congenital heart disease has prompted us to evaluate this group specifically and focus on the pattern of heart disease encountered in their offspring.

Even in the presence of a normal fetal cardiac anatomy, the fetus of the diabetic mother is behaving differently. Differences in growth and in placental development impose a significant effect on the fetal circulation as is analyzed in a separate chapter in this thesis.

Finally this thesis discusses fetal rhythm disorders, which can be diagnosed prenatally and if needed, treated by maternal administration of anti-arrhythmic agents. The specific and well-defined group of fetal atrial flutter is described, including the required pharmaco-therapeutic intervention and eventual outcome.

Aim of the thesis

This thesis describes the possible advantages offered by prenatal diagnosis of congenital heart disease. Both structural and functional anomalies have been considered and benefits of prenatal detection on outcome have been investigated. Examples of both kinds of anomalies are given with special attention being paid to one of the largest referred groups, the fetus and infant of the diabetic patient.

Outline of the thesis

In **chapter 2** the effects of a prenatal diagnosis and maintenance of the acid-base-equilibrium after birth have been investigated in a multi-center study. Differences in the occurrence of severe preoperative acidosis have been examined in groups with and without a prenatal diagnosis of congenital heart disease. The whole spectrum of cardiac anomalies was considered. **Chapter 3** concerns a subpopulation of the study described in chapter 2. An in-depth investigation on the occurrence of lactacidosis in pre- and postnatally diagnosed patient groups is presented. In **chapter 4** we have investigated the effects of prenatal diagnosis and prevention of acidosis on developmental outcome. In **chapter 5** the hypoplastic left heart syndrome is explicitly investigated. Management and outcome have been considered

in both prenatally and postnatally diagnosed patients. Also differences in approach towards this anomaly between our clinic and centers in the United Kingdom and United States are described. **Chapter 6** deals with the experience of prenatally diagnosed Ebstein's anomaly. Management and outcome are described. The incidence of prenatal detection of congenital heart disease in the Utrecht area is described in **chapter 7**. Reasons for the mismatch between the potency of ultrasound detection and the actual percentage of prenatally diagnosed cases are examined.

As an example of a functional cardiac anomaly we have examined atrial flutter in **chapter 8**, a form of perinatal tachycardia. In this group a prenatal diagnosis is also possible and might have beneficial consequences. To obtain a large study group, we performed a multi-center study over a long period, since atrial flutter is only seldomly encountered. Diagnosis, management and outcome of this heart rate anomaly were studied. **Chapter 9** provides a review of the literature on cardiac anomalies encountered in type-1 diabetic pregnancies. Furthermore a multi-center study was performed in order to uncover the spectrum of cardiac anomalies associated with type-1 diabetes. In **chapter 10** we have investigated fetal blood flow in well-controlled type-1 diabetic pregnancies in comparison to a control group of normal pregnancies.

Chapter 11 is a general discussion and summary, and **chapter 12** is a general discussion and summary in Dutch.

The thesis concludes with the curriculum vitae of the authors and acknowledgements of those who assisted in the research.

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Chapter 2

Prenatal diagnosis of congenital heart disease affects preoperative acidosis in the newborn patient

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Abstract

Objectives
Congenital heart disease is the leading cause of death in the first year after birth. Prenatal diagnosis of the disease can optimize the preoperative condition of the patient and may help in the prevention of acidosis. In this retrospective study we compared the occurrence of metabolic acidosis in patients with and without prenatal diagnosis of a congenital heart disease.

Methods
Data of 408 patients who needed an operation for congenital heart disease within 31 days of life were analyzed retrospectively. Arterial blood gases at fixed time intervals and worst blood gas of 81 patients with and 327 patients without a prenatal diagnosis were compared, categorizing the patients on ductus-dependency, anticipated univentricular or biventricular repair, and left-sided, right-sided or no heart obstruction.

Results
In the overall group significant differences in lowest pH, lowest base excess, and highest lactate level were found, with metabolic acidosis more common among the patients with a postnatal diagnosis. In the group of patients with ductus-dependent congenital heart disease, the difference between patients receiving a prenatal diagnosis and those receiving a postnatal diagnosis was more significant than in the group with non-ductus-dependent lesions. Analyzing patients with right-sided, left-sided, and no obstruction separately, significant differences where found in the group with left-sided heart obstruction for lowest pH and base excess and in the group with right-sided heart obstruction for lowest base excess.

Conclusions
Prenatal diagnosis of congenital heart disease minimizes metabolic acidosis in patients with congenital heart disease and may be associated with improved longterm outcome and prevention of cerebral damage among this fragile group of patients, although no significant effect on direct surgical outcome was encountered.

Introduction

Congenital heart disease remains the most important cause of death in the first year after birth.[1] Mortality occurs mainly in patients with severe forms of congenital heart disease requiring immediate surgical intervention. Secondary to the improvement of surgical techniques over the last years, mortality has decreased dramatically, but important neurological sequelae have been noted that may affect the quality of survival.[2-4] Perfection of operative techniques has resulted in only minimal operative mortality and morbidity compared with the preoperative risk factors, as described by Soongswang et al.[5] Achieving a further decrease in mortality and morbidity will predominantly require improved preoperative stabilization of the patient.[5,6] We hypothesize that the prenatal diagnosis of congenital heart disease facilitates the initiation of therapeutic intervention immediately after birth, including planned delivery at a cardiac center and immediate postnatal stabilization, which may include the initiation of prostaglandin therapy[7] and intubation and ventilation if required. These measures may prevent neonatal hypoxemia, hypoperfusion, and acidosis. A salutary effect of prenatal cardiac diagnosis on neonatal survival has been proven for transposition of the great arteries by Bonnet et al.[8] This is the only paper in the literature thus far that has the statistical power to show this effect. Some studies suggest improved outcomes in some subgroups of patients with prenatally diagnosed congenital heart disease.[9-12] A significant effect on the overall group of patients with structural heart disease has not been shown. The purpose of this study was to evaluate retrospectively the effect of prenatal diagnosis on the newborn with congenital heart disease, comparing the incidence of metabolic acidosis in prenatally and postnatally diagnosed groups of patients with similar diagnoses.

Patients and Methods

This retrospective study included patients diagnosed with congenital heart disease between January 1, 1991, and July 30, 1998, originating from three institutions, Wilhelmina Children's Hospital/University Medical Center, Utrecht, the Netherlands; Yale-New Haven Children's Hospital, USA; and University of Maryland Medical System in Baltimore, USA. All patients who required operations for structural heart disease in the first 31 days of life or died before the operation could take place were included. Excluded were patients with severe, life-threatening extracardiac or chromosomal anomalies.

Two different groups of patients with structural heart disease were compared, one in which the diagnosis was made prenatally and the other in which the cardiac anomaly was discovered after birth. Both groups received similar care at the same institutions.
The patients having a prenatal diagnosis were delivered within the University Hospitals, where indicated prostaglandin was started immediately and infants were intubated and ventilated if needed. The other patients were treated after congenital heart disease was suspected.

Outcome variables
Medical records were reviewed for age at diagnosis, mode of delivery, gestational age at delivery, Apgar scores, prostaglandin administration and laboratory values, including arterial pH, base excess (BE), Pco2, Po2, and, if measured, lactate values. Arterial blood gases were those reported at 1 and 4 to 6 hours postpartum and worst blood gas, regardless of postnatal age in hours. These data were used to compare not only the two different groups described above but also to compare several sets of subgroups, including patients with and without ductus-dependent lesions, patients with a future possibility of biventricular repair, and those with an anticipated single ventricular repair. The outcomes in patients with left ventricular outflow tract obstruction, right ventricular outflow tract obstruction, and without any obstruction were compared seperately.

Statistical Analysis
Data were analyzed by using SPSS software (SPSS Inc, Chicago, Ill, USA). The Student's *t*-test was used for comparing both groups for values of pH, BE, Pco2, Po2, and lactate values. Chi-square testing was used for comparison of both groups with regard to univentricular or biventricular repair, ductus-dependency, and mode of delivery.

Results

Between January 1, 1991, and June 30, 1998, 408 patients with congenital heart disease requiring operations within 31 days of life were admitted to the three participating institutions. Prenatal diagnosis in this group was established in 81 (20%) patients at an average gestational age of 30.5 weeks, whereas 327 (80%) patients only had postnatal diagnosis of their heart disease. Cesarean delivery was performed in 30.4% of the prenatal cases and 21.8% of the postnatal cases (P=0.31). The gestational age at delivery was 37.5 ± 0.4 weeks (mean ± SEM) in the group with prenatal diagnosis, whereas the patients with a postnatal diagnosis were delivered signifi-

cantly later (39.1 ± 0.2 weeks; P<0.001). Apgar scores were not different. Prostaglandin administration was required in 71% of both the prenatal and the postnatal patients. In the prenatal group prostaglandin was always started on the first day of life (SEM = 0), and this differed significantly from the postnatal group, in which prostaglandin was started at 2.6 ± 0.6 days (P< 0.001). No difference was found in the dosage or duration of prostaglandin administration (**Table 1**).

Table 1. Gestational age at delivery, Apgar scores, and duration of prostaglandin E1 administration, prostaglandin E1 dose per minute, and total cumulative dosage of prostaglandin E1.

	Prenatal Diagnosis	n	Mean	SEM	P
Gestational age at delivery (weeks)	Yes	44	37.45	0.40	<0.001
	No	90	39.08	0.22	
Apgar score, 1 min	Yes	43	7.60	0.22	0.93
	No	95	7.58	0.18	
Apgar score, 5 min	Yes	43	8.56	0.13	0.55
	No	95	8.66	0.10	
Prostaglandin E1 administration (days)	Yes	30	4.30	0.40	0.44
	No	55	4.89	0.52	
Prostaglandin E1 dose/min (microg/kg.min)	Yes	36	0.044	0.009	0.16
	No	66	0.060	0.007	
Prostaglandin E1 total dose (mg/kg)	Yes	29	0.282	0.071	0.24
	No	51	0.565	0.174	

n = Number, SEM = Standard error of mean, P = Probabilty

Patients with a prenatal diagnosis stayed in the hospital a mean time of 15.4 days, and those with a postnatal diagnosis stayed 19.9 days (P=0.55). The difference in outcome was not significant either. Of the prenatal

group, 17% died within 31 days after birth compared with 19% in the postnatal group (P=0.87).

Laboratory results

Significant differences were found in the lowest arterial pH (prenatal vs postnatal, 7.31 ± 0.01 vs 7.28 ± 0.01; P=0.004) and the lowest preoperative BE (prenatal vs postnatal, -4.90 ± 0.45 mEq/L vs -7.26 ± 0.35 mEq/L; P<0.001), with acidosis more common among the postnatally diagnosed group. Lactate was only measured in the patients seen in Utrecht because this is not a standard procedure in the two American centers in this study. The patients receiving prenatal and postnatal diagnosis had a highest lactate value of 3.14 ± 0.57 mmol/L and 6.33 ± 0.58 mmol/L, respectively (P<0.001). No significant differences were found in highest arterial Pco2 and lowest Po2 (**Table 2**).

Table 2. Arterial blood gases in the preoperative period.

	Prenatal Diagnosis	n	Mean	SEM	P
Lowest pH	Yes	67	7.31	0.01	0.004
	No	293	7.28	0.01	
Lowest BE (mEq/L)	Yes	67	-4.90	0.45	<0.001
	No	291	-7.26	0.35	
Highest Pco2 (mm Hg)	Yes	41	45.14	2.03	0.244
	No	88	48.72	1.86	
Lowest Po2 (mm Hg)	Yes	41	42.90	2.46	0.956
	No	83	42.68	2.49	
Highest lactate (mmol/L)	Yes	11	3.14	0.57	<0.001
	No	99	6.33	0.58	

n = Number, SEM = Standard error of mean, P = Probabilty

Because very few blood gases were obtained 1 and 4 to 6 hours postpartum in the postnatal group, no significant differences were encountered for pH or BE at these times. The only significant difference was found for Pco2 after 1 hour (prenatal vs postnatal, 45.4 ± 2.5 vs 34.1 ± 3.7 mm Hg; P=0.015; **Table 3**).

Table 3. Arterial blood gases 1 hour and 4 to 6 hours post partum.

	Prenatal Diagnosis	n	Mean	SEM	P
PH, 1 h	Yes	14	7.31	0.02	0.287
	No	10	7.35	0.03	
BE, 1 h	Yes	14	-4.32	1.12	0.461
(mEq/L)	No	9	-5.78	1.68	
Pco2 ,1 h	Yes	14	45.43	2.54	0.015
(mm Hg)	No	10	34.10	3.67	
Po2 ,1 h	Yes	14	43.50	4.39	0.744
(mm Hg)	No	10	45.90	6.01	
PH, 4-6 h	Yes	18	7.37	0.02	0.216
	No	11	7.31	0.05	
BE, 4-6 h	Yes	18	-0.82	0.58	0.051
(mEq/L)	No	12	-4.81	1.77	
Pco2 ,4-6 h	Yes	18	43.06	1.95	0.063
(mm Hg)	No	12	37.08	2.40	
Po2, 4-6 h	Yes	18	44.39	2.95	0.840
(mm Hg)	No	12	43.25	5.23	

n = Number, SEM = Standard error of mean, P = Probabilty

The percentage of patients with markedly abnormal labaratory results was also compared. Lactate values over 7.5 mmol/L were found in none of the patients in the prenatal group compared with 24.5% in the postnatal group (P=0.29). The pH was lower than 7.20 in 8.8% of those having prenatal diagnosis and 20.7% of those having postnatal diagnosis (P=0.02). Base excess lower than –9.0 mEq/L was found in 11.8% in the prenatal group and in 28.3% in the postnatal group (P=0.005).

Ductus-dependent lesions versus non-ductus-dependent lesions
In the same patient population, a difference was made between two groups, those with (n=265) and those without (n=109) a circulation depending on the persistence of a ductus arteriosus. When the same set of variables was compared for these groups, lowest pH (prenatal vs postnatal, 7.32 ± 0.01 vs 7.27 ± 0.01; P=0.005) and lowest BE (prenatal vs postnatal, -5.15 ± 0.54 vs -7.44 ± 0.45 mEq/L, P=0.002) differed significantly in the ductus-dependent group, whereas only the lowest BE (prenatal vs postnatal, -4.08 ± 0.87 vs -6.83 ± 0.58 mEq/L; P=0.027) differed in the non-ductus-dependent group.

Single ventricular repair versus biventricular repair
Differences found between patients in this population requiring a single ventricular repair and those patients going for a biventricular repair were the percentage of prenatal diagnosis made in these groups (univentricular vs biventricular, 33% vs 14%; P<0.001) and lowest Po2 (univentricular vs biventricular, 37.5 ± 1.8 vs 45.0 ± 2.5; P=0.018).

Right-sided heart obstruction: prenatal versus postnatal diagnosis
When comparing blood gases of prenatally and postnatally diagnosed infants with a right ventricular outflow tract obstruction, a significant difference was found in lowest arterial BE (prenatal vs postnatal, -4.38 ± 0.69 vs –6.64 ± 0.59 mEq/L; P=0.024).

Left-sided heart obstruction: prenatal versus postnatal diagnosis
In the group with a left ventricular outflow tract obstruction, both lowest BE (prenatal vs postnatal, -5.03 ± 0.78 vs –7.80 ± 0.62 mEq/L; P=0.007) and lowest pH (prenatal vs postnatal, 7.32 ± 0.02 vs 7.27 ± 0.02; P=0.027) differed significantly.

Prenatally diagnosed right-sided heart obstruction versus prenatally diagnosed left-sided heart obstruction
In comparing patients with a prenatal diagnosis of right and left ventricular outflow tract obstruction, significant differences were found in lowest arterial Po2 (right vs left, 37.2 ± 2.6 vs 48.7 ± 4.0 mmHg; P=0.038) and highest arterial lactate (right vs left, 3.6 ± 0.4 vs 1.3 ± 0.3 mmol/L, P=0.024).

Discussion

Prenatal diagnosis of congenital heart disease demands a high level of skill but one that is achievable during routine obstetric ultrasonography.[13] The most convincing justification for such an effort would be to demonstrate that patients with a prenatal diagnosis have a better chance on a good outcome as a result of early initiation of therapy.

In 43% of the patients the diagnosis was made before 24 weeks gestation, an age at which termination of pregnancy is still a legal option, but the parents opted for continuation of the pregnancy with a planned delivery. Although the number of cesarean deliveries was not significantly higher, the gestational age at delivery was significantly lower in infants with a prenatal diagnosis, probably because of the planned induction of the delivery to insure optimal postnatal care.

No difference was found in Apgar scores between both groups, which could be expected because cardiac status in the delivery room rarely differed between the two groups as a result of ductal patency and the absence of significant left-to-right shunting before the postnatal drop in pulmonary vascular resistance.

Total cumulative dosage of prostaglandin E1 was no different, and therefore no difference in side effects is to be expected between the two patient groups.[14-17] Prostaglandin E1 administration was, if required, always started on the first day of life in the prenatal group, whereas administration was started after 2.6 days in the postnatal group. This is likely due to the fact that decreased ductal flow among the infants with a postnatal diagnosis resulted in the symptoms leading to initial diagnosis.

Although hypoxemia or ischemia may result in metabolic acidosis, highest Pco2 and lowest Po2 values were no different between the two patient groups, suggesting that the predominant cause of acidosis is hypoperfusion rather than hypoxemia with early prostaglandin E1 infusion affecting systemic perfusion.

In our study prenatal diagnosis did lead to a significant prevention of deterioration of the acid-base-equilibrium. A positive effect of prenatal detection on surgical outcome has been suggested in previous reports,[8-12] but we could not affirm such a direct effect. Eapen et al.[12] analyzed a specific population with left ventricular outflow tract obstruction and found a significant difference in BE in first blood gases in favor of the prenatally

diagnosed group. Our study covers the entire spectrum of congenital heart disease and reports on representative information about the actual acidosis obtained at fixed time intervals after birth or by analyzing worst blood gases and demonstrates a significant difference in the severity of acidosis in favor of the group of patients with a prenatal diagnosis of congenital heart disease. This outcome suggests that immediate management of heart disease facilitated by the prenatal diagnosis of the disease diminishes acidosis and allows immediate stabilization of the acid-base-equilibrium. Comparison of markedly abnormal laboratory values shows that a prenatal diagnosis helps in prevention of extreme acidosis.

The importance of avoidance of severe metabolic acidosis to prevent brain damage has been suggested in previous reports. Enhanced acidosis may exaggerate ischemic glial and vascular cell damage because it accelerates delocalization of protein-bound iron, with an ensuing free-radical damage to membrane lipids and proteins.[18-21] Prevention of metabolic acidosis might, in addition, lead to better surgical outcomes. Postoperative lactate levels are higher for nonsurvivors and may be a useful predictor of mortality in children less than 1 year of age.[22-25]

The comparison of prenatally and postnatally diagnosed patients with ductus-dependent lesions showed significant differences for lowest BE and lowest pH, and in patients with non-ductus-dependent lesions, only lowest BE differed significantly in favor of the prenatal group. This implicates that especially the early initiation of prostaglandin E1 administration in the ductus-dependent group prevents acidosis, whereas the difference in the non-ductus-dependent group, although less significant, suggests that early initiation of medical care, other than prostaglandin therapy, is another positive factor of prenatal diagnosis. In most cases, however prostaglandin administration can be delayed for 2 to 3 hours after birth because the ductus arteriosus will normally stay widely patent in the first several hours.

Comparing patients with a future possibility of biventricular repair to those with an anticipated single ventricular repair, the only statement to be made is the obvious higher percentage of prenatal diagnosis in the last group because of the presence of a distinctly abnormal four-chamber view, which facilitates early diagnosis.

The separate analysis of patients with and without prenatal diagnosis of right-sided heart obstruction, left-sided heart obstruction, or no obstruction, reveals a significant difference in lowest BE in favor of the prenatal group for the right-sided heart obstruction, lowest BE and pH for left-sided

heart obstruction, and no significant difference for the group without obstruction. This indicates that also in the group with right-sided heart obstruction, prenatal diagnosis has a positive effect on prevention of metabolic acidosis.

The power of the numbers is small, especially when groups of patients are separated out, which makes significance hard to reach in subgroups. This includes the important group of transposition of the great arteries, where Bonnet et al.[8] showed that prenatal detection reduced neonatal mortality. Our data did not allow such a conclusion, although the surgical outcomes of all patients have been investigated. The number of influencing parameters, such as different surgeons, different institutions, and different protocols prevented a clean analysis.

In conclusion, prenatal diagnosis diminishes the development of metabolic acidosis in the newborn patient with congenital heart disease without an apparent effect on immediate surgical outcome. Although in this study the differences are significant but small, they indicate a first step towards a better-controlled preoperative approach, which will allow an optimization of the preoperative condition of the patient with severe congenital heart disease. We postulate that this improvement in preoperative condition may lead to improved longterm outcome and prevention of cerebral damage among this fragile group of patients.

Acknowledgments

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Chapter 3

Lactacidosis in the neonate is minimized by prenatal detection of congenital heart disease

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Abstract

Objectives
To investigate the impact of prenatal detection of congenital heart disease on preventing severe preoperative lactacidosis.

Methods
Patients operated upon for congenital heart disease during the first 31 days of life (n=209) were studied retrospectively, 21 were diagnosed prenatally and 188 patients had not been diagnosed prenatally. Preoperative lactate, pH and base excess were evaluated.

Results
Differences were noted in preoperative pH (7.28 ± 0.03 vs 7.24 ± 0.01; P=0.29), base excess (-5.83 ± 0.64 vs -6.93 ± 0.46 mmol/L; P=0.10) and lactate (3.05 ± 0.35 vs 6.08 ± 0.45 mmol/L; p<0.001), indicating a significant difference in blood lactate values in favor of the prenatally diagnosed group.

Conclusions
Prenatal diagnosis of congenital heart disease and the resulting immediate postnatal care prevent lactate increase in the preoperative period of these patients. This may decrease the risk of cerebral damage and result in the patient being in better condition at surgery.

Introduction

Severe congenital heart disease may require urgent surgical intervention in the first weeks of life. The improvement of surgical techniques and increased surgical experience have diminished mortality in these patients significantly. Due to the already low surgical mortality, a further improvement should be located in the preoperative period.[1,2] Prenatal detection of congenital heart disease might be one way to achieve this improvement, as it is supposed to improve and optimize care in the short postnatal and preoperative period.[3-7] Prenatal diagnosis facilitates planned delivery and immediate prostaglandin administration[8], which supposedly improves preoperative management and leads to better blood gas control, thus preventing severe preoperative lactacidosis. In this study, two groups of patients with and without a prenatal diagnosis of severe congenital heart disease were compared. Both groups required comparable surgery in the neonatal period. Our hypothesis is that prenatal diagnosis of congenital heart disease and the resulting immediate postnatal care prevent lactate increase in the preoperative period of these patients.

Methods

Patient population

This retrospective study included patients diagnosed with congenital heart disease between January 1, 1991, and January 1, 2000, at the Wilhemina Children's Hospital/University Medical Center, Utrecht, the Netherlands. All patients required surgery for congenital heart disease within the first 31 days of life. Medical records were studied retrospectively for diagnosis, randomly obtained blood gas values and outcome. Two groups of patients with structural heart disease were compared, one diagnosed prenatally and the other in which the cardiac anomaly was only discovered after birth. All prenatally diagnosed patients were delivered within the university hospital, received low dose prostaglandin immediately when ductal-dependent, and were intubated and ventilated if needed in our tertiary-level neonatal intensive care unit. The other patients were all born in outlying hospitals or at home and were transported after congenital heart disease was suspected. Both groups of patients received similar care, depending on the kind and severity of the malformation once they were admitted.

Statistical Analysis
Data were analyzed by using SPSS software (SPSS Inc, Chicago, Ill, USA). The Student's *t*-test and Fisher's exact test were used for comparing both groups for values of pH, base excess and lactate. All data are presented as mean ± standard error of the mean.

Results

Patient population
Between January 1, 1991, and January 1, 2000, 209 patients with congenital structural heart disease requiring surgery within 31 days of life were admitted to this institution. In 21 patients (10%) prenatal diagnosis was established, whereas 188 patients (90%) had only a postnatal diagnosis of their structural heart disease. In the postnatal group, 80.2% had had general ultrasound screening but congenital heart disease was not detected. A prenatal diagnosis could not be made in 32% of the patients because the ultrasound investigation was performed at a gestational age when the heart could not yet be properly evaluated. The four-chamber view was not reported in 23% and was missed in 26% despite a four-chamber view being visible at the right gestational age. **Table 1** shows the distribution of congenital defects in the two groups.

Postoperative intensive care duration was 4.40 ± 1.54 days in the prenatal group vs 9.51 ± 2.29 days in the postnatal group (P=0.48). The prenatally diagnosed neonates were operated on at a mean age of 5.38 ± 1.05 days, which is significantly different from the postnatal group that was operated on at 9.21 ± 0.50 days' age (P=0.023). No difference in survival was found between the two patient groups.

Table 1. Distribution of congenital defects

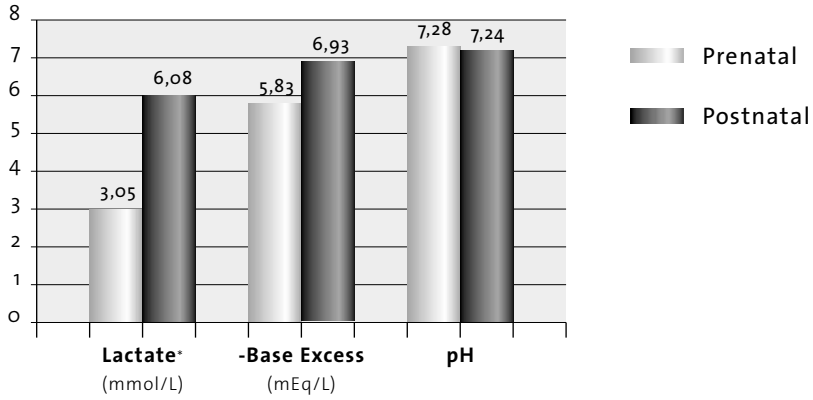
	Prenatal (n)	Postnatal (n)	Surgery
Transposition of the great arteries	5	68	Switch
Coarctation of the aorta	4	42	End-end anastomosis
Hypoplastic left heart syndrome	2	15	Norwood
Ventricular septum defect	0	4	VSD repair
Tetrology of Fallot	2	7	One stage/two stage-repair
Hypoplastic right heart syndrome	0	1	Single ventricle repair
Pulmonary atresia	4	15	Unifocalization
Pulmonary stenosis	0	3	Valvulotomy
Aortic stenosis	0	2	Aortic valvulotomy
Tricuspid atresia	0	5	Single ventricle repair
Rhabdomyoma	1	0	Excision
Interrupted aortic arch	0	7	Arch repair
Total anomalous pulmonary venous connection	1	8	TAPVC-repair
Double outlet right ventricle	1	4	DORV-repair
Double inlet left ventricle	0	3	Single ventricle repair
Truncus arteriosus	1	4	Truncus repair

Laboratory results

The values for worst preoperative arterial lactate of the prenatally diagnosed group were 3.05 ± 0.35 vs 6.08 ± 0.45 mmol/L in the postnatal group, indicating a significant difference in worst preoperative blood lactate in favor of the prenatally diagnosed group (P<0.001).
Worst preoperative pH of the prenatally diagnosed group was 7.28 ± 0.03 vs a preoperative pH of 7.24 ± 0.01 in the postnatally diagnosed group (P=0.29). Worst base excess of the prenatal group was -5.83 ± 0.64 mEq/L, while the value for the postnatal group was -6.93 ± 0.46 mEq/L (P=0.10) (**Figure 1)**.

Figure 1

Worst values of preoperative lactate, base excess and pH in both prenatal and postnatal groups. * = P<0.001 for lactate difference between groups

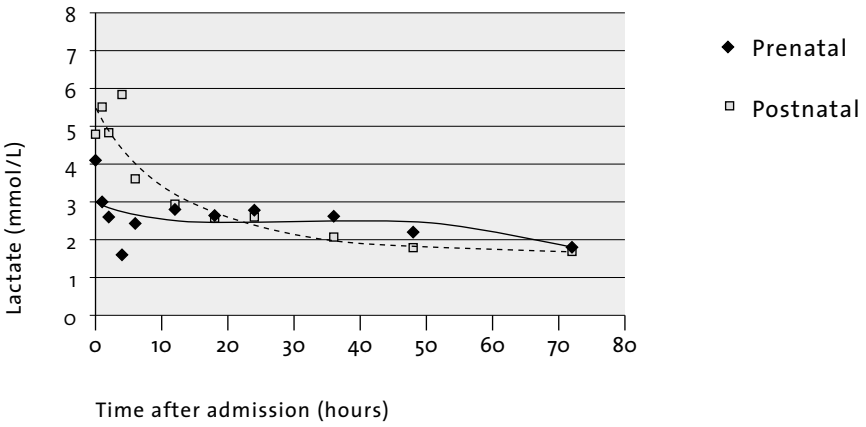


Normalization of preoperative lactate values occurred after 21.5 h, normalization of pH after 5.3 h and normalization of base excess after 0.41 h.
Figure 2 shows lactate values at different time points after admission.
A significant difference in favor of the group with a prenatal diagnosis was found when the patients were divided into groups with a worst preoperative lactate greater or less than 7.5 mmol/L. Of the patients without a prenatal diagnosis 22.3% had a worst preoperative lactate greater than 7.5 mmol/L, whereas none of the patients with a prenatal diagnosis had a worst lactate greater than 7.5 mmol/L (P=0.026).
Statistical analysis on the subgroup of ductal-dependent lesions also shows a significant difference in worst lactate values in favor of the prenatal group supporting the null hypothesis in the highest-risk group. The prenatal group had a worst arterial lactate of 3.03 ± 0.39 vs 6.07 ± 0.49

mmol/L in the postnatal group. In this subgroup the differences in base excess (-5.88 ± 0.65 vs −6.89 ± 0.50 mEq/L; P=0.225) and pH (7.29 ± 0.04 vs 7.26 ± 0.01; P=0.32) were not significant.

Figure 2

Arterial lactate values at different time points after admission: prenatal and postnatal



Discussion

The purpose of this study was to investigate the impact of prenatal diagnosis on the preoperative condition of the neonate. This study showed a significant prevention of lactate formation in the preoperative period in the group with a prenatal diagnosis. This means the patient is in better condition at surgery and might result in a decrease of the risk of cerebral damage, as high lactate values are correlated with possible cerebral damage and complications.[9-13] In our study none of the prenatally diagnosed patients had a worst lactate greater than 7.5 mmol/L vs 22.3% of the group with a postnatal diagnosis, a level that would threaten the neonatal brain.

This study demonstrates the positive effect of prenatal diagnosis on the overall group of congenital heart disease in a small population. This accords with previous publications of Bonnet et al.[3] showing that prenatal detection of transposition of the great arteries actually reduced neonatal mortality and Chang et al.[5] who reported a decrease in preoperative metabolic acidosis and cardiopulmonary arrest in a group of neonates with left ventricular outflow tract obstruction. These publications support the view that prenatal detection may lead to a better preoperative condition and

possible improvement of surgical outcome. This is parti-cularly important in neonates with ductus-dependent lesions, who receive constant prostaglandin infusion to prevent unfavorable hemodynamic changes.[14,15]

Normalization of lactate values takes significantly more time than normalization of either pH or base excess, as titration of bicarbonate will almost immediately normalize pH and base excess. The extent of the hypoxia and the severity of the resulting acidosis threatening the neonatal brain seem therefore better reflected by lactate measurements.

Several studies have reported perinatal hypoxic ischemic injury as a significant cause of neurodevelopmental impairment and neuronal damage.[16-17] Hanrahan et al.[18] investigated the relationship between elevated cerebral lactate levels in children with birth asphyxia and their neurodevelopment at one year of age. Elevated levels had a predictive value of 86% for adverse outcome, i.e. death or neurodevelopmental impairment. Other studies also showed the correlation between initial brain lactate levels measured and adverse outcome in children experiencing perinatal asphyxia.[19-21]

Comparable information has surfaced in recent years on the outcome of open-heart surgery in the pediatric age group. Prospective observational studies have been published by Siegel et al.[22] on the predictive value of serum lactate measurement after pediatric open-heart surgery on outcome. These studies showed that nonsurvivors after open-heart surgery have significantly higher serum lactate levels than the surviving group of patients and that an initial lactate level greater than 4.5 mmol/L had a positive predictive value for mortality of 100%. Cheifetz et al.[23] also reported that an elevated level of serum lactate could be seen as an important indicator of potential mortality in children less than 1 year of age undergoing surgery for complex congenital heart disease. These elevated lactate levels reflect tissue hypoperfusion and hypoxemia. According to another study the occurrence of metabolic acidosis and the need for preoperative respiratory support were greater in the nonsurviving patients.[1]

A number of studies indicate the importance of lactate levels over arterial pH or base excess.[22,24,25] They support the finding that the anion gap and arterial pH, often used to screen for hyperlactatemia, are poor predictors for outcome after open-heart surgery and cannot replace serum lactate measurements. Deshpande and Platt[26] state that pH and negative base excess are both insensitive indicators of raised lactate concentrations and stress the importance of high lactate concentration as an early warning signal and prognostic information in the critically ill infant. The lack of cor-

relation of pH with hyperlactatemia is explained by the titration of bicarbonate to maintain the patient at normal pH.[22]

Progress in surgery for congenital heart disease has led to the successful operation in infancy of complex heart lesions that were previously thought to be inoperable. However, there is still an increasing disquiet about the high incidence of acute neurological events in the immediate postoperative period.[27] Our study showed that the prenatal diagnosis of congenital heart disease could have an important role in the prevention of neurological sequelae by preventing lactate increase in the preoperative period. We support the opinion that the most significant contribution for a positive outcome for the newborn patient after cardiothoracic surgery would be intervention in the preoperative period. A diagnosis of the cardiac lesion before birth allows physicians to initiate therapy immediately after birth and helps prevent these problems.

Acknowledgments

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Chapter 4

Predictive value of acidosis on developmental outcome in newborns with congenital heart disease

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Submitted

Abstract

Objectives
This study is aimed at the evaluation of parameters for acidosis and their predictive value on developmental outcome in newborns with congenital heart disease. Attempts have been made to identify indices that may predict outcome or morbidity, as mortality for congenital heart disease has declined. Prenatal diagnosis has shown to decrease preoperative acidosis and might prevent the occurrence of disturbed developmental outcome.

Methods
117 patients, requiring surgery for structural heart disease in the first 31 days of life were included. Diagnosis was established either prenatally or postnatally. Preoperative values of lactate, pH and base excess levels were compared to the occurrence of disturbed developmental outcome, i.e. an underperformance of more than 10% from the P_{90} on a standardized Dutch developmental scale. Patients were divided into groups according to blood levels of parameters of acidosis, using Receiver Operating Characteristics curves for determining cut-off values for pH, base excess and lactate.

Results
No significant difference in developmental outcome was found using values for pH or base excess as a cut-off level. Preoperative lactate values exceeding 6.1 mmol/L resulted in a significant increase in impaired development: 40.9% as compared to 15.1% in infants with a preoperative lactate lower than 6.1 mmol/L (P=0.03).

Conclusions
Preoperative lactate values have a prognostic value on developmental outcome in newborns with a congenital heart disease. The limited prognostic value of pH can be explained by the fact that pH can be easily corrected, while lactate better reflects the total oxygen debt experienced by these patients.

Introduction

Congenital heart disease is the leading cause of neonatal death.[1] Improved surgical and cardiopulmonary bypass techniques and timing of surgery however, have led to a substantial improvement of survival in patients requiring surgery for their structural heart anomaly.[2] Advances in surgical and cardiopulmonary bypass techniques made it possible to correct the majority of congenital heart diseases successfully in infancy or childhood.[3] This shifted our research emphasis to the identification of indices that may predict outcome or morbidity along with possible strategies to attenuate adverse clinical responses[2], since a broad spectrum of developmental disorders has been reported in patients surviving heart surgery.[3-6] PH, base excess and lactate measurements have been proposed in numerous studies as prognostic indicators to identify patients with a considerable risk to experience substantial shortterm morbidity.[7,8]
Postoperative serum lactate levels have clearly shown to correlate with outcome after pediatric open-heart surgery.[9-11] The predictive value of preoperative measurements of acidosis in patients with congenital heart disease, which is heavily influenced by prenatal diagnosis of the anomaly[12,13], is unclear.

Prenatal detection of congenital heart disease may lead to a better control of the acid-base-equilibrium and thus prevent the development of severe acidosis in the neonate with congenital heart disease.[12,13] A decline in morbidity and mortality has been shown after prenatal detection of transposition of the great arteries[14] and left outflow tract obstruction.[15,16] The longterm developmental effects have never been evaluated for the overall group of congenital heart disease.

In this study we have investigated the correlation between prenatal detection of congenital heart disease, preoperative measurements of acidosis and outcome. We have studied the prognostic value of different parameters of acidosis and have considered both shortterm and longterm outcome.

Methods

This retrospective study included 117 patients diagnosed with congenital heart disease between December 1, 1994, and January 1, 2000, in the Wilhelmina Children's Hospital/University Medical Center Utrecht, the Netherlands. All patients, requiring surgery for structural heart disease in the first 31 days of life or who died before surgery could take place, were

included. Excluded were patients with severe, life threatening extracardiac or chromosomal anomalies.

Preoperative values of lactate, pH and base excess levels were retrieved of all patients. These blood samples had been randomly obtained in the preoperative period, i.e. between admission for operative intervention and surgery itself. In all patients several blood samples had been taken and in this study the worst values obtained were used for studying relationships with outcome.

Both shortterm and longterm outcome were investigated. Documented were the occurrence of disturbed developmental outcome. Data on developmental outcome were obtained retrospectively and extrapolated to a standardized and validated Dutch developmental scale, the 'Van Wiechen' classification.[17] Classification consisted of age-dependent assessment of motoric behavior, speech, communication and social skills. In case patients had been evaluated on more than one occasion, then the best (most optimal) score was used to extrapolate to the developmental scale. The 'Van Wiechen' classification indicates age-dependent skills that 90% of the children of an average population should be able to perform. An underperformance of more than 10% from the P_{90} in one of the above mentioned domains of the developmental scale was considered to indicate disturbed development. Scores at developmental screening tests are in line with learning capacity in later life and these tests enable the detection of children at risk of school achievement problems.[18-20]

Patients were split into groups with extreme values of parameters of acidosis. Receiver Operating Characteristic (ROC) curves were used for determining cut-off values for pH, base excess and lactate.
Using SPSS software (SPSS Inc, Chicago, Ill, USA) the correlation between prenatal diagnosis of congenital heart disease, measurements of acidosis and outcome parameters were tested.

Results

Between December 1, 1994, and January 1, 2000, 117 patients with congenital structural heart disease requiring surgery within 31 days of life were admitted to this institution. In 15 cases (13%) prenatal diagnosis had been established, while 102 patients (87%) only had a postnatal diagnosis of their structural heart disease. No significant differences in lactate, base excess and pH values were encountered in groups with and without deve-

lopmental problems, with and without mortality within 31 days and with and without longterm mortality (**Table 1**).

Table 1. No significant differences in parameters of acidosis are found comparing groups with and without disturbed developmental outcome and with or without longterm or shortterm mortality.

	Disturbed developmental outcome	**Value ± SEM**	**P-value**
Lactate	Yes	8.94 ± 2.33 mmol/L	0.123
	No	5.05 ± 0.49 mmol/L	
Base excess	Yes	-9.60 ± 1.86 mEq/L	0.333
	No	-7.66 ± 0.57 mEq/L	
pH	Yes	7.19 ± 0.16	0.239
	No	7.24 ± 0.11	

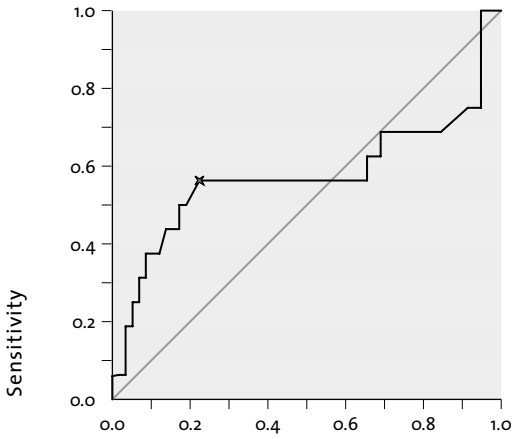
	Mortality < 31 days	**Value ± SEM**	**P-value**
Lactate	Yes	4.61 ± 1.18 mmol/L	0.388
	No	6.20 ± 0.58 mmol/L	
Base excess	Yes	-7.51 ± 1.18 mEq/L	0.745
	No	-8.04 ± 0.58 mEq/L	
pH	Yes	7.25 ± 0.03	0.832
	No	7.24 ± 0.01	

	Mortality > 31 days	**Value ± SEM**	**P-value**
Lactate	Yes	7.59 ± 2.54 mmol/L	0.388
	No	5.87 ± 0.54 mmol/L	
Base excess	Yes	-8.13 ± 2.47 mEq/L	0.928
	No	-7.97 ± 0.53 mEql/L	
pH	Yes	7.26 ± 0.03	0.609
	No	7.24 ± 0.01	

Patients were split into groups with extreme values of parameters of acidosis. Receiver Operating Characteristic curves were used for determining cut-off values for pH, base excess and lactate. The cut-off values with the best combination of sensitivity and specificity were 7.25 for pH, -9.6 mEq/L for base excess and 6.1 mmol/L for lactate (**Figure 1**). These groups were compared using chi-square testing on differences in developmental outcome and longterm and shortterm mortality. No significant differences were found using values for pH or base excess as a cut-off level, although significance is almost reached using values of base excess (P=0.057). However, preoperative lactate values exceeding 6.1 mmol/L resulted in a significant difference in disturbed developmental outcome. Of the children with a preoperative lactate lower than 6.1 mmol/L, 15.1% had disturbed developmental outcome in later life, compared to 40.9% of the children with a lactate exceeding 6.1 mmol/L (P=0.03; OR=3.88; 95%-CI= 1.47-10.24) (**Table 2**).

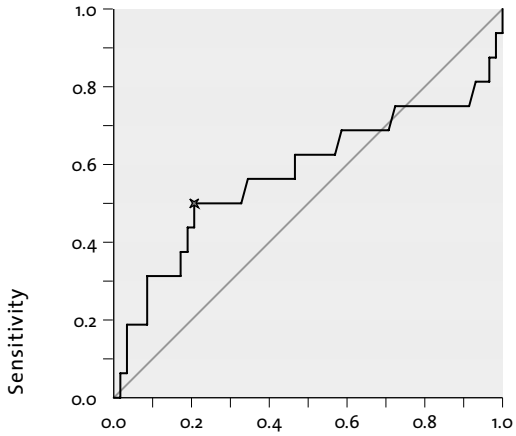
Figure 1

1.1 ROC Curve for lactate



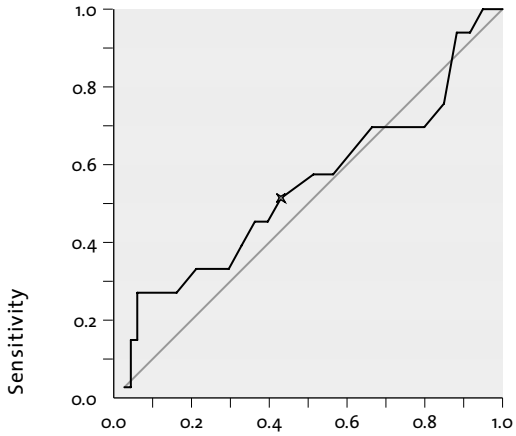
Lactate (mmol/L)	Sensitivity	Specificity
1.3	1.00	0.02
3.1	0.56	0.35
5.2	0.56	0.64
6.1	**0.56**	**0.78**
7.2	0.44	0.83
8.4	0.38	0.88
11.4	0.31	0.91
15.6	0.19	0.97
18.5	0.06	0.98
26.6	0.06	1.00

1.2 ROC Curve for base excess



Base excess (mEq/L)	Sensitivity	Specificity
-1.2	0.88	0.03
-5.1	0.75	0.24
-6.8	0.56	0.55
-8.0	0.56	0.64
-9.6	**0.50**	**0.79**
-10.8	0.38	0.81
-12.2	0.31	0.85
-15.1	0.19	0.91
-19.4	0.06	0.97
-22.7	0.00	0.98

1.3 ROC Curve for pH



pH	Sensitivity	Specificity
7.37	1.00	0.05
7.32	0.75	0.16
7.29	0.56	0.45
7.25	**0.5**	**0.59**
7.24	0.44	0.62
7.22	0.38	0.69
7.19	0.31	0.74
7.11	0.25	0.91
7.05	0.19	0.97
6.86	0.00	0.98

Table 2. Prognostic value of lactate, base excess and pH for developmental outcome. Disturbed developmental outcome is defined as an underperformance of more than 10% from the P_{90} on the Van Wiechen developmental scale. (*P<0.05)

		Disturbed developmental outcome	P-value	Odds ratio	95% CI
Lactate	Yes	40.9%	0.031*	3.88	1.47 - 10.24
> 6.1 mmol/L	No	15.1%			
Base excess	Yes	40.0%	0.057	3.37	1.25 - 9.03
< -9.6 mEq/L	No	16.1%			
pH < 7.25	Yes	26.7%	0.578	1.45	0.58 - 3.62
	No	20.0%			

No significant differences in shortterm and longterm survival between the prenatally and the postnatally diagnosed group were found. In the group with a prenatal diagnosis 19.0% died within 31 days after birth compared to 7.4% of the newborns without a prenatal diagnosis (P=0.11). In the first group 6.7% died beyond the neonatal period, while in the second group 9.4% died more than 31 days after birth (P=1.0). Disturbed developmental outcome was encountered in 25.4% of the children in the postnatal group compared to 13.3% in the prenatal group (P=0.50).

Worst preoperative arterial lactate of the prenatally diagnosed group was 3.03 ± 0.40 versus 6.39 ± 0.59 mmol/L in the postnatally diagnosed group (P<0.001). Worst preoperative pH of the prenatally diagnosed group was 7.26 ± 0.02 versus 7.24 ± 0.01 in the postnatally diagnosed group (P=0.62). Worst base excess of the prenatal group was –6.87 ± 0.71 mEq/L, and this value for the postnatal group was –7.84 ± 0.59 mEq/l (P=0.30).

In **Table 3** a breakdown of cardiac diagnoses in the study cohort is described. The relations of different cardiac diagnoses to preoperative lactate, base excess and pH values and outcome are given.

Table 3 Breakdown of cardiac diagnoses in the study cohort and relations of different cardiac diagnoses to preoperative lactate, base excess and pH values and outcome.

Heart disease	n	Prenatal diagnosis	pH	Base excess (mEq/L)	Lactate (mmol/L)	Disturbed development	Normal development	Deceased
AS	1	0	7.31	-3.0	5.2	0	1	0
AS + VSD	1	0	7.23	-17.2	18.3	0	1	0
CoA	16	1	7.29	-5.1	4.7	0	15	1
CoA + AVSD	3	0	7.31	-2.9	4.8	2	1	0
CoA + VSD	7	0	7.16	-12.3	8.4	3	3	1
CoA/VSD/MS	1	0	7.37	0.2	2.2	0	1	0
DILV/TGA/VSD	1	0	7.36	1.8	1.7	1	0	0
DIRV/CoA	1	1	7.36	-0.8	1.0	0	0	1
TOF	8	1	7.34	-6.2	3.4	2	6	0
DORV	1	0	7.30	-5.0	2.5	0	0	1
DORV/TGA	1	1	7.38	-4.0	2.1	0	1	0
DORV/TGA/PA	1	1	7.29	-5.5	2.5	0	0	1
HLHS	13	2	7.25	-9.6	8.4	1	3	9
Borderline HLHS	3	2	7.22	-6.8	3.2	0	2	1
HRHS	1	0	6.90	-19.9	5.3	0	1	0
PA	6	1	7.19	-8.7	5.8	2	4	0
PA +VSD	1	1	7.04	-18.6	17.6	1	0	0
PS	1	0	7.26	-10.0	3.5	0	1	0
TA	2	0	7.30	-6.5	3.1	0	1	1
TA/CoA/TGA	1	0	7.33	-0.7	1.9	1	0	0
TAPVC	2	1	7.00	-12.3	6.2	0	1	1
TGA	28	2	7.21	-9.1	6.9	4	24	0
TGA + VSD	11	1	7.23	-8.5	5.5	3	8	0
TGA/PS/VSD	1	0	7.34	-3.4	1.2	0	0	1
Truncus Arteriosus	2	0	7.24	-4.0	5.2	0	0	2
VSD	3	0	7.32	-3.7	2.5	0	3	0

AS = Aortic stenosis, **VSD** = Ventricular septal defect, **CoA** = Coarctation of the aorta, **AVSD** = Atrioventricular septal defect, **DILV** = Double inlet left ventricle, **TGA** = Transposition of the great arteries, **HRH** = Hypoplastic right heart, **DIRV** = Double inlet right ventricle, **DORV** = Double outlet right ventricle, **PA** = Pulmonary atresia, **HLHS** = Hypoplastic left heart syndrome, **HRHS** = Hypoplastic right heart syndrome, **MS** = Mitral stenosis, **PAPVC/ TAPVC** = Partial/Total anomalous pulmonary venous connection, **MA** =Mitral atresia, **PS** = Pulmonary stenosis, **TOF** = Tetralogy of Fallot, **TA** = Tricuspid atresia

Discussion

The purpose of this study was to investigate the prognostic value of different preoperative parameters in patients with congenital heart disease requiring surgery. Longterm, shortterm and developmental outcome were considered.

Worst preoperative lactate values appeared to be of prognostic significance for the occurrence of disturbed developmental outcome. Forty-one percent of the patients with a lactate over 6.1 mmol/L had a disturbed developmental outcome in later life. PH and base excess did not show a significant relation with developmental outcome. The limited prognostic value of pH can be explained by the fact that pH is easily and rapidly corrected with bicarbonate infusion, while lactate better reflects the total oxygen debt experienced by the patient with congenital heart disease. Base excess is also not as good a marker of tissue hypoxia as lactate, since its value is also dependent on the Pco2, thus exaggerating any metabolic acidosis.[21,22] In sick, ventilated, newborn infants no correlation between lactate and base deficit was shown.[23] Lactate on the other hand is the end product of anaerobic metabolism and represents a better measure of hypoxia.[24]

No significant differences in shortterm or longterm mortality were found in the groups with and without a prenatal diagnosis. Death within 31 days occurred more often, although not significant, in the prenatal group. This can be explained by the higher incidence of severe cardiac malformations in this group.[25,26] Especially the significant presence of hypoplastic left heart syndrome in the prenatal group has a considerable influence on early demise.[27]

Conclusion

In this study a significant correlation between preoperative lactate values and disturbed developmental outcome was shown. PH and base excess did not show such a correlation. Lactate therefore seems to be the most suitable parameter when trying to relate the preoperative condition of the newborn to outcome. Because of the small numbers of patients in this study no significant relation between prenatal diagnoses and developmental outcome was found. Since previous publications have shown that prenatal diagnosis of congenital heart disease does help in the prevention of severe acidosis,[12,13] a positive effect of prenatal diagnosis on developmental outcome might be expected if larger numbers will be analyzed.

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Chapter 5

Prenatal diagnosis of the fetus with a hypoplastic left heart syndrome: management and outcome

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Submitted

Abstract

Objectives
To review our 13 year experience with prenatally detected hypoplastic left heart syndrome (HLHS) which management remains controversial.

Methods
A retrospective study on the management and outcome of HLHS, diagnosed prenatally in a tertiary level referral center for pediatric cardiology and cardiac surgery between January 1988 and July 2001.

Results
The diagnosis of HLHS was made in 32 fetuses. One mother had two pregnancies associated with HLHS. In 16 cases parents opted for termination of pregnancy and in five for compassionate care. Four fetuses died in utero and seven patients received a palliative Norwood procedure. In seven fetuses associated anomalies were detected: three chromosomal and structural and four only structural. In six fetuses other associated intracardiac anomalies were detected. Of seven operated infants, six had no associated anomalies and only one is alive at an age of 17 months.

Conclusions
The low percentage of intention to treat among patients in our center (34%) is in accordance with the percentage found in another study from the United Kingdom (36%), but differs significantly from reported series in the US (67%). Prenatal diagnosis of the HLHS provides opportunities not only for getting patients in optimal preoperative condition when surgery is offered, but also for in-depth counseling of the parents on this severe malformation. Parents faced with the difficult decision of possible termination of pregnancy, compassionate care or the Norwood strategy, choose in a minority for surgical treatment which might be based on the socioreligious differences and in the interpretation of the longterm quality of life.

Introduction

The hypoplastic left heart syndrome (HLHS) encompasses a spectrum of structural cardiac malformations that are characterized by severe underdevelopment of the structures in the heart-aorta complex, including the left ventricular cavity and mass.[1-3] This syndrome ranges from operable lesions to lesions associated with other anomalies not compatible with life. At an estimated prevalence of 1 to 4 per 10.000 life births, the hypoplastic left heart syndrome accounts for 7 to 8% of congenital heart disease (CHD) and is the most common cause of death due to heart disease in the newborn period. The introduction of the palliative Norwood procedure in 1985 has led to an increasing number of infants operated for a HLHS.[4-7]

The HLHS is readily detectable before 20 weeks gestation by echocardiographic examination of the four-chamber view of the fetal heart and is one of the most common abnormalities detected in utero.[8,9] Before surgical treatment options were introduced, no treatment was available and compassionate care therefore was the only option available for the infant.[10] Although surgical options are available, the results reported so far are encouraging but not yet comparable to the results of other types of neonatal cardiac surgery. The neurological outcome and the longterm quality of life are until now still questionable.[7,11-14]

Management of the HLHS remains controversial. Some centers favor the palliative Norwood procedure or cardiac transplantation,[15,16] while others continue to withhold from surgery.[3] At our institution the palliative Norwood procedure is currently offered as the primarily surgical treatment option to patients with HLHS as neonatal heart transplantation is not yet performed in the Netherlands. This descriptive paper aims to review the management and outcome of prenatally diagnosed HLHS in a single center over 13 years and to compare it with the management strategy and outcome in the United Kingdom (UK) and United States (US).

Materials and Methods

In this retrospective study we reviewed the medical records of 31 mothers whose children had a HLHS diagnosed in utero by fetal echocardiographic examination at the University Medical Center Utrecht in the Netherlands between January 1, 1988, and June 30, 2001. Management, intervention, outcome, fetal karyotyping and other possible intra- and extracardiac anomalies were documented. The diagnosis of HLHS was based on

two-dimensional echocardiographic evidence of a diminutive ascending aorta, aortic atresia or stenosis and a hypoplastic left ventricle.[17] The anomalies varied from a classic HLHS[18] to a HLHS associated with other intracardiac, extracardiac or chromosomal anomalies. Data on the management of postnatally detected cases were obtained from a previous study from our center.[7] Data were analyzed using SPSS software (SPSS Inc, Chicago, Ill, USA). Data were compared using the chi-square test. Associations with $P<0.05$ were considered statistically significant.

Results

In this study one mother had two HLHS associated pregnancies. Of the 32 cases 16 sets of parents opted for termination of pregnancy, five sets of parents chose not to treat the infant surgically after delivery and chose for compassionate care. Four fetuses died in utero and seven patients received a palliative Norwood procedure (**Table 1**).

Extracardiac anomalies

In this present study in seven patients extracardiac anomalies were detected in utero. One hydropic fetus with bilateral agenesis of the kidneys died in utero at 22 weeks gestation. In four cases parents opted for termination of pregnancy at 19, 22, 23 and 24 weeks gestation. These fetuses were found to have syndrome of Patau, Turner syndrome with associated congenital defects, Pierre Robin syndrome and Edwards Syndrome. Parents opted for compassionate care in two fetuses of which one had an intracranial cyst and the other microencephaly and severe growth retardation with hypoplasia of the lungs and kidneys. These patients died at day one and day 10 respectively.

Intracardiac anomalies

In six fetuses associated intracardiac anomalies were prenatally detected. Three pregnancies, two with endocardial fibroelastosis and one with fetal bradycardia, were terminated. One hydropic fetus with endocardial fibroelastosis died in utero at 26 weeks gestation. The three fetuses with endocardial fibroelastosis were all found to have aortic atresia associated with a hypoplastic left ventricle. One other fetus with complex associated lesions, including ventricular inversion, died postoperatively on day 2. Finally parents opted for compassionate care in one fetus with significant tricuspid valve insufficiency.

Table 1 Outcome and associated anomalies in prenatally diagnosed patients with HLHS.

Patient	Outcome	Category of associated anomaly	Associated anomaly	Age of death (weeks GA)
1	TOP	Extracardial/ Chromosomal	Patau Syndrome (Trisomy 13)	19
2	TOP	Extracardial/ Chromosomal	Turner syndrome	22
3	TOP	Extracardial	Pierre Robin syndrome	23
4	TOP	Extracardial/ Chromosomal	Edwards Syndrome (Trisomy 18)	24
5	TOP	Intracardial	Endocardial fibroelastosis	24
6	TOP	Intracardial	Endocardial fibroelastosis	24
7	TOP	Intracardial	Fetal bradycardia	22
8 - 16	TOP	None	None	19,20,22,22, 23,23,23,23,24
17	CC	Extracardial	Intracranial cyst	Day 1
18	CC	Extracardial	Microcephaly/Lung-/ kidneyhypoplasia	Day 10
19	CC	None	None	Day 2
20	CC	Intracardial	Tricuspid valve insufficiency	Day 4
21	CC	None	None	Day 10
22	IUD	Extracardial	Kidney agenesis/Hydrops	22
23	IUD	Intracardial	Endocardial fibroelastosis/ hydrops	26
24	IUD	None	None	35
25	IUD	None	None	35
26	N	Intracardial	Ventricle inversion	Day 2
27	N	None	None	Day 4 (PO)
28	N	None	None	Day 4 (PO)
29	N	None	None	Day 13
30	N	None	None	Day 77
31	N	None	None	Day 240
32	PCPC	None	None	Alive at 17 months

TOP = Termination of pregnancy, CC = Compassionate care, IUD = Intrauterine death, GA = Gestational age, N = Norwood procedure, PCPC = Partial cavopulmonary connection, PO = peroperatively

Surgical outcome
Of the seven patients who received surgical intervention, one had severe associated cardiac pathology including ventricle inversion. Two patients deceased peroperatively at an age of 4 days following the palliative Norwood procedure. Four patients died between the palliative Norwood procedure and the partial cavopulmonary connection at an age of 2, 13, 77 and 240 days and one patient is alive at an age of 17 months, after the palliative Norwood procedure on day 2 and partial cavopulmonary connection (PCPC) at 4 months. All deceased patients died of cardiac dysfunction.

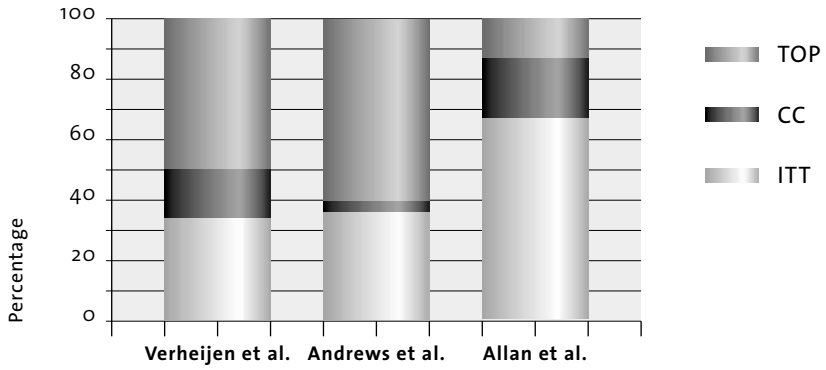
Management of postnatal cases
In the same time period 45 cases of HLHS were only discovered postnatally. In 27 cases (60%) parents opted for compassionate care. In 18 cases (40%) parents chose for surgical treatment. Of these 18 patients 17 patients underwent a palliative Norwood procedure. Of these patients six died peroperatively and four before the partial cavopulmonary connection could take place. Five patients underwent the PCPC procedure and two are still awaiting this procedure. One patient having received a PCPC died postoperatively and three are still awaiting a total cavopulmonary connection (TCPC). One patient received a TCPC and this infant is alive at an age of 10 years.

Discussion

There is a noteworthy difference in the management of prenatally detected HLHS between centers in Europe and those in the US. Although our numbers are small, the management of the HLHS in our institution is comparable with the management seen in a study performed by Andrews et al. in the UK. The percentages of the intention-to-treat group are 34% (our study) versus 36% (Andrews et al.). However, there is a slight difference in the choice of termination of pregnancy (50% vs 60%) and compassionate care (16% vs 3.5%) between our and Andrews' study respectively. If we compare these above mentioned studies with the study performed by Allan et al. from the US, a striking significant difference ($P<0.05$) is encountered in the choice of all treatment options. As the intention-to-treat group constitutes 67% of all patients (Allan et al.), we may conclude that this center in the United States favors a surgical treatment policy. The group of parents that opt for termination of pregnancy constitutes only 13%, and in 20% of all cases parents declined treatment and chose for compassionate care (**Figure 1**).

Figure 1

Management of prenatally detected HLHS: comparison of three centers



TOP = Termination of pregnancy, CC = Compassionate care, IUD = intrauterine death, ITT = Intention-to-treat

The different approach to this structural cardiac anomaly may be attributed to different socioreligious opinions on the management of this type of lesion. We might carefully state that clinicians and parents in Europe are more concerned with the longterm psychoneurological outcome and eventual quality of life of these infants and therefore chose for a less aggressive management venue, i.e. no surgical treatment in the prenatal group. This might well change in the future as survival rates of the palliative Norwood procedure improve, the shortterm neurological deficit seems to decrease and as more documented information on the longterm neurological outcome and quality of life for these infants will become available.

Since the Netherlands have no pediatric heart transplantation programme parents of patients with a HLHS are exclusively offered the staged palliative Norwood strategy[21-26] and no palliative Norwood procedures are offered with the intention of performing a cardiac transplantation at a later stage. Because of the short history of the palliative Norwood procedure no data are available on the consequences of the procedure on the longterm condition of the right ventricle, which serves as the systemic ventricle.

In our surgery group of seven patients, one patient was found to have another associated malformation. Of the six patients without associated anomalies one is alive at an age of 17 months, and three out of six patients (50%) have survived the first stage of the palliative Norwood procedure. This is in accordance with the study reported by Allan et al. in which an early survival rate of 50% (7/14) after the first stage is described.[8] Andrews et al. reported on the outcome of staged reconstructive surgery and showed an early survival of 52%.[20] More recently however, Tworetzky et al. showed an improved early survival of 100% (14/14) after the first stage palliative procedure in prenatally diagnosed patients. Unfortunately we did not see an apparent better outcome of staged reconstructive surgery for HLHS following prenatal diagnosis. This might be due to the small numbers we describe in our series.

The above mentioned studies and our study are dealing with early survival of patients with an in utero diagnosis of the HLHS, where a palliative Norwood procedure is successfully performed and patients are discharged home in good condition. Tworetzky also described the management of postnatally detected cases. Reviewing his excellent results for the prenatal group we have to take into consideration that because of prenatal diagnosis these patients probably arrive in an optimal condition at surgery, preventing lactates to increase, which opens a brighter future with a better neurophysiologic outcome.[27] Tworetzky even states that the difference in early survival between the surgical groups with and without a prenatal diagnosis of the anomaly, is likely based on the more stable preoperative clinical condition of the prenatally diagnosed patients. This is most probably the determining factor in the difference in improved survival between the two groups.[19] This corresponds with Verheijen et al. who showed a significant improvement of the preoperative metabolic condition of the neonate with a prenatal diagnosis of the heart defect due to the possibility of ideal perinatal care.[27-29] This study included the whole range of structural cardiac anomalies.

A study by Plantinga et al.[7] on the surgical treatment of HLHS in our center included 45 patients with a postnatal diagnosis of the anomaly. Parents opted for surgical treatment in 18 cases (40%) and for compassionate care in 27 (60%). In the intention-to-treat group one patient died before the first stage of the Norwood procedure could be performed. These numbers are significantly different compared to the results Tworetzky et al. showed for their postnatal population: intention-to-treat was 69% and the choice for compassionate care 31%. Remarkable is that in the postnatal group parents make a different choice in the US than in the Netherlands despite

the comparable numbers for early survival after first stage palliation: our postnatal population undergoing the palliative Norwood procedure had an early survival rate of 65% (11/17) compared to 66% in Tworetzky's population.[19] This different approach to postnatally detected cases may again be attributed to different socioreligious opinions on the management of this type of lesion, on the emphasis on the eventual quality of life in the Netherlands and on the impact of a more defensive type of medicine in the US (**Figure 2**).

Figure 2

Management of postnatally detected HLHS: comparison of two centers

CC = Compassionate care, ITT = Intention-to-treat

As the HLHS is associated with a high incidence of extracardiac or other intracardiac anomalies (in our series 13 out of 32 infants: 41%), its management is complicated. As mentioned earlier this cardiac anomaly is readily detectable before 20 weeks gestation by echocardiographic examination.[8,9] Although the detection of major malformations seen in the four-chamber view is still not 100%, the pick-up rate of HLHS is reported to be improving.[8] Eapen et al.[30] reported a sensitivity of 25% for the prenatal detection of critical left heart obstructive lesions whereas Buskens et al.[31] reported a sensitivity of 43% for structural cardiac anomalies. In our population we found a prenatal: postnatal ratio of patients with a HLHS of 0.71.

Once a HLHS is diagnosed in utero parents have several options to choose from. It is our policy to inform parents on all the current and future aspects

of the HLHS and provide them with a Patient Information Document (PID), which describes in detail the various possibilities for management of this anomaly, surgical results, and surgical and neurological hazards. In this PID, the results are described of the study by Plantinga et al. Although these surgical results are relatively poor, the technique and operative results are still improving. After this extensive counseling, it is made clear that parents will be fully supported in their decision.

The largest group of parents chose to terminate the pregnancy. This choice was based on the presence of associated lesions or the need for multiple operative procedures for their young infant combined with a questionable longterm quality of life. In the Netherlands parents may opt for TOP if the lesion is detected before a gestational age of 24 weeks. Termination of pregnancy after 24 weeks gestation is only a possible option when it is certain that the structural or chromosomal lesions encountered are not compatible with life.

Parents may opt for compassionate care after delivery for reasons mentioned above. Advanced gestational age or socioreligious reasons usually exclude a TOP in this group. Parents will be counseled and supported during this difficult period and the infant cared for by their general practitioner in the home situation, while stress or discomfort of the infant will be prevented medically.

The longterm effect on neurodevelopmental outcome, as a potential advantage of in utero diagnosis, has not been clarified yet.[6] Although no consensus exists on the occurrence of neurological complications in infants with a HLHS, some authors have reported data on the neurological development of these infants. They most often function in the low-normal range of intelligence and adaptive behaviour.[13,18,32-34] Mahle and Rogers evaluated the neurodevelopmental outcome in infants with HLHS who underwent staged surgical repair and reported varying degrees of mental retardation and severe cerebral palsy.[6,12] The surgical procedure in infancy may have contributed to these neurological hazards, as they might be attributable to cardiopulmonary bypass and deep hypothermic cardiac arrest necessary during open-heart surgery.[11,35]

Conclusion

This descriptive paper aims to review the management and outcome of the HLHS diagnosed prenatally in a single center over 13 years and to compare its management with other centers. The management at our center is in accordance with the management in another center from the UK. However, our data show a significant difference in the prenatally diagnosed group as far as intention to treat and rates of termination of pregnancy are concerned, when we compare our series with that in the United States. The management of postnatally diagnosed patients also shows a significant difference, but the percentages of early survival after the palliative Norwood procedure do not differ between the reported series. Although our numbers are small compared to reports of other recently published reports show that prenatal diagnosis allows informed decisions about management options, and facilitates preoperative care. Mortality following the palliative Norwood procedure is high, but medium term outcome for survivors is good.

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Chapter 6

Prenatal features of Ebstein's anomaly

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In press Prenatal Diagnosis

Abstract

Objectives
A meta-analysis of the literature on Ebstein's anomaly and a comparison of the results in a tertiary level referral center for pediatric cardiology and cardiac surgery. Included is a review of the diagnosis, management and outcome in cases of Ebstein's anomaly.

Methods
A diagnosis of tricuspid valve anomaly was made in 14 fetuses. Isolated Ebstein's anomaly occurred in 4 patients. One patient had Ebstein's anomaly associated with discordance of the great arteries, congenitally corrected transposition of the great arteries. Tricuspid valve dysplasia was encountered in 10 fetuses.

Results
In the group with Ebstein's anomaly (n=4) two fetuses died in utero at a gestational age of 29 and 36 weeks. Parents opted for compassionate care in one fetus that died at an age of 2 days. One patient with congenital corrected transposition of the great arteries is alive at an age of 9 years after receiving pulmonary artery banding, a partial cavopulmonal connection and a Damus-Kay-Stansel operation. In this group two fetuses had hypoplasia of the lungs, of which one had a chromosomal anomaly (trisomy 18).

Conclusion
Patients with a prenatal diagnosis of Ebstein's anomaly or dysplasia of the tricuspid valve represent the most serious component of the spectrum of Ebstein's malformation. The very poor outcome is representative for this selected population and cannot be compared to patients in which the anomaly is detected in later life. Parental counseling of these patients can therefore not be based upon the natural history of these older patients. Prenatal diagnosis provides opportunities for in-depth counseling of the parents before the medical and emotional complexities associated with the neonatal intensive care setting are encountered. Surgical procedures of tricuspid valve repair or replacement are offered for this anomaly, but this option is almost exclusively provided for patients with a diagnosis in later life, as very few patients survive the neonatal period.

Introduction

Anatomy

Dysplastic malformations of the tricuspid valve (TV) include a wide range of morphologic features.[1] The pathological spectrum of dysplasia of the tricuspid valve starts with deformation of the leaflets and the tension apparatus, but without downward displacement, an arrangement primarily described as dysplasia, and ranges to lesions in which the primary lesion is downward displacement of the proximal attachment of the posterior and septal leaflets, known as Ebstein's anomaly (EA). Although the anatomical spectrum varies, the clinical expression is similar and the outcome depends primarily on the severity of the tricuspid insufficiency, rather than the anatomical substrate.[2-7]

Prevalence

The prevalence of Ebstein's anomaly and tricuspid valve dysplasia (TVD) is approximately 0.5-1.0 % of patients with congenital heart disease.[8,9] Patients with Ebstein's anomaly may present at any age, including the prenatal period. Most cases are sporadic, but familial occurrence has been documented. Fetal echocardiography is a very sensitive (91.6%) and specific (99.9%) tool for antenatal diagnosis of congenital heart disease in high-risk pregnancies.[10,11] The experience with prenatal detection of structural congenital heart defects is still increasing and the methods of prenatal examination become more sensitive.[12] Therefore more lesions of this kind, even the milder cases, will be detected in utero which might improve the overall outcome and will raise questions about the management of the fetus during pregnancy and in immediate postnatal life.

Indications for intrauterine evaluation

Fetal factors

Fetal factors for reference include fetal arrhythmias, fetal hydrops and/or hydramnion, but most patients with an in utero diagnosis are referred because of an abnormal four-chamber view on a routine prenatal ultrasound.[13,14] This abnormal four-chamber view is not infrequently associated with the existence of non-immune hydrops fetalis and associated arrhythmias.

Maternal factors

Maternal factors for referral include: a history of congenital heart disease in the previous offspring of the mother, gestational diabetes and teratoge-

nic exposure to drugs, mostly lithium therapy, during pregnancy.[6,15-17] The latter forms a special indication for referral. A direct teratogenic effect of lithium on the atrioventricular junction is thought to facilitate the development of Ebstein's anomaly.[18] While initial information regarding the teratogenic risk of lithium treatment was derived from retrospective reports, more recent epidemiological data indicate that the teratogenic risk of first trimester lithium exposure is lower than previously suggested. An incidence of 2-8% of the occurrence of Ebstein's anomaly has been reported with lithium use during pregnancy, whereas the normal incidence of EA is 1 in 20.000 births.[19] Finally, one study reported that the development of polyhydramnios in the last trimester could be explained by lithium crossing the placenta and causing fetal polyuria, which results in the detected polyhydramnios.[20] As a general rule most authors state that the administration of lithium should be avoided during pregnancy at least during the first trimester and, if used, the patients should definitely have a timely fetal echocardiographic investigation.

Echocardiographic features

As cardiac structural anomalies and functional problems in the fetus can be detected by prenatal echocardiography from 16 weeks gestation, a systemic assessment of the four-chamber view can pick up more than half of the intracardiac abnormalities such as Ebstein's anomaly and tricuspid valve dysplasia.[21-23] The echocardiographical examination is dominated by the enlarged right atrium and the dilated atrioventricular annulus. In Ebstein's anomaly the degree of the tricuspid valve displacement divides the right ventricle in a proximal or inlet portion, which is atrialized, and the distal trabecular portion, which makes up the remaining functional ventricle. The wall of the atrialized portion is usually thinner than that of the functional right ventricle.[24,25] Early presentation is more frequently associated with cardiac lesions, usually pulmonary stenosis or atresia. Serious underdevelopment of pulmonary tissue, caused by either primary pulmonary hypoplasia or secondary pulmonary dysplasia is frequently encountered.

Associated abnormalities

Intracardiac abnormalities

Other intracardiac malformations reported in Ebstein's anomaly are atrial septal defects, ventricular septal defect, pulmonary stenosis or atresia, mitral valve prolapse, endocardial fibroelastosis and less frequently the rare combination of Ebstein's anomaly with ventricular L-loop, corrected transposition of the great arteries.[26-28] One study reported cardiac rhabdo-

myomata.[29] Fetal rhythm disorders such as supraventricular tachycardia (SVT) and atrial flutter (AF) are also frequently encountered.[30]

Extracardiac abnormalities

Other extracardiac malformations reported in Ebstein's anomaly are hydrops fetalis associated with the presence of SVT or AF.[30] The presence of tuberous sclerosis was seen in one case-report.[31]
Other anomalies described associated with Ebstein's anomaly are the Holt-Oram syndrome, a dominantly inherited syndrome of skeletal abnormalities.[32] The association of Ebstein's anomaly and chromosomal abnormalities, such as Down syndrome, is extremely unusual.[33,34]

Pathophysiology

The pathophysiology is similar in both groups of the anomaly of the tricuspid valve. The natural history depends on the varying degrees of severity of incompetence of the tricuspid valve, the presence or absence of an atrial septal defect, the degree of impairment of right ventricle function and associated clinical findings. Although the right ventricular abnormalities might be explained by hemodynamic stress in utero, abnormalities of the left ventricular free wall, which are also sometimes encountered, suggest that either genetic or non-hemodynamic environmental factors are involved in the morphogenesis of this condition.[35,36]

The fetal and neonatal period however are dominated by the extent and pathophysiology of the pulmonary hypoplasia. Once the crucial neonatal phase is survived and pulmonary problems prove to be surmountable, the outlook becomes more comparable to that of older children and adults and is usually associated with an excellent outcome.[3,13,24,25]

Intrauterine course and mode of delivery

Spontaneous intrauterine death is reported, as high as 48%, and 35% of those who were live-born died despite vigorous medical and, when necessary, surgical management, of a combination of hypoxia and severe congestive heart failure.[31] Early detection of tricuspid valve disease has led parents to the option of termination of pregnancy in view of the poor postnatal course of the anomaly. For those deciding to continue the pregnancy no advantage of a cesarean section has been proven and a normal delivery is therefore suggested.

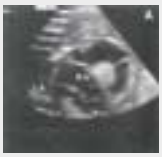
Postnatal interventions and outcome

The diagnostic potential and importance of fetal echocardiography during prenatal evaluation of cardiac malformations allows for adequate perinatal planning and management, with an obvious impact on morbidity and mortality.[30] Some report a policy of induction at term and immediate surgical intervention when Ebstein's anomaly was diagnosed prenatally.[37]
Despite these efforts most patients with a prenatal diagnosis surviving the fetal period die of a combination of pulmonary and cardiac insufficiency shortly after birth. The prognosis of Ebstein's anomaly during fetal life is not influenced by criteria described for postnatal life but is primarily related to the hypoplastic lungs and to factors that control the volume load of the left ventricle. Previous studies have indicated that in cases with dilation of the chambers of the right heart, pulmonary atresia and an intact ventricular septum the prognosis is even worse. The degree of cardiomegaly may provide useful information about secondary lung compression or cardiac failure and therefore assists in giving an accurate prognosis for postnatal survival.[38] When surgical intervention becomes necessary, it is essential to make a detailed assessment of both valvular and ventricular abnormalities (**Figure 1 and 2**).

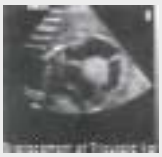
Experience

Prenatal diagnosis of Ebstein's anomaly or tricuspid valve dysplasia was established in 14 patients at the University Medical Center Utrecht in the Netherlands between January 1, 1988, and July 31, 2001. The diagnosis of EA was based on two-dimensional echocardiographic evidence of a downward displacement of the septal leaflet of the TV, as seen in the apical four-chamber view. If the TV inserts on the ventricular septum more than 8 mm/m^2 below the insertion of the mitral valve, the diagnosis can be made.[24] In case of TVD only an abnormal thickened and irregular TV but no apparent downward displacement is seen on echocardiography.[16]
In these 14 patients with a dysplastic tricuspid valve Ebstein's anomaly was only documented in four. One fetus with Ebstein's anomaly died in utero at a gestational age (GA) of 29 weeks and another with associated hypoplasia of the lungs and trisomy 18 died at a GA of 36 weeks. Parents opted for compassionate care in one fetus that died at an age of 2 days. In another fetus parents chose for surgery in which Ebstein's anomaly was associated with a congenitally corrected transposition of the great arteries. This patient received a pulmonary artery banding at one week of life, later a partial cavopulmonary connection (PCPC), and at a later stage a Damus-Kay-Stansel operation. This patient is still alive at an age of 9 years.

Figure 1



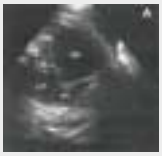
[**A**] Fetal chest with enlarged heart.
LA = Left atrium, **LV** = Left ventricle, **RA** = Right atrium, **RV** = Right ventricle.



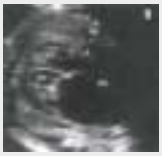
[**B**] Fetal chest with Ebstein's anomaly and the typical downward displacement of the tricuspid valve.

[**C**] Fetal chest with Ebstein's anomaly and hypoplastic lungs.

Figure 2



[**A**] Ebstein's anomaly with downward displacement of the tricuspid valve and enlarged right atrium compressing the left atrium.



[**B**] Dysplastic tricuspid valve syndrome with downward displacement of the tricuspid valve but with enlarged right atrium compressing the left atrium.

Discussion

Patients with Ebstein's anomaly may present at any age, including the prenatal period. Patients with an in utero diagnosis were most commonly referred because of an abnormal routine prenatal ultrasound.[13,14] Fetuses may also be referred for an associated arrhythmia, gestational diabetes, a history of maternal lithium ingestion, and a history of congenital heart disease in the offspring.[16,17,30]

Ebstein's anomaly and dysplasia of the tricuspid valve can both be easily recognized during routine prenatal ultrasonography, since it tends to produce significant cardiomegaly and regurgitation. These structural abnormalities should prompt the need for an in-depth fetal echocardiographic evaluation and search for associated malformations.[39, 40]
The clinical presentation of Ebstein's anomaly varies for the different age groups. In utero patients may develop significant right ventricular outflow tract obstruction, congestive heart failure, cardiomegaly, pulmonary hypoplasia and hydrops fetalis. Presentation in utero is associated with a significant risk of death, which can be predicted by the echocardiographic appearance and presence of associated lesions. Early presentation was frequently associated with other cardiac lesions, usually pulmonary stenosis or atresia. The high incidence of intrauterine death in our series is in accordance with other studies.[13] Neonatal survivors mostly present with cyanosis and heart failure.[9]

The poor prognosis of the fetus is mainly due to the incompetence of the tricuspid valve, leading to right atrial enlargement and subsequently pulmonary hypoplasia or cardiac failure.[13,38] Some authors have suggested that a myocardial problem and not pulmonary artery atresia or stenosis is the leading pathologic factor for the incompetence of the tricuspid valve. The dominating problem in the perinatal age group, the reduction in size of the lungs, may simply be a consequence of the dilation of the chambers of the heart. During the crucial fetal period of development, the lungs have no space to grow since the heart occupies the larger part of the thoracic cavity.[3] The possibility exists that if cardiac dilation could be avoided by therapeutic measures during fetal life, the lungs would grow normally, giving a much better prognosis.[40]

Patients presented with Ebstein's anomaly in utero should be monitored on a regular basis for the development of arrhythmias and effusions. Some fetal arrhythmias can be managed by maternal administration of antiarrhythmic agents.[41] The presence of enlarging effusions and hydrops are

poor prognostic signs and may be an indication for premature delivery after administration of steroids to maximize lung maturity.

Once a fetus survives the perinatal period, further management depends on the severity of the tricuspid valve anomaly. If it is technically possible, the preferred surgical procedure is repair rather than replacement of the tricuspid valve and closure of the atrial septal defect under cardiopulmonary bypass. Variations on this theme have been proposed by others.[4,42,43] In milder cases the full-term neonate presenting with cyanosis might benefit from treatment with prostaglandine E1 to maintain ductal patency.

Conclusion

Ebstein's anomaly remains a severe and frequently fatal disorder in the fetus, with gross echocardiographic abnormalities, readily detectable by routine obstetrical ultrasound.[14] In Ebstein's anomaly visualization of an apical displaced septal tricuspid leaflet has been shown to be the most diagnostic feature. There is much overlap between valvular dysplasia and Ebstein's anomaly, and therefore the two conditions can be readily confused with each other on the echocardiogram. Differentiation is very important, but sometimes difficult. Knowledge of the natural history and the observed poor outcome in continuing pregnancies, allows us to counsel parents on the course of the disease in the fetus and possible management during fetal life. In general, the earlier the patient presents with the malformation, the poorer the prognosis. Fetal and neonatal presentation is typically associated with a dismal outcome secondary to the almost always occurring pulmonary hypoplasia.[24,44]

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Chapter 7

Prenatale diagnostiek bij structurele congenitale hartafwijkingen; effectiviteit en gevolgen

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Inleiding
De zorg voor patiënten met een congenitale hartafwijking lijkt door een prenatale diagnose geoptimaliseerd te kunnen worden. Deze retrospectieve studie analyseert aan de ene kant de groep met een prenatale diagnose van een structurele hartafwijking en aan de andere kant de groep die in de neonatale periode chirurgie nodig had voor een hartafwijking.

Methode
Binnen de prenatale groep werd gekeken naar management en follow-up en bij de chirurgie groep werd er gekeken in hoeverre er prenatale diagnostiek had plaatsgevonden en of een prenatale diagnose invloed had op de mate van verzuring.

Resultaten
Prenatale echogroep: Van de 170 prenataal gediagnosticeerde hartpatiëntjes overleed 64% tijdens of kort na de zwangerschap of werd de zwangerschap beëindigd, terwijl 14% binnen 31 dagen post partum werd geopereerd. Deze vormen dus een overlap met de chirurgie-groep.
Chirurgie-groep: Chirurgie in de neonatale periode werd bij 191 patiënten uitgevoerd, inclusief de 24 uit de prenatale groep. 87% was prenataal niet gediagnosticeerd. Significant betere preoperatieve lactaatwaarden werden gevonden bij de groep met een prenatale diagnose.

Conclusie
Slechts 13% van de patiënten uit de chirurgiegroep werd prenataal gedetecteerd, ondanks dat dit technisch mogelijk was bij 46%. Een verbetering van dit percentage is van belang voor het maken van een weloverwogen keuze tussen zwangerschapsbeëindiging, conservatieve therapie of spoedchirurgie, waarbij prenatale diagnostiek voor een verbetering wat betreft mortaliteit en morbiditeit zou kunnen zorgen.

Abstract

Objectives
Prenatal diagnosis of congenital heart disease (CHD) is likely to contribute positively to the care of patients with a CHD. This retrospective study analyzes data from one group, whose cardiac anomaly was diagnosed prenatally and another group, who required surgery for their CHD in the neonatal period.

Methods
In the prenatal group management and follow-up were analyzed while in the surgery group the percentage in which ultrasound investigations were performed, the efficacy of prenatal ultrasound and the influence of a prenatal diagnosis on the severity of acidosis were analyzed.

Results
Prenatal group: 64% of the prenatally diagnosed patients died before or right after birth, while 14% needed surgery in the neonatal period. These patients are also included in the surgery group.
Surgery group: Surgery in the neonatal period was required in 191 patients, including the 24 from the prenatal group. 87% had no prenatal diagnosis of their heart disease. In the group with a prenatal diagnosis preoperative lactate values were significantly better.

Conclusions
Only 13% of the patients from the surgery group were prenatally detected, while this was technically feasible in 46%. A larger percentage of prenatally diagnosed CHD could contribute to a better counseling of parents in their choice between termination, conservative treatment or emergency surgery with prenatal detection hopefully leading to a decrease in morbidity and mortality.

Inleiding

Er zijn in toenemende mate aanwijzingen dat prenatale diagnostiek een positieve invloed heeft op de uitkomst van congenitale hartafwijkingen, zowel in relatie tot de morbiditeit[1,2] als tot de mortaliteit.[3,4]
Prenatale diagnostiek van hartafwijkingen gebeurt door middel van foetale echocardiografie. Indicaties voor deze foetale echocardiografie zijn beperkt tot de bekende maternale en foetale risicogroepen.[5,6] Deze vormen echter ondanks hun verhoogde risico slechts een zeer klein deel van de totale hoeveelheid patiënten met een congenitaal hartdefect.[7] De overgrote meerderheid wordt geboren uit gezonde moeders zonder enige indicatie voor een verhoogd risico. Het opsporen van deze patiënten middels routine echocardiografische screening is een arbeidsintensieve en daardoor kostbare zaak.

In deze studie is gekeken naar de resultaten van prenatale diagnostiek van structurele congenitale hartafwijkingen en de impact ervan op beleid en behandeling. Daarnaast wordt de effectiviteit van de huidige prenatale screening in kaart gebracht met als doel een eventuele discrepantie tussen de vermeende potentie van screenende prenatale echografie van aangeboren hartafwijkingen enerzijds en de huidige situatie in de praktijk in Nederland anderzijds op het spoor te komen.

Methode

In deze retrospectieve studie zijn twee verschillende, deels overlappende, groepen patiënten betrokken afkomstig uit dezelfde regio in de periode januari 1991- juli 1999. De eerste groep bestaat uit patiëntjes met een structurele congenitale hartafwijking, die prenataal gediagnosticeerd is door middel van foetale echocardiografie. De tweede groep bestaat uit patiëntjes die in de neonatale periode geopereerd werden aan een congenitale hartafwijking.

Prenatale echogroep
Tussen 1 januari 1991 en 1 juli 1999 werden 3086 zwangere vrouwen naar het foetale cardiologie programma van het UMC Utrecht verwezen voor specifieke cardiale evaluatie van de foetus, welke wordt verricht door een echografist onder supervisie van een kindercardioloog. In deze regio bestaat geen routine echocardiografische screening voor alle zwangeren maar wordt een prenatale hartecho pas gemaakt op indicatie na verwijzing. Indicaties voor verwijzing waren maternale en foetale risicofactoren. Onder maternale risicofactoren worden hartafwijkingen bij eerste of twee-

degraads familieleden, maternale diabetes mellitus, maternale leeftijd en maternale teratogeen expositie verstaan. Foetale risicofactoren zijn elders gediagnosticeerde extracardiale anomalieën, hydrops foetalis en foetale aritmieën. Daarnaast vond verwijzing in 53% van de gevallen plaats op basis van verdenking op een abnormaal vierkamerbeeld bij tweedelijns echografisch onderzoek.

In totaal werd bij 170 patiënten (5,5%) een congenitale hartafwijking gediagnosticeerd. Bij deze patiënten werd behalve naar de indicatie voor de echo ook gekeken naar de echodiagnose, het gevoerde beleid, follow-up tot juli 1999, eventuele geassocieerde chromosoomafwijkingen en de uitkomst van de obductie. De prenataal gestelde diagnose werd vergeleken met de diagnose bij postnatale echografie. De ouders werd in het kader van de opsporing van vals negatieve echo-uitslagen verzocht bij eventuele postnatale cardiale problematiek contact op te nemen.

Chirurgie-groep
In dezelfde periode werden 191 patiëntjes in het kinderhartcentrum van het Wilhelmina Kinderziekenhuis binnen de neonatale periode geopereerd aan een congenitale structurele hartafwijking. Er is gekeken welke patiëntjes uit de prenatale echogroep van het UMC Utrecht kwamen. Middels informatie van huisartsen, verloskundigen, kinderartsen en gynaecologen werd verder nagegaan of er bij de overige patiënten een prenatale echo gemaakt was, wat de indicatie was, of er een vierkamerbeeld gemaakt was en wat de echodiagnose was. Bij deze patiëntjes zijn tevens middels statusonderzoek de at random afgenomen bloedgaswaarden geanalyseerd. Waarden voor base excess, lactaat en pH werden in de analyse meegenomen.

Resultaten

Prenatale echogroep
Bij 5,5% (170) van de zwangere vrouwen, waarbij echocardiografie plaatsvond, werd een structurele congenitale hartafwijking geconstateerd. Chromosoom analyse werd 125 maal uitgevoerd, waarbij bij 55 patiënten een anomalie geconstateerd werd.

Spontane intra-uteriene vruchtdood trad bij 23/170 patiënten op. Bij negen van deze 23 patiënten werd door de ouders toestemming tot obductie gegeven. Zeven van deze negen patiënten hadden bij obductie dezelfde diagnose als prenataal. Een patiënt waarbij prenataal een hydrops en een klein inlet VSD werd gezien bleek bij obductie het syndroom van Turner te

hebben en geen VSD meer. Tenslotte werd bij een patiënt, prenataal gediagnosticeerd met een milde hypertrofie van de ventrikels naast een prune-belly, bij obductie geen hartafwijking gevonden.
Tot beëindiging van de zwangerschap werd in 56/170 gevallen besloten (**Tabel 1**).

Tabel 1 Hartafwijkingen en overige malformaties bij de 56 afgebroken zwangerschappen uit de *prenatale echogroep*.

Cardiaal en overige afwijkingen		**36 patiënten**
Hartafwijking		**Geassocieerde afwijking**
Single ventricle	(4 patiënten)	Trisomie 13/18, 68 XX, aangezichtsschisis, nierpathologie
Malalignment VSD	(6 patiënten)	Trisomie 13/18, hernia diafragmatica, verwijde hersenventrikels, anus agenesie, darm malrotatie
AVSD	(11 patiënten)	Trisomie 18/21, T12-T19 translocatie, omfalocèle
VSD	(8 patiënten)	Trisomie 18, omfalocèle, encefalocèle, hygroma colli
AVSD, TAPVC	(2 patiënten)	Heterotaxie
Ectopia cordis	(2 patiënten)	Gastroschisis, omfalocèle, buikwanddefect, anencephalie
RV hypertrofie, fibro-elastose		Cerebrale AV-malformatie
Gefuseerd hart		Conjoined twin
Twin transfusion syndroom		

Enkel cardiale afwijkingen	**20 patiënten**
Hartafwijking	
Malalignment VSD met extreme pulmonaal arterie hypoplasie	(4 patiënten)
Single ventricle	(4 TA en 11 HLHS)
PA	

AVSD = Atrioventriculair septum defect, HLHS = Hypoplastisch linker hart syndroom, PA = Pulmonalis atresie, RV = Rechter ventrikel, TA = Tricuspidaal atresie, TAPVC = Totaal abnormale pulmonale veneuze connectie, VSD = Ventrikel septum defect

Bij 36 van deze 56 patiënten werd door de ouders toestemming tot obductie gegeven. Vijfendertig van deze 36 patiënten hadden na obductie dezelfde diagnose als prenataal. Een patiënt met een trisomie 18 bleek postnataal een VSD te hebben in plaats van een AVSD. Ruim de helft van de prenataal gediagnosticeerde patiënten, 91 in totaal, werd levend geboren. Bij 29 van deze 91 zuigelingen werd gekozen voor abstinentie van elke vorm van therapie vanwege de infauste prognose van de hartafwijking (**Tabel 2**).[8] Van deze 29 patiëntjes overleden er 14 ten gevolge van cardiale afwijkingen, de overigen ten gevolge van andere geassocieerde afwijkingen. Bij 12 van deze 29 patiëntjes werd door de ouders toestemming gegeven tot obductie. Bij alle 12 was er geen verschil tussen de prenatale diagnose en het resultaat van de obductie. Bij de overige 17 patiënten werd de diagnose in alle gevallen bevestigd door middel van postnatale echografie. Bij 24 van de levend geboren kinderen vond chirurgie plaats in de eerste 31 dagen post partum. De overige 38 levend geboren kinderen hadden geen spoedoperatie nodig, maar ondergingen ofwel electieve chirurgie op een later tijdstip of hadden geen chirurgie voor hun hartafwijkingen nodig. Zie voor een overzicht **Figuur 1**. Bij de levendgeborenen werd de diagnose bevestigd door postnatale echografie. Veertien maal was er een verschil tussen de gestelde diagnose pre- en postnataal (**Tabel 3**). Tenslotte werd twaalf keer een klein VSD gezien, dat later niet meer aanwezig bleek te zijn. Mogelijk ging het hier om defecten die intra-uterien dichtgegaan zijn en derhalve worden de desbetreffende diagnoses in deze studie niet als vals positief beschouwd.

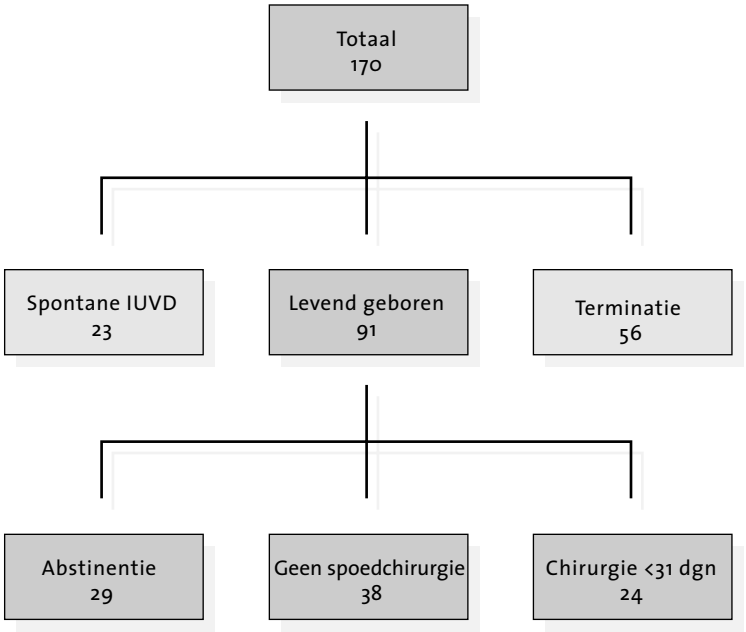
Tabel 2 Hartafwijkingen en overige malformaties bij de 29 patiënten uit de prenatale echogroep waarbij tot een abstinerend beleid is besloten.

Cardiaal en overige afwijkingen		**16 patiënten**
Hartafwijking		**Geassocieerde afwijking**
Malalignment VSD	(3 patiënten)	Longhypoplasie/nieragenesie/Trisomie 18
AVSD	(7 patiënten)	Trisomie 18/21/Arnold Chiari
Ebstein's anomalie, ASD, PS		Trisomie 21
VSD	(3 patiënten)	Trisomie 18, hernia diafragmatica/buikwanddeffect/multipele cong. afwijkingen
LVOTO	(2 patiënten)	22q11 translocatie/hydrops

Enkel cardiale afwijkingen		**13 patiënten**
Hartafwijking		
ASD, hydrops, bradycardie, cardiomyopathie		
Single ventricle	(9 patiënten)	
Tetralogie van Fallot		
TAPVC		
Ebstein's anomalie, PA		

ASD = Atrium septum defect, AVSD = Atrioventriculair septum defect, LVOTO = Left ventricular outflow tract obstruction, PA = Pulmonalis atresie, PS = Pulmonalis stenose, TAPVC = Totaal abnormale pulmonale veneuze connectie, VSD = Ventrikel septum defect

Figuur 1
Prenatale echogroep



Verwijzing vond bij 18/170 patiënten plaats op basis van maternale factoren, bij 43/170 patiënten op basis van foetale risicofactoren, bij 5/170 patiënten op basis van andere factoren (eigen verzoek, maternale leeftijd, IVF zwangerschap) en bij 91/170 patiënten naar aanleiding van een afwijkend vierkamerbeeld bij echografie elders.

Chirurgie-groep
In totaal werden in de periode tussen januari 1991 en juli 1999 191 patiëntjes binnen 31 dagen (gem. 9 ± 3 dagen) na de geboorte geopereerd. Prenatale echografie was bij 158/191 uitgevoerd. Vierentwintig van de 191 patiëntjes (13%) vormen een overlap met de prenatale echogroep (**Figuur 2**). Bij 43/191 patiënten werd een vierkamerbeeld vervaardigd op een tijdsstip dat het hart goed te beoordelen was en als normaal geïnterpreteerd. Tenminste 17 van deze 43 patiënten hadden malformaties, die een verandering in het vierkamerbeeld tot gevolg hebben. Bij 38/191 patiënten werd een echo gemaakt bij een zwangerschapsduur > 17 weken, maar werd de anatomie van het hart niet geëvalueerd of werd er geen verslag van gedaan. Bij 53 patiënten werd de prenatale echo te vroeg in de zwangerschap gemaakt om het hart te kunnen beoordelen.

Tabel 3 Veertien maal een verschil tussen de diagnose pre- en postnataal.

Vals negatief	(8 patiënten)
Aortaklep atresie met VSD en pulmonalisklep dysplasie	
Pulmonalisatresie met een klein VSD	
Multipele musculeuze VSD's	
Abnormale inmonding van de longvenen	
Coarctatio aortae met een VSD	
Klein VSD	(3 patiënten)

Diagnose onvolledig	(2 patiënten)
Prenataal	**Postnataal**
LV hypertrofie	LV hypertrofie, uitstroom-obstructie, apicaal VSD
AVSD	Eisenmenger VSD

Vals positief	(4 patiënten)
Mogelijke coarctatio aortae	
Mogelijke dubbele aortaboog, coarctatio niet uit te sluiten	
Cardiomegalie	
RV>LV, mogelijk coarctatio aortae	

Negenentwintig van de patiëntjes die binnen een maand chirurgie moesten ondergaan waren prenataal niet echografisch geëvalueerd. Tenslotte bleef de antenatale geschiedenis van 4/191 patiënten onbekend. Gemiddeld is de slechtste lactaatwaarde bij de groep zonder prenatale diagnose 6.08 ± 0.45 mmol/L t.o.v. 3.05 ± 0.45 mmol/L bij de groep met een prenatale diagnose (P<0.001). De slechtste preoperatieve pH is 7.28 ± 0.03 in de prenatale en 7.24 ± 0.01 in de postnatale groep (P=0.29). Slechtste preoperatieve base excess is −5.83 ± 0.64 mEql/L voor de prenatale en −6.93 ± 0.46 mEq/L voor de postnatale groep (P=0.10). Ook in de risicogroep van patiënten met ductus-afhankelijke laesies zien we een significant verschil in slechtste preoperatieve lactaatwaarde in het voordeel van

de groep met een prenatale diagnose, 3.03 ± 0.39 versus 6.07 ± 0.49 mmol/L (P<0.05).

Figuur 2
Overlap tussen chirurgie-groep en prenatale echogroep

Chirurgie-groep	**191**
Onbekend	4
4-kamerbeeld	43
Geen 4-kamerbeeld	38
Echografie < 17 wkn	53
Geen echografie	29
Prenataal gediagnostiseerde chirurgische patiënten	24
Intra uteriene vruchtdood	23
Zwangerschaps beëindiging	56
Geen OK <31 dgn	38
Abstinentie	29
Prenatale echogroep	**170**

Discussie

Het opvallend hoge percentage kinderen met een structurele congenitale hartafwijking binnen de prenatale echogroep kan verklaard worden door het feit dat we hier te maken hebben met een door tweedelijns echografie geselecteerde populatie. Daarom kan het gevonden percentage niet vergeleken worden met percentages die gevonden worden in screeningsprogramma's voor de hele bevolking.[7,9]

Het primaire doel van de prenatale diagnostiek van hartafwijkingen is gelegen in het scheppen van betere voorwaarden voor de behandeling van deze patiënten in het directe postnatale traject. Het belangrijkste voordeel van een prenatale diagnose valt wellicht dan ook te behalen bij de

patiënten die in de neonatale periode geopereerd dienen te worden voor hun hartafwijking. Door een prenatale diagnose kan het patiëntje in een hartcentrum geboren en direct gestabiliseerd worden, waardoor stabilisatie van het zuur-base evenwicht mogelijk is.

Bij een niet onaanzienlijk deel van deze diagnoses blijken de ouders echter te besluiten tot de beëindiging van de zwangerschap of af te zien van behandeling na de geboorte, omdat een voor de ouders acceptabele kwaliteit van leven voor het kind niet bereikbaar lijkt. In 34% van de gevallen werd besloten de zwangerschap af te breken. In de helft van de gevallen gaat het om geïsoleerde, zeer ernstige en moeilijk corrigeerbare hartafwijkingen en bij de andere helft is sprake van congenitale hartafwijkingen gecombineerd met chromosomale en/of orgaanafwijkingen. Bij 29 levend geboren patiëntjes werd tot een abstinerend beleid besloten.[8] In deze groep ging het om zeer ernstige aandoeningen die echter pas na de 24ste zwangerschapsweek gediagnosticeerd werden, zodat beëindiging van de zwangerschap vanuit juridisch perspectief niet in aanmerking kwam of om gevallen, waarbij de ouders vanwege socio-religieuze gronden geen zwangerschapsbeëindiging verkozen. Prenatale diagnostiek bood in deze gevallen de mogelijkheid tot het voorkomen van postnataal lijden voor de patiënt door snelle pijnstilling en sedatie in goed overleg met de ouders.

Aangezien een groot aantal harten niet pathologisch-anatomisch kon worden onderzocht en er de mogelijkheid bestaat dat binnen het gebruikte studie-ontwerp een aantal vals-negatieve diagnosen postnataal onopgemerkt blijven is een harde uitspraak over de daadwerkelijke effectiviteit moeilijk.

Binnen de chirurgie-groep zien we een discrepantie tussen de pogingen om een groot gedeelte van de hartafwijkingen prenataal te diagnosticeren en de mate waarin prenatale diagnostiek heeft plaatsgevonden in de groep waarbij een spoedoperatie is uitgevoerd. Zevenenentachtig procent van de patiëntjes had geen cardiale evaluatie ondergaan in de derde lijn. Bij 43% was geen echo of een echo voor de zeventiende zwangerschapsweek gemaakt en kon er dus ook geen sprake zijn van een eventuele vroegtijdige herkenning van het hartgebrek. Bij 42% was echter wel een echo gemaakt, maar het vierkamerbeeld niet of als niet afwijkend beoordeeld. Deze inadequate echografie beoordeling verminderde het aantal patiëntjes dat prenataal gediagnosticeerd had kunnen worden, zorgde voor een aanzienlijk behandelingsdelay en verminderde daarmee de kansen voor deze patiëntjes. Daarnaast gaf deze situatie vaak aanleiding tot een groot onbegrip bij de ouders, die na vaak diverse echo's begrepen hadden dat alles met hun kind in orde was.

Het feit dat er wel een verschil in lactaatwaarden en niet in pH of BE-waarden gevonden wordt kan verklaard worden door het feit dat een verhoging van lactaat veel langer meetbaar blijft terwijl pH en BE zeer snel door bicarbonaat-toediening genormaliseerd kunnen worden. Het at random afnemen van bloedmonsters zou wel eventueel de mogelijkheid van een bias met zich mee kunnen brengen.

Conclusie

Aangezien in de regio Utrecht slechts 13% (24/191) van de congenitale hartafwijkingen, die 'emergency chirurgie' nodig hebben, prenataal wordt gediagnosticeerd, blijft er een grote ruimte voor verbetering. Aangezien er steeds meer aanwijzingen komen dat prenatale diagnostiek een positieve invloed heeft op uiteindelijke morbiditeit en mortaliteit en in de onderzochte populatie een positief effect van prenatale diagnostiek op het voorkomen van metabole acidose wordt gevonden, lijkt een hogere detectiegraad ook in Nederland wenselijk.[1-3,10] Adequate en laagdrempelige trainingsmogelijkheden zouden de basis moeten vormen om dit doel te bereiken, waarbij een betere training noodzakelijk lijkt aangezien alleen uitbreiding van het aantal 'views' onvoldoende blijkt te zijn. Een prenatale diagnose blijft te vaak achterwege ten gevolge van misinterpretatie of technisch onjuist verrichte echografie.

Als conclusie kan gesteld worden dat er een grote discrepantie bestaat tussen de vermeende potentie van screenende prenatale echografie van aangeboren hartafwijkingen enerzijds en anderzijds de huidige situatie in de praktijk in Nederland.

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Chapter 8

Atrial flutter in the perinatal age group: diagnosis, management and outcome

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Abstract

Objectives
The aim of this retrospective study was to evaluate perinatal atrial flutter (AF) and the efficacy of maternally administered antiarrhythmic agents, postpartum management and outcome. Perinatal AF is a potentially lethal arrhythmia and management of this disorder is difficult and controversial.

Methods
Forty-five patients with documented AF were studied retrospectively.

Results
Atrial flutter was diagnosed prenatally in 44 fetuses and immediately postnatally in 1 neonate. Fetal hydrops was seen in 20 patients, 17 received maternal therapy, 2 were delivered and 1 was not treated because it had a severe nontreatable cardiac malformation. In the nonhydropic group of 24 patients, 18 were treated and the remaining 6 were delivered immediately. In the hydropic group, 10 received single-drug therapy (digoxin or sotalol) and 7 received multi-drug therapy. In the nonhydropic group, 13 received a single drug (digoxin or sotalol) and 5 received multiple drugs. One patient with rapid 1:1 atrioventricular conduction (heart rate 480 beats/min) died in utero and another died due to a combination of severe hydrops because of the AF, sotalol medication, stenosis of the venous duct and hypoplastic placenta. Of the 43 live-born infants, 12 were in AF at birth. Electrical cardioversion was successful in eight of nine patients. No recurrences in AF have occurred beyond the neonatal period. Four patients with fetal flutter and hydrops showed significant neurological pathology immediately after birth.

Conclusions
Fetal AF is a serious and threatening rhythm disorder; particularly when it causes hydrops, it may be associated with fetal death or neurological damage. Treatment is required and primarily aimed at reaching an adequate ventricular rate and preferably conversion to sinus rhythm. Digoxin failed in prevention of recurrence at time of delivery in a quarter of our patients, whereas with sotalol no recurrence of AF has been reported, suggesting that class III agents may be the future therapy. Once fetuses with AF survive without neurological pathology, their future is good and prophylaxis beyond the neonatal period is unnecessary.

Introduction

Atrial flutter (AF) is an uncommon form of tachycardia in infancy and childhood, the management and particularly the pharmacological treatment of which continue to pose a challenge to clinicians and electrophysiologists. This pertains even more to perinatal AF, a rhythm disorder in which the rate differs from that seen in adult patients and of which underlying etiology and pathophysiology (in the presence or absence of structural heart disease and secondary atrial dilation) still need to be determined in humans. The description of intrauterine AF by Carr and McLure[1] in 1931 is probably the first published report; Blumenthal et al.[2] documented intrauterine AF with the use of fetal electrocardiography in 1968. Currently, fetal echocardiography is the best method and remains the cornerstone for in utero diagnosis.

Observations from the early reports[1-5] of atrial flutter in the fetus and newborn infant include a rapid intrauterine heart rate and an abrupt irregular rhythm. Postnatal electrocardiograms (ECGs) show typical AF waves type I, the common form of AF. In 1965, Hassenruck et al.[6] were the first to report successful direct current cardioversion (DCC) of a newborn with AF. The next successful outcome was not published until 1972 by Barclay and Barr.[7] The purpose of our retrospective study was to present our experience with 45 fetuses with AF, 44 diagnosed in utero. The course, management and outcome are analyzed.

Patients and Methods

Our retrospective multi-center study comprised 45 patients, 44 fetuses with AF diagnosed in utero and one neonate with longstanding AF (probably from 24 weeks gestation) diagnosed only at birth. The review includes patients with AF referred from obstetrical units because of an irregular or fast fetal heart rate from January 1984 to December 1998.

Cross-sectional echocardiography, M-mode and echo-Doppler were used for diagnosis. Conventional fetal echocardiographic views of the heart were obtained to exclude structural heart malformation. Atrial rate was determined using M-mode echocardiography, while ventricular rate was determined with the use of M-mode and/or echo-Doppler. A complete fetal scan was simultaneously performed to determine indices of fetal growth, the presence of hydrops, hydramnion or associated anomalies.

The decision to institute maternofetal therapy was related to gestational age at presentation, state of lung maturity and the presence of hydrops. Mode of delivery was decided based upon the fetal condition and the further stress that vaginal delivery might impose.

Results

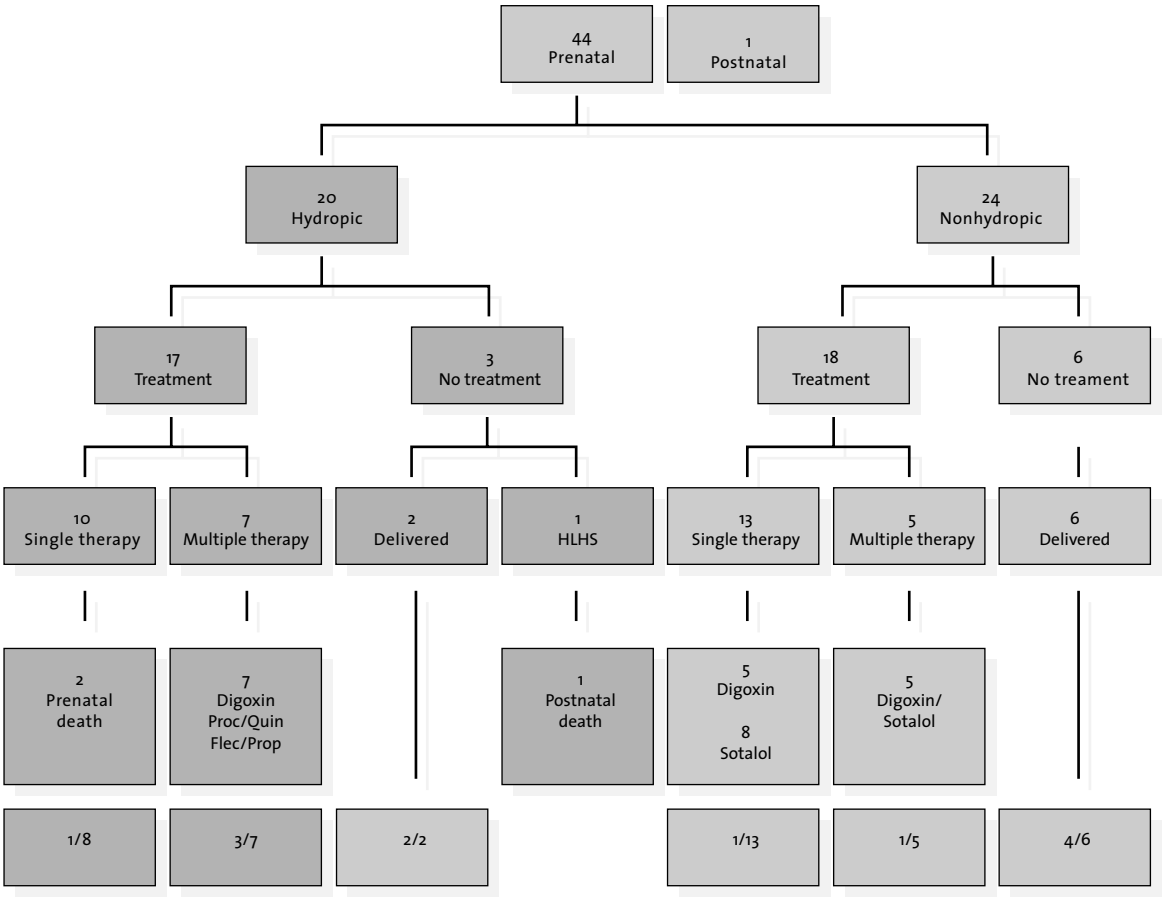
Forty-four fetuses with in utero AF were diagnosed at a median gestational age of 31.5 weeks, range 19 to 40 weeks. At time of presentation, mean atrial rate was 450 beats/min (median 440, SD 42.8) and mean ventricular rate was 224 beats/min (median 220, SD 21.8). At time of diagnosis, 20 out of 44 fetuses were hydropic.

Maternofetal therapy

As outlined in **Figure 1**, 17 out of 20 hydropic fetuses received therapy. Nine of these received single-drug therapy with digoxin (loading dose of 1.5 mg and maintenance dose of 0.25 mg twice daily) and one with sotalol (80 mg q 8 hrs). In this group, one patient died in utero shortly after diagnosis and 2 hours after maternal loading with intravenous (IV) digoxin. The AF was associated with 1:1 atrioventricular (AV) conduction, with a ventricular rate of 480 beats/min. This ventricular rate, and not the initiation of digoxin therapy, probably caused the demise of this fetus. Another patient was treated with sotalol and died abruptly intrauterine at 38 weeks gestation within 24 hours after the oral sotalol medication was increased to 160 mg q 12 hrs, because of persisting AF. This could very well be a pro-arrhythmic effect, but in this hydropic patient an associated hypoplastic ductus venosus was found at autopsy. Of the remaining eight patients, one was in AF at time of birth.

Seven of the 20 hydropic fetuses received more than one drug, digoxin as the drug of first choice in each. Drug combinations included digoxin and procainamide, quinidine, flecainide, propaphenone and sotalol. One of these patients received direct umbilical vein digoxin and procainamide. Of these seven patients, three (including the latter) were born in AF. Of the 24 nonhydropic patients, 18 were treated. Thirteen of them had single-drug therapy, five with digoxin and eight with sotalol. The remaining five patients received a combination of digoxin and sotalol.
Surveillance of mother and fetus occurred twice weekly. Fetal heart rate was examined, and the mother was questioned on subjective maternal

Figure 1
Allocation of fetal patients with atrial flutter into two study groups at time of recognition: hydropic and nonhydropic. Patients are further subdivided into treated and nontreated for each group.



HLHS = Hypoplastic left heart syndrome, **proc/flec/quin/prop** = procainamide/quinidine/flecainide/propaphenone
The bottom boxes describe the number of cases with atrial flutter at birth per number of infants born alive.

complaints; however, no maternal problems other than slight dizziness occurred. All mothers had an ECG made before therapy initiation, but no irregular heart rates were found. No blood levels were measured during the period of this review, but recently this policy has been changed, and blood levels are monitored. Before a second drug was introduced, the initial therapy was maximized (sotalol 160 mg q 8 hrs and digoxin 0.25 mg q 8 hrs). **Table 1** contains a summary of clinical data, and dosages for the different drugs are indicated in **Table 2**.

Table 1 Summary of clinical data

Patient	GA at recognition (weeks)	Hydrops	In utero treatment	Delivery mode	GA (weeks)	AF at birth	Treatment at birth	Duration of prophylaxis (months)
1	40	-	no	cs	40	yes	DCC	12
2	36	-	yes	nvd	40	no	no	1,25
3	33	+	yes	cs	33	yes	DCC	7,5
4	37	-	no	cs	37	yes	DCC	6
5	34	-	yes	cs	35	yes	DCC	7
6	39	-	no	nvd	40	no	no	no
7	34	-	yes	nvd	36	no	no	9
8	37	-	no	nvd	38	no	no	no
9	35	-	no	cs	35	yes	TVAOP	12
10	19	+	yes	nvd	38	no	no	12
11	29	+	yes	cs	30	yes	yes	6
12	35	+	no	cs	35	yes	DCC	3
13	24	+	yes	nvd	39	yes	yes	6
14	19	+	no	nvd	29	no	HLHS	no
15	28	+	yes	nvd	38	yes	yes	12
16	36	-	yes	nvd	40	no	no	no
17	37	-	no	nvd	37	yes	DCC	9
18	37	-	yes	nvd	42	yes	DCC	12
19	34	-	yes	cs	38	no	no	12
20	34	-	yes	nvd	38	no	no	12
21	-	+	no	nvd	39	yes	DCC	died day 2

Patient	GA at recognition (weeks)	Hydrops	In utero treatment	Delivery mode	GA (weeks)	AF at birth	Treatment at birth	Duration of prophylaxis (months)
22	32	+	yes	nvd	37	no	no	3
23	33	+	yes	nvd	38	no	no	12
24	36	+	yes	nvd	38	no	no	6
25	36	-	yes	nvd	38	no	no	no
26	34	+	yes	nvd	37	no	no	3
27	34	+	yes	nvd	37	no	no	6
28	35	+	yes	nvd	39	no	no	3
29	28	+	yes	nvd	36	no	no	no
30	31	+	yes	nvd	38	died in utero	died in utero	died in utero
31	36	+	yes	nvd	38	no	no	no
32	38	+	yes	nvd	39	no	no	no
33	-	+	yes	nvd	36	no	yes	yes
34	31	+	no	cs	35	no	no	no
35	-	-	yes	nvd	34	no	no	no
36	35	-	yes	cs	39	no	no	no
37	36	-	yes	nvd	-	no	no	no
38	30	-	yes	nvd	-	no	no	no
39	21	-	yes	nvd	40	no	no	no
40	31	-	yes	nvd	39	no	no	no
41	34	-	yes	nvd	34	no	no	no
42	-	-	yes	nvd	36	no	yes	0.75
43	30	-	yes	nvd	-	no	no	no
44	36	-	yes	nvd	39	no	yes	yes
45	33	+	yes	nvd	39	died in utero	died in utero	died in utero

GA = Gestational age, **Cs** =Cesarean section, **nvd** = Normal vaginal delivery, **DCC** = Direct current cardioversion, **AF** = Atrial flutter, **TVAOP** = Transvenous atrial overdrive pacing, **HLHS** = Hypoplastic left heart syndrome

Table 2 Drugs used for control of fetal atrial flutter

Drug	Dose	Maternal therapeutic concentration	Fetal: Maternal concentration ratio
Digoxin	Loading: iv 3 dd 0.5 mg	1 - 2 mg/ml	0.6
	Maintenance: po 0.25 - 1.0 mg/24h		
Flecainide	Loading: po 2dd 150 mg	0.2 - 1 mcg/ml	0.86
	Maintenance: po 2dd 100mg		
Sotalol	Maintenance: po 160-320 mg/24 h	2 - 7 mcg/ml	1.05
Amiodarone	Loading: po 1200 mg/24 h	Amiodarone: 1 - 2.5 mcg/ml	0.1 - 0.3
	Maintenance: po 400-600 mg/24 h	Desethylamiodarone 0.2 - 2.6 mcg/ml	

iv = Intravenous, po = Per os

Nontreated fetuses

Three of the 20 hydropic patients were not treated, one due to an associated hypoplastic left heart syndrome (HLHS) and the other two were delivered soon after diagnosis because they were near term. Six of the 24 nonhydropic fetuses received no medication, as they were delivered within a week of diagnosis and beyond 35 weeks gestation (when the lungs were assumed to be mature).

Structural heart disease
Only one of the 44 fetuses was found to have a cardiac malformation. Atrial flutter in this fetus was detected at 19 weeks gestation, and a HLHS was diagnosed. In light of the prognosis a decision was made not to treat, and spontaneous delivery occurred at 29 weeks gestation.

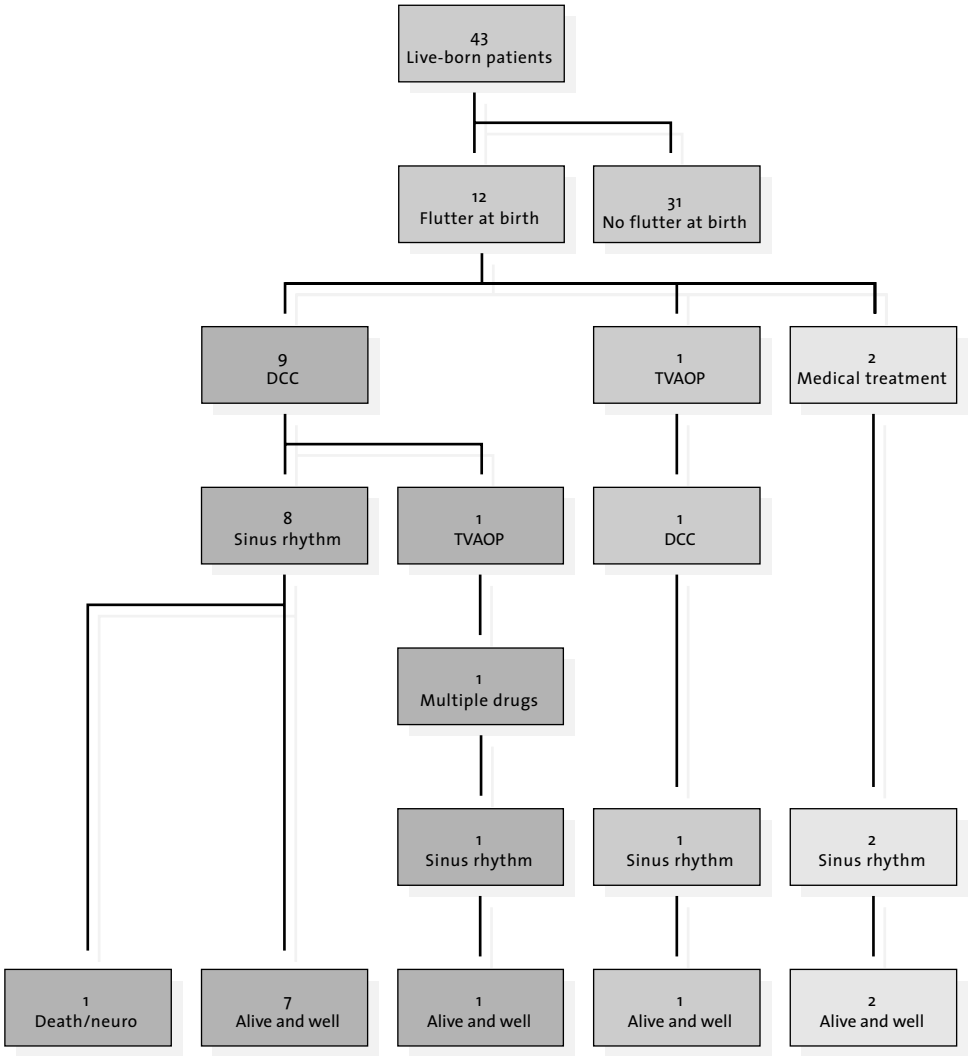
Mode of delivery
Delivery through means of a cesarean section was deemed necessary in 10 of the 44 fetuses (median gestational age 37 weeks, range 30 to 40 weeks) as normal vaginal delivery was considered to impose further stress on an already compromised heart. Cesarean section was performed soon after presentation and diagnosis of AF in five cases, which were not treated. A hydropic fetus diagnosed at 33 weeks gestation was treated with digoxin for 24 hours with no improvement and was therefore delivered by cesarean section. In another fetus presenting at 34 weeks gestation, maternofetal digoxin was administered for four weeks before cesarean section delivery. In a third patient, presented at 35 weeks gestation, sotalol and digoxin failed to establish normal sinus rhythm, and delivery was performed at 39 weeks gestation by cesarean section. Two other fetuses with AF diagnosed at a gestational age of 29 and 34 weeks were delivered by cesarean section.

Atrial flutter at birth
Of the original 45 patients, two patients died in utero, and 12 out of the 43 live-born infants were in AF at birth. Twelve-lead ECG confirmed AF with monomorphic undulating negative flutter waves in leads II, III and avF (common type). Flutter waves were commonly seen in lead V1. No sign of aberrant conduction was noted on these ECGs. Three infants were in serious trouble with poor Apgar scores at birth.

Nine of the 12 patients in AF received DCC as initial treatment. Eight of these converted to sinus rhythm. One patient remained in AF despite undergoing subsequent transvenous atrial overdrive pacing (TVAOP). This baby received a multitude of medications including IV digoxin and procainamide. Loading with IV amiodarone and repeat of TVAOP were successful in conversion to sinus rhythm. One other patient born with AF initially underwent unsuccessful TVAOP and reverted to sinus rhythm after electrocardioversion.

Two patients were treated medically, one with digoxin alone, the other with digoxin and quinidine. Both reverted to sinus rhythm on medication. In one other patient, AF had not been diagnosed before birth. At 26 weeks

Figure 2
Outcome for the entire study group and treatment strategies



DCC = Direct current cardioversion, **TVAOP** = Transvenous atrial overdrive pacing,
Death/neuro = Death due to a neurological cause

gestation polyhydramnion had been detected, and an irregular CTG (cardiotonography) suggested a possible existence of AF, but this was not recognized and no further investigations or treatment were performed. Delivery at 39 weeks gestation revealed a hydropic and acidotic baby with an extremely poor Apgar score requiring immediate resuscitation and artificial ventilation. On referral, the pulse was irregular, between 120 and 140 beats/min. Blood pressure was low, 40/22, mean 29 mm Hg. A narrow QRS rhythm could be seen on ECG, but no detectable P waves. Twelve-lead ECG confirmed AF at a rate of 480 to 540 beats/min with varying AV block. On cross-sectional echocardiography the atria were markedly dilated and seen to flutter, while the ventricles were dilated. Synchronized electrocardioversion was successful. The infant was digitalized. Over the ensuing 4 hours the rhythm changed from AF with varying block to AV-re-entry supraventricular tachycardia with ventricular rates of up to 300 beats/min. Six hours later the infant was in sinus rhythm with a good blood pressure and improved peripheral perfusion. Ultrasound of the head showed evidence of cortical necrosis most likely on the basis of longstanding cerebral hypoperfusion. Two days later the child died from cerebral inactivity. **Figure 2** indicates outcome and treatment strategy after birth for the whole study group.

Neurological complications

In four of the 45 patients, including the one described above, neurological morbidity was documented immediately postnatally, suggesting an association with the prenatally existing arrhythmia. The neurological damage ranged from severe cerebral hypoxic-ischemic lesions to intraventricular hemorrhage, resulting in a hydrocephalus. One patient had a small periventricular infarction that is resolving.

Management and follow-up

Prophylactic antiarrhythmic medication was given to 25 of the infants. Median duration of prophylaxis was 7.25 months and ranged from 3 weeks to 12 months. Prophylactic antiarrhythmic drugs included digoxin alone in 17 patients, digoxin and quinidine in one patient, digoxin and sotalol in one patient and sotalol alone in six patients.

Recurrence of AF after initial conversion to sinus rhythm did not occur in any of the patients. Longterm follow-up for the group ranges between 6 months to 10 years and 3 months, median 5 years and 2 months.

Discussion

Early reports

Atrial flutter is a primary atrial tachyarrhythmia confined solely to the atrium. The specialized AV conduction system does not participate in the primary mechanism. Early reports[1-5,8] of AF in the fetus and newborn stressed that the intrauterine heart rate was rapid, and the rhythm was abruptly irregular. Digoxin did not seem to be effective in converting the rhythm to sinus and after birth the ECG showed typical flutter waves. Furthermore, if the infant had a cardiac malformation, the prognosis was poor. Even in the absence of associated structural heart disease, the prognosis has been reported to be poor.

Our series

In our series of 45 patients with perinatal AF, the mortality and neurological morbidity were each 9% and were confined to the subgroup of hydropic fetuses. One patient died postnatally from severe associated structural heart disease (hypoplastic left heart syndrome) and another intrauterine after treatment with digoxin. We do not consider this patient's death a consequence of digoxin therapy, because under ideal circumstances, transplacental passage of this drug is slow (up to a few days) in order to achieve an adequate therapeutic level in the fetus. In this patient with a hydropic placenta, the transplacental transfer of digoxin was further hampered. At autopsy an accessory AV connection was identified, which we contend was responsible for the 1:1 AV conduction.

In the third severely hydropic patient, AF had been missed before birth, but was present immediately after birth. Despite successful DCC after birth, the patient ultimately died from cerebral damage probably due to longstanding and/or fluctuating cerebral hypoperfusion as a result of intrauterine AF.

Potential mortality and morbidity

The potentially lethal outcome in perinatal AF is not to be underestimated. In 1969 Moller et al.[5] were the first to report increased birth weight, which suggested to them the presence of anasarca from intrauterine cardiac fai-

lure secondary to arrhythmia. They reviewed the outcomes of 36 infants with AF. Nine infants died, of whom six had received digoxin but failed to respond. In 1970 van der Horst[9] reported a case of fetal hydrops secondary to intrauterine AF.

Even more worrisome were the four patients in the present study with neurological damage. In a previous publication we reported the assumption that AF was responsible for the disturbance of the maintenance of adequate cerebral perfusion.[10] This causes loss of cerebrovascular autoregulation and will result in a pressure-passive phenomenon, whereby a reduction or increase in mean arterial blood pressure is accompanied by a concomitant reduction or increase in cerebral blood flow. In the distressed newborn, cerebral autoregulation is lost, exposing the brain to ischemia in even moderate hypotension and to an increased pressure gradient across the capillary wall in even moderate hypertension, with increased risk of intracranial hemorrhage.[11] Experimental studies in the fetal lamb have shown that this certainly applies to the distressed fetus in utero; a period of intrauterine distress causes abolition of cerebral autoregulation leading to severe impairment of the maintenance of constant cerebral perfusion.[12,13] A fetus presenting with hemodynamic compromise and hydrops secondary to fetal tacharrhythmia is therefore at increased risk of development of a pressure-passive cerebral circulation and the cerebral complications that may result from this.

Intrauterine treatment

In light of these findings, we have opted for a policy to treat all fetuses with AF at time of presentation, unless immediate delivery is possible. Despite active treatment, we were confronted with AF at birth in six out of 33 medically treated live-born patients (18%). Conversion to sinus rhythm in our patients while receiving maternofetal therapy is a debatable issue. Was this indeed a result of the antiarrhythmic medication or was it part and parcel of the natural history of AF in these patients? One may postulate that both a paroxysmal and sustained form of AF exist in the fetus and newborn infant, as is seen with adult patients. Alternatively, we are unsure whether the stress of delivery and release of catecholamines may have an influence on retriggering the onset of AF, as seen in fetuses with supraventricular tachycardia.[14]

Digoxin may be useful through its action in slowing ventricular rate, allowing more ventricular filling, and improving cardiac output. Its inability in breaking or converting AF to sinus rhythm in pediatric and adult patients has been well documented.[14-16] In the collaborative study reported by Garson et al.[17], digoxin used alone was successful in preventing

recurrences of AF in only 44% of patients. Wellens and Durrer[18] stress that digoxin is contraindicated in the presence of an accessory pathway, which conducts anterogradely. This is most likely to have been the case in our fetus with 1:1 AV conduction.

These studies suggest that although digoxin has been used for treatment in the past, it might have lost some of its attraction for treatment of AF. Alternatively, antiarrhythmic drug treatment with class I drugs is often unsuccessful in the conversion of AF to sinus rhythm, possibly explained by experimental data, suggesting that prolongation of the atrial-effective refractory period is more critical than slowing conduction in the termination of re-entrant atrial flutter.[19] Action potential prolongation in the absence of conduction slowing seems more effective in terminating human AF than depression of the excitability.[19]

Current literature in adult patients advocates the use of class III agents such as sotalol. Sotalol appears to be an effective agent in the treatment of AF, seems suitable in treating the fetus, and has excellent transplacental passage in a dosage regimen of 160 mg twice daily.[20,21] Monitoring of the maternal QT-interval is essential in excluding maternal pro-arrhythmia; fetal pro-arrhythmia, however, is a troublesome aspect of this therapy and might force the fetal cardiologist eventually to abandon this agent. Amiodarone, also a class III agent, has been used for fetal arrhythmias but has many side effects and does not cross the placenta as readily as does sotalol.[22]

Dophitilide, a new class III agent, may be even more promising in the future for both in utero treatment and in the newborn infant. Although current data on the use of dophitilide in the fetus and neonate are lacking, dophitilide is found to be more effective than flecainide in the conversion of AF to sinus rhythm in adult patients, yet flecainide produces a more prolonged flutter cycle length.[19]

Although both digoxin and sotalol are effective drugs in the treatment of fetal AF, we use sotalol as the drug of choice because digoxin transplacental passage is slower, relapse into AF occurs more often at birth and subjective maternal complaints are more prominent than with sotalol.

Postnatal flutter and treatment

The relapse of patients at birth into AF remains a troublesome issue and requires intensive-care admission of these fragile patients. Synchronized DCC (eight out of nine patients) was useful in the conversion of AF to sinus

rhythm[6,7], and TVAOP was successful in one of two patients, and only after loading with amiodarone. Esophageal or TVAOP has been used in children to terminate atrial flutter.[23,24]

Once AF is converted to sinus rhythm, one may elect to wait and observe if flutter recurs.[25] Alternatively, one may elect to treat for six months to a year, although it appears from this review that recurrence of AF is exceedingly rare beyond the neonatal period. This questions the need for prophylaxis; our current policy is not to treat prophylactically.

Conclusion

Finally, we can state that AF is a serious and life-threatening rhythm disorder of the human fetus. Specifically, when it causes hydrops it is associated with fetal death or neurological damage. Treatment therefore is required, primarily aiming at reaching an adequate ventricular rate and preferably conversion to sinus rhythm. It seems important that relapses back and forth and in and out of flutter should be prevented at all cost to protect the fetal brain. Once fetuses with AF survive, their future is bright, and prophylaxis beyond the neonatal period is unnecessary.

Acknowledgments

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Chapter 9

Congenital heart disease in pregnancies complicated by maternal diabetes mellitus: an international clinical collaboration, literature review and meta-analysis

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Submitted

Abstract

Objectives
To investigate the incidence and distribution of congenital heart disease in the offspring of type-1 diabetic mothers and the influence of periconceptional glycemic control reflected by glycosylated hemoglobin (HbA1c) levels.

Methods
A multi-center retrospective clinical study, literature review and meta-analysis. The incidence and pattern of CHD in our study populations and in the literature in offspring of type-1 diabetic mothers were compared with those in the offspring of nondiabetic mothers registered by EUROCAT Northern Netherlands. Medical records were reviewed for HbA1c during the first trimester.

Results
The distribution of CHD in our diabetic study population was in accordance with reports in the literature. This distribution differed considerably from that in the nondiabetic population. Approximately half the CHD were conotruncal anomalies (persistent truncus arteriosus (PTA), tetralogy of Fallot (TOF) and transposition of the great arteries (TGA)). In our series TGA was the single most frequently encountered conotruncal abnormality, and no cases of double-outlet right ventricle (DORV) were detected. Our study demonstrated an increased likelihood of visceral heterotaxia and single ventricle. Elevated first trimester HbA1c values were associated with fetal CVD.

Conclusions
This study shows an increased likelihood of transposition of the great arteries, persistent truncus arteriosus, visceral heterotaxia and single ventricle among offspring of diabetic mothers. This suggests a profound teratogenic effect at a very early stage in cardiogenesis, with overlap between malformations that relate to single gene defects versus teratogenic exposure. Our study emphasizes the frequency with which the offspring of diabetes-complicated pregnancies suffer from complex forms of CHD.

Introduction

Maternal type-1 diabetes mellitus is a relatively common illness that complicates pregnancy and results in an increased incidence of congenital malformations.[1-5] Offspring of diabetic mothers have a fivefold incidence of congenital malformations compared to pregnancies in the general healthy population. Major congenital malformations, of which congenital heart disease (CHD) constitutes a significant part, are the most important single cause of perinatal mortality amongst the offspring of diabetic mothers.[6-13] In general, the pattern of CHD encountered among offspring of diabetic mothers, with an emphasis on abnormalities of laterality, looping and conotruncal septation, suggests that the maternal metabolic state affects cardiogenesis at a very early stage of the developmental period, prior to 7 weeks' gestation.[14,15]

It was the aim of this investigation to study the pattern of cardiac anomalies among offspring of pregnancies complicated by type-1 diabetes mellitus and to assess the importance of periconceptional glycemic control, reflected by HbA1c levels, during the first trimester. Our working hypothesis was that detection of CHD among the fetuses of diabetic mothers would uncover a high incidence of complex anomalies of laterality, looping and conotruncal malformations that are ductal-dependent for sustained pulmonary and systemic blood flow. Such abnormalities are particularly amenable to early medical and surgical intervention.[16]

Methods

We studied the incidence and the spectrum of congenital cardiac malformations among fetuses and neonates born to mothers with type-1 diabetes mellitus in three populations and compared our data with those reported in the literature.

Study population
We studied the incidence of congenital cardiac malformations in three populations:

1 Yale New Haven Medical Center: this population consisted of the offspring of mothers with type-1 diabetes mellitus undergoing routine fetal echocardiography at the Yale Fetal Cardiovascular Center during the interval between 1988 and 1998. Medical records were reviewed retrospectively.

2 Retrospective review in the Netherlands: a retrospective study in which data were obtained from a review of medical records from pregnancies (> 16 weeks in women with type-1 diabetes) at the University Medical Center Utrecht, University Hospital Groningen, and Isala Clinics Zwolle, the Netherlands, between 1988 and 1998.
3 Prospective nationwide study in the Netherlands: data were obtained from a nationwide prospective cohort-based study on type-1 diabetes and pregnancy, in which all (n=118) hospitals in the Netherlands participated between April 1999 and April 2000.

Literature review

A systematic review of published articles, in English, concerning maternal insulin-dependent diabetes mellitus (IDDM) and congenital malformations was conducted using the Medline (1970-April 2002) and Pubmed databases. The incidence and the detailed diagnosis of congenital cardiac malformations in the literature were extracted only from reports in which the anomalies could be assigned to a well-defined diagnosis. Various anomalies were grouped, in order to make meaningful comparisons. Conotruncal malformations included persistent truncus arteriosus (PTA), double-outlet right ventricle (DORV), tetralogy of Fallot (TOF) and complete transposition of the great arteries (TGA). Other major categories included visceral heterotaxia, atrioventricular septal defect (AVSD), atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), coarctation of the aorta (CoA), anomalies of the aorta or pulmonary artery, single ventricle (SV), hypoplastic left heart syndrome (HLHS), Ebstein's anomaly, anomalies of the tricuspid, mitral, pulmonic or aortic valve, total (TAPVC) or partial anomalous pulmonary venous connection (PAPVC) and other anomalies of the great veins.

The incidence and spectrum of congenital heart disease in our population and in the literature among offspring of type-1 diabetic mothers were compared with those in the offspring of nondiabetic mothers registered by EUROCAT (European registration of congenital anomalies and twins) Northern Netherlands. In this registry obstetricians, pediatricians, clinical geneticists, surgeons, general practitioners, midwives, well-baby clinics, pathologists and the national obstetric registry provided data from 1989 to 1999.

Hemoglobin A1c measurement

HbA1c determination was performed by high-pressure liquid chromatography (HPLC) at Yale and at the centers in the Netherlands (normal reference value: 4.0–6.3 %). HbA1c values of diabetic pregnancies complicated by CHD were compared with those resulting in the birth of a healthy infant.

Statistical analysis
Data were analyzed using SPSS software (SPSS Inc., Chicago, Ill, USA). Data are presented as mean and standard error of the mean (SEM) or percentages. Continuous data were compared using the Student's *t*-test and categorical data were compared using the chi-square test or the Fisher's exact test. Associations with $p<0.05$ were considered statistically significant. Odds ratios (OR) for incidences and their 95% confidence intervals (CI) were calculated.

Results

At the Yale New Haven Medical Center 624 fetal echocardiographic scans were performed on 557 pregnant women with type-1 diabetes mellitus. Congenital heart disease was diagnosed in 19 pregnancies (3.0%). These cases were all confirmed postnatally, with no false-negative or false-positive diagnoses encountered. In the retrospective study in the Netherlands 172 type-1 diabetic women had 220 (212 single and 8 twin) pregnancies and a total of 14 (out of 228 infants; 6.1%) cases of CHD were encountered postnatally. In the prospective cohort-based study in the Netherlands, in which 324 infants (from 305 singleton pregnancies, 8 twins and 1 triplet pregnancy) were born after 24 weeks' gestation, a total of 8 (2.5%) cases of CHD were encountered. Details are shown in **Table 1.**

Initial hemoglobin A1c
The 19 patients whose fetuses had CHD in the study group from Yale were diagnosed at a mean gestational age of 27.9 ± 1.2 weeks. First trimester HbA1c concentration in this subgroup of 19 patients (CHD; 9.8 ± 0.7%) were significantly higher than those in mothers with unaffected infants (controls; 8.1 ± 0.3%; $P<0.05$). The mean age of the mothers was 30.7 ± 0.9 (CHD) versus 29.1 ± 0.8 years (controls; $P=0.212$). The mean duration of diabetes was 11.5 ± 2.2 (CHD) versus 10.9 ± 1.1 years (controls; $P=0.791$).

The 14 patients in the retrospective study group and the 8 patients in the prospective study group from the Netherlands had initial HbA1c values of 6.4 ± 1.4% and 7.4 ± 1.2% respectively. The HbA1c values in the control groups were 6.3 ± 1.3 % ($P=0.361$) and 6.5 ± 1.0 % ($P=0.009$) respectively.

Literature review versus study population
The literature review of studies of CHD among the offspring of IDDM uncovered a total of 26 reports. [4,10,11,13-15,17-35] The incidence and distribution of malformations in this series is shown in **Table 1**; there was no statistically

Table 1 Incidence and spectrum of cardiovascular malformations in fetuses and infants of women with type-1 diabetes in study population and literature.

CHD	Our study n (%)	Literature review n (%)	Combined studies n (%)	P -value
PTA	3 (7.3)	9 (3.4)	12 (3.9)	0.224
TGA	9 (22)	30 (11.2)	39 (12.7)	0.054
DORV	0 (0)	7 (2.6)	7 (2.3)	-
T4F	1 (2.4)	15 (5.6)	16 (5.2)	0.393
Conotruncal	**13 (31.7)**	**61 (22.8)**	**74 (24.0)**	**0.149**
SV	4 (9.8)	13 (4.9)	17 (5.5)	0.202
VSD	8 (19.5)	80 (30.0)	88 (28.6)	0.114
AVSD	2 (4.9)	9 (3.4)	11 (3.6)	0.628
ASD	3 (7.3)	17 (6.4)	20 (6.5)	0.818
PDA	2 (4.9)	15 (5.6)	17 (5.5)	0.847
HLHS	1 (2.4)	8 (3.0)	9 (2.9)	0.844
CoA	3 (7.3)	12 (4.5)	15 (4.9)	0.434
Other anom. Aorta	1 (2.4)	5 (1.9)	6 (1.9)	0.807
Anom. Pulm. artery	1 (2.4)	15 (5.6)	16 (5.2)	0.393
Heterotaxia	2 (4.9)	5 (1.9)	7 (2.3)	0.229
TAPVR	1 (2.4)	1 (0.4)	2 (0.6)	0.125
PAPVR	0 (0)	1 (0.4)	1 (0.3)	-
Anom. Ao. valve	0 (0)	2 (0.7)	2 (0.6)	-
Anom. Mi. valve	0 (0)	4 (1.5)	4 (1.3)	-
Anom. Pulm. valve	0 0)	15 (5.6)	15 (4.9)	-
Anom. Tric. valve	0 (0)	1 (0.4)	1 (0.3)	-
Ebstein	0 (0)	0 (0)	0 (0.0)	-
Unspec. anom.	0 (0)	3 (1.1)	3 (1.0)	-
Total	**41 (100)**	**267 (100)**	**308 (100)**	

significant difference in incidence of the malformations between the literature and our study groups. Thirty percent of patients in the literature review were reported to have ventricular septal defects and 23 percent had conotruncal malformations (CTM). Approximately half (49%) of the patients with CTM were reported to have TGA, followed by a smaller number of patients with TOF (25%) or PTA (15%). Only 2.6 percent of offspring with cardiac anomalies were reported to have DORV. AVSD (3,4%), while less common than conotruncal malformations, was more prevalent than double-outlet right ventricle. Visceral heterotaxia was reported in 3.0% of the cases.

EUROCAT Registry

In **Table 2**, we compare the distribution of specific cardiovascular defects in our study population and literature on diabetes taken together, with that in the nondiabetic population (EUROCAT Registry). For each diagnostic subgroup, the number of cases and the risks of these specific cardiac disorders in the offspring of diabetic mothers are shown. Conotruncal malformations (persistent truncus arteriosus: OR 4.72, transposition of the great arteries: OR 2.85), single ventricle: OR 18.24, and visceral heterotaxia: OR 6.22, are most highly associated with pregestational diabetes (all $P<0.05$).

Table 2 Distribution and relative risk of specific cardiovascular defects in offspring of women with pregestational diabetes in comparison with that in a large nondiabetic population (EUROCAT). (Combined studies = Our study population and literature on diabetic grouped together)(*P<0.05)

CHD	EUROCAT	Combined studies n (%)	P-value n (%)	OR	95% CI
PTA	16 (0.9)	12 (3.9)	<0.05*	4.72	2.21 – 10.08
TGA	91 (4.8)	39 (12.7)	<0.05*	2.85	1.92 – 4.23
DORV	35 (1.9)	7 (2.3)	0.652	1.23	0.54 - 2.78
T4F	59 (3.1)	16 (5.2)	0.088	1.69	0.96 – 2.98
Conotruncal	**201 (10.7)**	**74 (24.0)**	**<0.05***	**2.64**	**1.96 – 3.56**
SV	6 (0.3)	17 (5.5)	<0.05*	18.24	7.13 – 46.63
VSD	552 (29.4)	88 (28.6)	0.839	0.96	0.74 – 1.26
AVSD	85 (4.5)	11 (3.6)	0.549	0.78	0.41 – 1.48
ASD	211 (11.2)	20 (6.5)	0.012*	0.55	0.34 – 0.88
PDA	116 (6.2)	17 (5.5)	0.797	0.89	0.53 – 1.50
HLHS	44 (2.3)	9 (2.9)	0.547	1.26	0.61 – 2.60
CoA	87 (4.6)	15 (4.9)	0.884	1.05	0.60 – 1.85
Other anom. Aorta	91 (4.8)	6 (1.9)	0.024*	0.39	0.17 – 0.90
Anom. Pulm artery	40 (2.1)	16 (5.2)	0.005*	2.52	1.39 – 4.56
Heterotaxia	7 (0.4)	7 (2.3)	<0.05*	6.22	2.17 – 17.86
TAPVR	11 (0.6)	2 (0.6)	0.892	1.11	0.25 – 5.03
PAPVR	15 (0.8)	1 (0.3)	0.366	0.41	0.05 – 3.08
Other anom. veins	38 (2.0)	0 (0)	-	-	-
Anom. Ao. valve	62 (3.3)	2 (0.6)	0.006*	0.19	0.05 – 0.79
Anom. Mi. valve	36 (1.9)	4 (1.3)	0.646	0.67	0.24 – 1.91
Anom. Pulm. valve	151 (8.0)	15 (4.9)	0.062	0.59	0.34 – 1.01
Anom. Tric. valve	36 (1.9)	1 (0.3)	0.052	0.17	0.02 – 1.22
Ebstein	6 (0.3)	0 (0.0)	-	-	-
Other spec. anom.	71 (3.8)	0 (0.0)	-	-	-
Unspec. anom.	13 (0.7)	3 (1.0)	0.590	1.41	0.40 – 4.98
Total	**1879 (100)**	**308 (100)**			

Discussion

Congenital malformations emerged as a leading cause of infant mortality in the western world during the past two decades, accounting for 22.1% of US infant mortality in 1997 vs 15.1% in 1970.[36] During that period malformations of the nervous, cardiovascular and respiratory systems accounted for 60% of that mortality

The frequency with which type-1 diabetes is encountered among pregnant women (0.1–0.3%)[37] and the high frequency (3-6%), with which congenital cardiac anomalies are encountered during these pregnancies, account for the interest in the diabetic pregnancy. Although perinatal mortality has declined dramatically in diabetic pregnancies during the latest decades, most studies of large populations continue to encounter a higher mortality among these patients than in control populations.[5,38] Studies from the United Kingdom have shown that there is a persistently high level of non-attendance of preconceptional care, late registration for prenatal care and poor glycemic control in diabetic pregnancies. However, the Dutch populations show that there is still a significantly increased occurrence of congenital malformations among the offspring of women with type-1 diabetes who planned their pregnancy, with good periconceptional glycemic control and adequate use of folic-acid supplementation. In both Dutch studies 70 percent of women had a HbA1c less than 7 % during the first trimester.[39,40]

The potential for cardiac abnormalities among offspring of pregnancies complicated by maternal diabetes mellitus has been recognized for over 50 years. In 1937 Hurwitz and Irving described cardiomegaly in such a conceptus.[41] In 1946 Miller reported two cardiac malformations (i.e. cor biloculare with aortic hypoplasia and bicuspid pulmonic valve) among a series of 19 autopsies.[42]
Our study shows an increased absolute and relative incidence of transposition of the great arteries, persistent truncus arteriosus, visceral heterotaxia, and single ventricle when compared to the nondiabetic population (EUROCAT), suggesting teratogenesis at an early stage in heart development (during cardiac looping and conotruncal septation). Our series was compatible with the previous literature concerning the predilection for infants of diabetic mothers to have offspring with particularly complex cardiovascular malformations, but differed ($p<0.05$) from the Baltimore Washington Infant Study (BWIS) in the rarity with which we encountered cases of double-outlet right ventricle, which was the most frequent association found by Ferencz and Loffredo et al. [22,43]

The increased prevalence of abnormalities of bulboventricular looping, conotruncal septation, and migration of the atrioventricular canal among infants of IDDMs clearly relates to a teratogenic impact at a very early point in heart development. Between weeks 5 and 8 the primitive heart tube undergoes a process of folding, remodeling and septation that transforms its single lumen into the four chambers of the definitive heart. The cephalad end of the bulbus cordis will form the distal outflow regions of the left and right ventricles, including the conus cordis and truncus arteriosus. Finishing by the 9th gestational week, the cardiac outflow pathway is divided into two by ridges that grow from opposite walls of the conus cordis and truncus arteriosus to fuse and twist counter clockwise. The latter may relate to tensile stress, hemodynamic changes and migration of neural crest-derived cells.[44] Animal models of transposition of the great arteries have shown that retinoic acid has effects on the neural crest cells, thus altering the development of the downstream structures of the heart.[45] Experimental embryogenesis in high glucose concentrations shows a similar effect on neural crest cellular migration and proliferative capacity, possibly partially explaining the pathogenesis of conotruncal anomalies in diabetic pregnancies.[46] A variety of outflow tract malformations result from errors in conotruncal septation, ranging from a persistent truncus arteriosus, with a common outflow tract, to tetralogy of Fallot and double-outlet right ventricle, through transposition of the great arteries.

Goldmuntz et al.[47,48] demonstrated that abnormalities of chromosome 22 (microdeletion at q11) may be associated with such abnormalities, and with DiGeorge syndrome. These findings suggest that conotruncal septation and abnormalities of the thymus and parathyroid glands may result from a single gene defect. On the other hand, two cases of infants born to diabetic mothers, with DiGeorge syndrome and normal chromosome 22q11, have been reported, suggesting that maternal diabetes may be a primary pathogenic factor in this anomaly.[49]
Similarly, while there has been significant progress in deciphering the genetic control of ventricular looping,[50,51] there is circumstantial evidence that the diabetic environment may alter this fundamental step in cardiac development. Slavotinek et al. reported three infants of diabetic mothers with abnormal left-right laterality, including one with the unusual association of left atrial isomerism with asplenia (usually associated with right atrial isomerism).[52] Strong associations between IDDM and left atrial isomerism and transposition of the great arteries have been reported.[53,54]

The tendency among offspring of IDDM toward multiple malformations in various organ systems suggests a teratogenic exposure during early embry-

ogenesis.[55,56] It appears likely that there is a genetic and environmental interaction that renders some embryologic pathways particularly susceptible to disruption by one or another metabolic perturbation associated with maternal diabetes mellitus. It is possible that specific fetuses are genetically predisposed to the teratogenic effect of specific metabolic fuels that may accumulate in IDDM-complicated pregnancies. Teratogenic agents are thought to act by causing embryonic cell death or altered cell growth or differentiation.[57] It is unclear which substances in the fetus of the IDDM are the specific teratogens, and it is unclear whether these are acting by altering nucleic acid chemistry, enzyme function, or through direct impact on cellular function (metabolic or cell membrane), resulting in cellular death, impaired cell-cell interaction, or abnormal cell migration. The overlap between the spectrum of congenital cardiac abnormalities among the offspring of diabetic mothers and those cardiac lesions at the foundation of our emerging understanding of the genetics of left-right asymmetry, cardiac looping, and conotruncal septation provides us with added insight, and raises important questions surrounding the developmental biology of the heart, and emphasizes the overlap between genetic and environmental influences in the causation of congenital heart disease.[7,58]

The initial HbA1c levels of patients in the prospective were above the normal range of 4.0–6.3% and emphasize the difficulty in obtaining adequate glycemic control. The significantly higher initial HbA1c levels in cases with cardiac malformations support the association between sub-optimal glycemic control and the occurrence of CHD.[1,4,59] Recent reports showed decreased dysmorphogenesis in experimental diabetic pregnancy in the rat using a combined treatment strategy of vitamin E and C to decrease oxidative stress.[60]

Despite the intuitively obvious recommendation that glucose metabolism in these patients should be strictly controlled during the preconceptual period and through embryogenesis, in many countries these patients may not register for obstetrical care until well into pregnancy. The data for the Netherlands show an increased incidence of CHD, even with only slightly increased HbA1c values. Such findings emphasize the continued importance of prenatal diagnosis in these patients. Previous studies from our centers have demonstrated that prenatal diagnosis of congenital heart disease may alter the postnatal course of affected neonates, by avoiding lactacidosis, and enhancing survival among patients with cardiac malformations reparable into a two-ventricular physiology.[16,61] Others have reported that prenatal cardiac diagnosis improves surgical morbidity and mortality among offspring with complete transposition of the great arteries[62], in

patients with hypoplastic left heart syndrome[63] and coarctation of the aorta.[64] Hence, the predilection of offspring of IDDM's for conotruncal malformations, including complete transposition of the great arteries, and lesions associated with ductal-dependent pulmonary or systemic blood flow, underscores the clear-cut role of detailed fetal echocardiography in the management of these pregnancies. Fetal echocardiography, therefore, should be included as a routine component in the management of such pregnancies.

Conclusions

Our study emphasizes the frequency with which the offspring of IDDM-complicated pregnancies suffer from complex forms of congenital heart disease. Pregnancies with poor first trimester glycemic control are more prone to the presence of fetal heart disease. The high incidence of conotruncal septation and bulboventricular looping abnormalities among these patients suggests a profound teratogenic effect during the first weeks of gestation. The perturbed maternal metabolic state appears to result in an accumulation of metabolic fuels that alter the expression of genes that control the most fundamental aspects of cardiac development. The predilection of these fetuses to have complex congenital cardiac malformations such as persistent truncus arteriosus, complete transpositon of the great arteries, visceral heterotaxia, and single ventricular complexes, emphasizes the crucial role that detailed fetal echocardiographic studies occupy in the perinatal management of these patients.

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Chapter 10

Altered fetal circulation in type-1 diabetic pregnancies

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Abstract

Objectives
Type-1 diabetic pregnancies (tIDP) are associated with congenital cardiac malformations, fetal cardiomyopathy, venous thrombosis and altered placental vascularization, even with tight maternal glucose control. It was the aim of this study to investigate if with good glucose control, achieved with continuous subcutaneous insulin infusion (CSII), normal blood flow over the fetal heart can be achieved.

Methods
Seventeen fetuses of women with well-controlled type-1 diabetes were studied longitudinally to evaluate effects on the fetal circulation. Doppler frequency shift tracings, valve diameters and intercept angles were measured at right and left atrioventricular valve (AVV) orifices at 4-week intervals starting at 15 weeks gestation. AVV flow was calculated and compared to normal fetal data obtained in previous studies.

Results
Maximal and mean temporal velocities (Vmax and MTV) increased in both groups during gestation but significantly more in fetuses of tIDP's. Combined ventricular output, absolute and per kg estimated fetal weight, were also greater in these fetuses. In the normal group the ratio of the right/left ventricular output decreased significantly during gestation (from 1.34 ± 0.28 to 1.08 ± 0.28), but in tIDP's this decrease did not occur (1.20 ± 0.26 to 1.25 ± 0.29).

Conclusions
These data indicate significant differences in the fetal circulation between normal pregnancy and well controlled tIDP, suggesting the existence of a compensatory mechanism that increases cardiac output and causes cardiac hypertrophy.

Introduction

Maternal type-1 diabetes is, among other complications, associated with congenital cardiac malformations and diabetic cardiomyopathy in the newborn infant. Offspring of diabetic mothers have a fivefold increase in incidence of congenital heart malformations compared to infants of non-diabetic women.[1] Diabetic cardiomyopathy occurs in 30% of the newborns of diabetic mothers.[2,3] Furthermore, thrombosis in fetal veins is known to occur[4,5], vascularization in the placental villi is abnormal, even with good glucose control[6], and pathologic fetal heart rates have been observed.[7] Using Doppler ultrasound, flow and flow velocity waveforms can be measured in various fetal vessels and over the atrioventricular (AV) orifices of the fetal heart. In the present study, longitudinal data are presented on blood flow over the AV orifices of 17 fetuses of type-1 diabetic women. It was the aim of this study to investigate if with good glucose control, achieved with continuous subcutaneous insulin infusion (CSII), normal blood flow over the fetal heart can be achieved.

Methods

Seventeen pregnant women with type-1 diabetes, who attended the outpatient clinic were asked to participate in this study. A detailed explanation of the investigation was given before informed consent was obtained. Initial Doppler recordings were attempted between 15 and 18 weeks gestation. Subsequent examinations were performed every 4 weeks until delivery. Blood flow velocities through mitral and tricuspid valve orifices and diameters of these orifices were measured. Blood flow volumes through the atrioventricular valve orifices were calculated using the equation:

$$\text{Blood flow} = \frac{\text{Mean temporal flow velocity} \times A}{\text{Cos } q}$$

In which A is the estimated area of the atrioventricular orifices and q is the angle between the Doppler beam and the estimated direction of the blood flow.

Flow over the atrioventricular valves was compared to normal fetal data obtained in 28 control fetuses. Data of these control fetuses have been published previously.[8] All ultrasound studies were performed following the same protocol as in an earlier study in normal fetuses by Reed et al.[9]

Fetal weight percentile was estimated from abdominal area measurements by two-dimensional ultrasound.

Maximal and mean temporal velocities, areas of AV orifices, ventricular output and combined ventricular output corrected for estimated fetal weight were evaluated. Ninety percent confidence intervals were calculated. Differences between fetuses of women with type-1 diabetes and control fetuses were analyzed. A normal distribution was present; therefore paired *t*-test could be performed.

The mean duration of diabetes was 11 years with a range of 2-20 years. According to the modified White classification two women had class B, five class C and ten class D diabetes. In six patients tight metabolic control with continuous subcutaneous insulin infusion had been started before conception. In nine CSII treatment was started between 7 and 14 weeks of gestation. Two women were well-controlled with conventional injections and remained on this regimen during pregnancy. Eighty-five percent of the women had a glycosylated Hb percentage (HbA1c) less than four standard deviations above the mean at early gestation, whereas HbA1c was less than 2 SD above the mean in all cases at the end of gestation. Average HbA1c at 9 to 12 weeks gestation was 5.6 ± 0.4% (1SD), at 17 to 28 weeks 5.1 ± 0.4% and at delivery 4.8 ± 0.6% with normal values of 4.0 to 6.3%.

Results

None of the newborns had a structural heart defect on two-dimensional real time ultrasound. Five infants had a birth weight above the 90th percentile (29%).

The control group consisted of 28 normal fetuses.[8] Mean and maximal temporal velocities were higher in fetuses of women with diabetes than in controls throughout gestation and these differences were significant at most ages. With increasing gestation the mean and maximum temporal velocities of the AV orifices increased in both groups during gestation. Maximal and mean temporal velocities however increased more with increasing gestational age in fetuses of diabetic women than in the control group (**Table 1, Figure 1**).

Until a gestational age of 32 weeks areas of mitral and tricuspid valves were significantly larger in the diabetic group. Later in pregnancy these differences disappeared (**Table 1**).

Table 1

15-20 weeks		**Maternal diabetes**	**Control group**	**p-value**
MTV	L	10.7 +/- 1.2	9.8 +/- 1.8	NS
	R	11.7 +/- 1.5	11.1 +/- 1.7	NS
V max	L	39.5 +/- 4.7	38.3 +/- 6.5	NS
	R	43.5+/- 5.1	43.0 +/- 6.7	NS
Area	MO	0.197 +/- 0.134	0.086 +/- 0.034	0.001<2p<0.01
	TO	0.198 +/- 0.120	0.100 +/- 0.040	0.001<2p<0.01
Output	L	131.8 +/- 88.2	53.7 +/- 21.4	0.001<2p<0.01
	R	141.3 +/- 77.9	66.7 +/- 25.2	0.001<2p<0.01

20-24 weeks		**Maternal diabetes**	**Control group**	**p-value**
MTV	L	13.2 +/- 1.7	11.2 +/- 2.0	0.001<2p<0.01
	R	13.7 +/- 2.8	12.0 +/- 1.5	0.01<2p<0.05
V max	L	45.8 +/- 7.5	41.5 +/- 6.0	NS
	R	47.3 +/- 8.0	44.7 +/- 6.3	NS
Area	MO	0.284 +/- 0.144	0.163 +/- 0.043	2p<0.001
	TO	0.297 +/- 0.188	0.190 +/- 0.044	0.01<2p<0.05
Output	L	232.7 +/- 99.5	112.1 +/- 33.2	2p<0.001
	R	249.2 +/- 128.3	141.4 +/- 32.8	2p<0.001

24-28 weeks		**Maternal diabetes**	**Control group**	**p-value**
MTV	L	14.2 +/- 2.5	13.1 +/- 2.0	NS
	R	15.4 +/- 2.0	13.8 +/- 2.1	0.01<2p<0.05
V max	L	46.1 +/- 7.9	42.4 +/- 7.8	NS
	R	50.8 +/- 5.0	46.2 +/- 8.4	0.01<2p<0.05
Area	MO	0.381 +/- 0.177	0.253 +/- 0.057	0.001<2p<0.01
	TO	0.410 +/- 0.209	0.272 +/- 0.065	0.001<2p<0.01
Output	L	347.9 +/- 119.9	199.7 +/- 56.4	2p<0.001
	R	395.5 +/- 191.4	230.5 +/- 67.4	0.001<2p<0.01

28-32 weeks		**Maternal diabetes**	**Control group**	**p-value**
MTV	L	16.3 +/- 2.4	14.4 +/- 2.5	0.001<2p<0.01
	R	16.2 +/- 2.5	14.6 +/- 2.8	0.01<2p<0.05
V max	L	48.6 +/- 7.3	44.9 +/- 8.3	NS
	R	50.0 +/- 10.1	48.0 +/- 8.3	NS
Area	MO	0.555 +/- 0.222	0.388 +/- 0.079	0.001<2p<0.01
	TO	0.644 +/- 0.234	0.425 +/- 0.077	2p<0.001
Output	L	547.6 +/- 226.1	329.6 +/- 74.7	2p<0.001
	R	611.9 +/- 218.3	372.5 +/- 86.1	2p<0.001

32-36 weeks		**Maternal diabetes**	**Control group**	**p-value**
MTV	L	16.8 +/- 3.1	15.5 +/- 2.7	NS
	R	17.4 +/- 2.9	15.8 +/- 2.0	0.01<2p<0.05
V max	L	49.0 +/- 10.2	45.3 +/- 8.7	NS
	R	54.0 +/- 9.9	50.1 +/- 7.0	NS
Area	MO	0.691 +/- 0.313	0.557 +/- 0.074	NS
	TO	0.700 +/- 0.258	0.653 +/- 0.238	NS
Output	L	700.6 +/- 339.6	518.2 +/- 114.1	0.01<2p<0.05
	R	730.3 +/- 260.8	605.5 +/- 184.7	NS

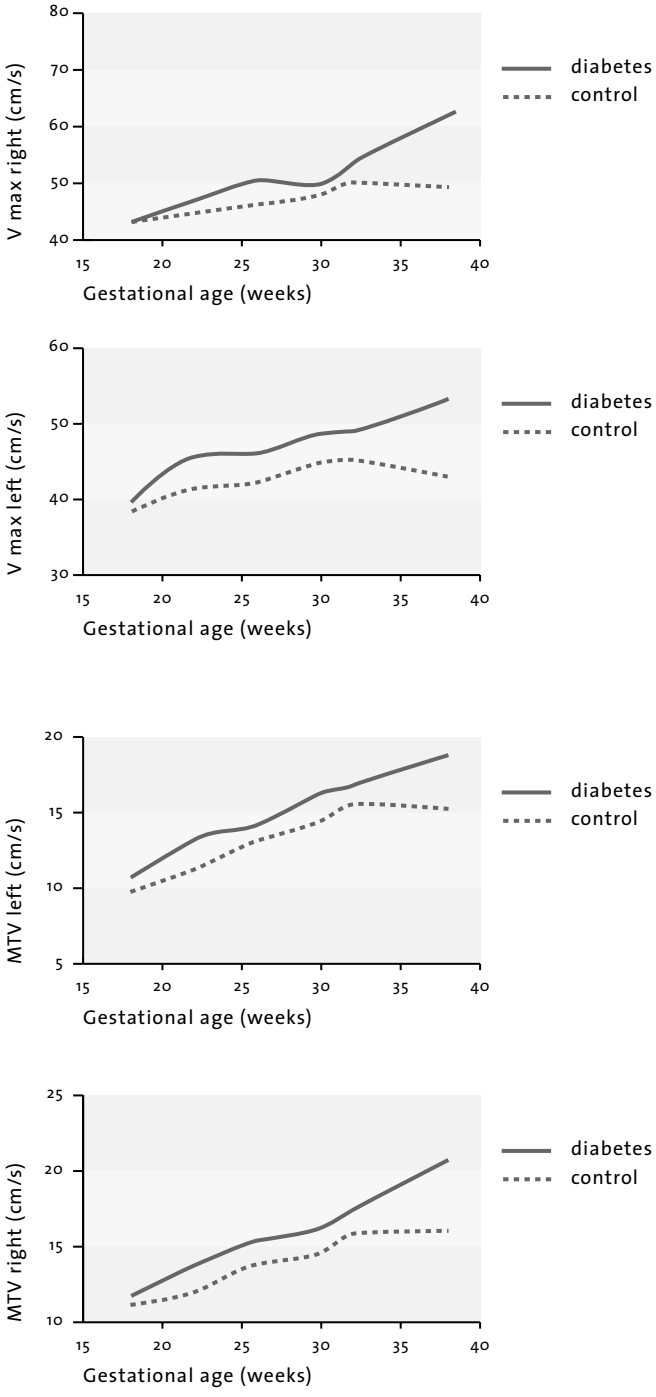
36-40 weeks		**Maternal diabetes**	**Control group**	**p-value**
MTV	L	18.8 +/- 4.7	15.2 +/- 2.3	0.001<2p<0.01
	R	20.7 +/- 3.7	16.0 +/- 3.1	2p<0.001
V max	L	53.4 +/- 12.8	43.1 +/- 7.0	0.001<2p<0.01
	R	62.1 +/- 9.5	49.4 +/- 7.7	2p<0.001
Area	MO	0.754 +/- 0.440	0.923 +/- 0.164	NS
	TO	0.977 +/- 0.428	0.995 +/- 0.202	NS
Output	L	708.7 +/- 329.4	820.4 +/- 164.4	NS
	R	1102.9 +/- 395.2	915.1 +/- 229.3	NS

MTV in cm/s, Vmax in cm/s, Area in cm^2, Output in ml/min

MO = Mitral orifice, TO = Tricuspid orifice, L = Left, R = Right

Figure 1

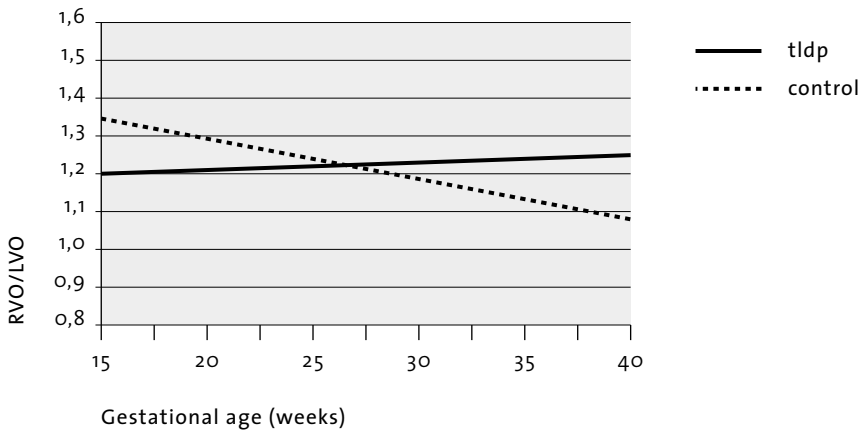
Temporal velocities in diabetic and control fetuses



Both the higher blood flow velocities and the greater AV orifices resulted in an increased combined cardiac output in the fetuses of diabetic women, absolute and per kilogram (kg) estimated fetal weight. Per kilogram estimated fetal weight the mean total cardiac output was also greater, with an average of 823 ± 308 ml/min/kg. In the case of diabetes the mean cardiac output decreased during gestation. This in contrast to control fetuses in which mean total cardiac output per kilogram estimated fetal weight remained constant throughout gestation, with an average of 553 ± 153 ml/min/kg. In the control group the ratio of right to left ventricular output decreased from 1.34 ± 0.28 at 15 weeks to 1.08 ± 0.28 at 40 weeks.[8] This decrease did not occur in the diabetic group and the ratios at 15 and 40 weeks were 1.2 ± 0.26 and 1.25 ± 0.29 respectively (**Figure 2**).

Figure 2

RVO/LVO ratio in diabetic and control fetuses



RVO = Right ventricular output, LVO = Left ventricular output

There was a positive relationship between the blood flow velocities obtained within two weeks before delivery and birth weight percentiles, and three of the five infants weighing more than the 90th percentile had a mean temporal velocity exceeding the normal range. Average birth weight and distribution of weight percentiles were not different between the two groups. The birth weights ranged from 2,590 to 5,250 g (mean 3,526 ± 587 g) in the control group and from 2,460 to 4,500 g (mean 3,296 ± 677 g) in diabetic pregnancies.

Discussion

Our data show that even in well-controlled diabetic pregnancies mean and maximum temporal velocities over the fetal AV orifices were significantly higher and increased more with advancing gestational age than those in normal pregnancies. Also the combined ventricular output, absolute and per kg estimated fetal weight, was greater in the fetuses of diabetic women. These changes in fetal circulation might be a compensatory reaction to the existence of a chronic hypoxemic situation. Such an existence is suggested by the higher hemoglobin levels in newborns of diabetic mothers as described in earlier publications[10-12] and also by the elevated number of nucleated red blood cells in well-controlled diabetic pregnancies.[10,13] Moreover, hypoxemia has been found at cordocentesis, especially in case of increased maternal and fetal glucose levels.[14]

Fetal hypoxemia may occur because of a relative immaturity of the placenta, with an increased distance over which oxygen diffusion has to occur from maternal to fetal side.[6,15]

Our results are different from those found by Jaeggi et al. who found no differences in indices of diastolic and systolic function between fetuses of diabetic pregnancies and an age-matched control group.[16]

In the diabetic group a decrease of the ratio of the right to left ventricular output did not occur. This indicates that there is a dominant role for the right ventricle until the end of pregnancy, whereas in normal pregnancy right and left ventricle transport both half of the cardiac output at the end of gestation. The reason for this right ventricle dominance is to be found in the fact that the head of the fetuses of women with diabetes is relatively smaller than the body.[17-19] Furthermore, as a result of the placental immaturity more blood has to be transported to the placenta and the right ventricle is responsible for delivery of blood to the placenta.

The control group of normal fetuses is from a population studied in 1987. This group was chosen because the techniques used and validation implemented were exactly comparable to the current study and measurements were performed by the same observers. Recent flow measurements on similar but updated ultrasound equipment show the same normal values, although a coherent longitudinal study on a normal population has not been undertaken.

Two sites for fetal ventricular output are available, i.e. the AV orifices and the great arteries. We performed measurements at the AV level since Doppler frequency shift tracings at the AV orifices are more easily obtained and have a lower velocity[9], avoiding the problems in velocity aliasing. In addition, the AV orifice has margins clearly defined by the bright echodense spots of the fibrous AV annulus tissue and has a larger diameter than the great artery orifices. The echodense spots allow an accurate diameter measurement, whereas the large diameter reduces the relative impact of errors of diameter measurement on the calculation of blood flow.[20, 21]

To minimize the variability of the method we calculated the mean temporal velocity by integrating the Doppler frequency shift on three consecutive cardiac cycles and performed these measurements three times. The diameter of the AV orifices was measured five times, averaging the results. This method was extensively validated in a previous study of which the results were published earlier.[21] We did not study the reproducibility of the ultrasound parameters regarding fetal weight estimation, nor did we study the reliability of fetal weight estimation in type-1 diabetic pregnancies. However, McLaren et al. found that the accuracy of predicting birth weight among diabetic women is similar to that among women without diabetes, regardless of the sonographic model used.[22]

Many publications have reported an abnormal ventricular filling pattern in fetuses of type-1 diabetic mothers. The ratio between early and active ventricular filling at the level of the ventricular valves is lower than in control fetuses caused by an interventricular septal hypertrophy affecting cardiac diastolic function and by differences in hematocrit and heart rate.[23-28] A ventricular hypertrophy might enable the increased cardiac output necessary in these fetuses. Rizzo et al. also showed that despite an adequate metabolic control an interventricular septal hypertrophy occurs, which affects cardiac diastolic function.[23]

We conclude that these data indicate significant differences in the fetal circulation between normal pregnancy and well controlled type-1 diabetic pregnancies and suggest the existence of a compensatory mechanism which increases cardiac output and causes cardiac hypertrophy.

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Chapter 11

General discussion and summary

Structural heart defects

Over the years there has been a steady increase in the number of patients with a prenatally detected structural congenital heart disease. Despite efforts to achieve the contrary, some pregnancies will end in intrauterine death. In these patients the sole advantage of the prenatal diagnosis is to facilitate thorough parental counseling concerning future pregnancies.

Another group consists of those patients, in whom prenatal diagnosis detects severe fetal heart disease, precluding a reasonable quality of life. In such circumstances parents may opt for termination of pregnancy or choose for compassionate care. Compassionate care is generally opted for if termination of pregnancy is not considered an option, based on the socioreligious background, or if the heart defect has been detected after 24 weeks gestation. Prenatal diagnosis in this situation enables physicians to prevent intensive, traumatic and lengthy treatment.

The primary goal of prenatal detection of cardiac defects is better care in the immediate postnatal period. The most convincing justification for the efforts taken would be to demonstrate that prenatally diagnosed patients have a better chance of a good outcome. We therefore studied in **chapter 2** the impact of prenatal diagnosis on management and outcome of newborns with congenital heart disease in a retrospective multi-center study. In this study the incidence of metabolic acidosis in prenatally and postnatally diagnosed groups of patients with similar diagnoses was compared. Although previous reports suggest a direct positive effect of prenatal detection on immediate surgical outcome, our study did not allow such a conclusion, most likely due to confounding factors such as different surgeons, different institutions and different protocols. Prenatal diagnosis however, proved to prevent deterioration of the acid-base-equilibrium. Significant differences were found for the worst arterial pH and for the lowest preoperative base excess with severe acidosis being more common among the postnatally diagnosed group. The study covers the entire spectrum of congenital heart disease and suggests that immediate management of heart disease, facilitated by the prenatal diagnosis of the disease, reduces the incidence and degree of acidosis and allows immediate stabilization of the acid-base-equilibrium. Our study covered the subgroups with and without ductal-dependent lesions. Significant differences for lowest base excess and lowest pH in favor of the prenatal group were found in the ductal-dependent group, while in patients with non-ductal-dependent heart disease only lowest base excess differed significantly. This indicates that especially the early initiation of Prostaglandin E1 (PGE1) administration

in the ductal-dependent group may prevent acidosis. The difference in the non-ductal-dependent group, although less significant, suggests that early medical care other than PGE1 therapy is also a positive effect of prenatal diagnosis. In conclusion, chapter 2 shows that a prenatal diagnosis reduces the development of metabolic acidosis in the newborn patient with congenital heart disease. Although no apparent positive effects on immediate surgical outcome could be found optimization of the preoperative condition of the patient with severe congenital heart disease can be expected to lead to improved longterm outcome and prevention of cerebral damage in this fragile group of patients.

A subpopulation of the study group of chapter 2 is used in **chapter 3**. An in-depth analysis of the occurrence of lactacidosis was performed and parameters of acidosis were more thoroughly investigated. This study was only conducted in the Dutch patient groups since lactate measurements were not a standard procedure in the two American centers participating in the previous study. Two-hundred-and-nine patients with congenital structural heart disease requiring surgery within 31 days of life were included. Worst preoperative arterial lactate of the prenatally diagnosed group was 3.05 ± 0.35 versus 6.08 ± 0.45 mmol/L in the postnatal group, indicating a significant difference in favor of the prenatally diagnosed group ($P<0.001$). No significant differences in pH or base excess were found. Normalization of preoperative lactate values occurred on average 21.5 hours after admission. The pH normalized 5.3 hours and base excess 0.41 hours after admission. Of the patients without a prenatal diagnosis 22.3% had a worst preoperative lactate greater than 7.5 mmol/L, while none of the patients with a prenatal diagnosis had a worst lactate greater than 7.5 mmol/L ($P=0.026$). Prenatal diagnosis, therefore, results in a better condition of the infants at surgery and might also result in a decrease of the risk of cerebral damage, since high lactate values (> 7.5 mmol/L) are correlated with cerebral damage and neurodevelopmental complications.

Normalization of lactate values takes significantly more time than normalization of either pH or base excess, since titration of bicarbonate will almost immediately normalize pH and base excess. The extend of the hypoxia and the severity of the resulting acidosis threatening the neonatal brain, seem therefore to be better reflected by lactate values. Several studies suggest a predictive role of serum lactate measurements for adverse outcome, since elevated lactate levels reflect tissue hypoperfusion and hypoxemia. Arterial pH and base excess are poorer predictors of the outcome.

Our study shows that the prenatal diagnosis of congenital heart disease has a role in the prevention of lactate acidemia in the preoperative period by optimizing direct neonatal therapy. In theory this should result in a better longterm neurological outcome. A diagnosis of the cardiac lesion before birth will allow physicians to initiate therapy immediately after birth and help to prevent these problems.

In **chapter 4** the correlations between prenatal detection of congenital heart disease, preoperative indicators of acidosis and short and longterm developmental outcome were investigated. One-hundred-and-seventeen patients with congenital structural heart disease requiring surgery within 31 days of life were included in this study. In 15 cases (13%) a prenatal diagnosis was established, while 102 patients (87%) had a postnatal diagnosis of the structural heart disease.

Preoperative values of lactate, pH and base excess levels were retrieved from all patients and the occurrence of disturbed developmental outcome at the age range of two to eight years was documented. Data were extrapolated to a standardized and validated Dutch developmental scale. An underperformance of more than 10% from the P_{90} was defined as disturbed development. Patients were split into groups with extreme values of parameters of acidosis. Receiver Operating Characteristic (ROC) curves were used for determining cut-off values for pH, base excess and lactate.
No significant differences in developmental outcome were found using values for pH or base excess as a cut-off level. However, preoperative lactate values exceeding 6.1 mmol/L resulted in a significant increase in impaired developmental outcome. Of the children with a preoperative lactate lower than 6.1 mmol/L, 15% had subsequent developmental problems compared to 41% of the children with a lactate exceeding 6.1 mmol/L (P=0.03; OR=3.88). Disturbed developmental outcome was encountered in 25.4% of the children in the postnatally diagnosed group compared to 13.3% in the prenatal group (P=0.50).

The purpose of this study was to investigate the prognostic values of different preoperative parameters concerning patients with congenital heart disease. Worst preoperative lactate values appeared to be of prognostic significance on developmental outcome, and 41% of the patients with a lactate over 6.1 mmol/L had a disturbed development. The limited prognostic value of pH can be explained, just as in the previous study, by the fact that pH is easily and rapidly corrected with bicarbonate infusion, while lactate better reflects the total oxygen debt experienced by the patient with congenital heart disease. Base excess is also not as good as lactate as a marker

of tissue hypoxia, since its value is also dependent on the Pco2, thus exaggerating any metabolic acidosis. Lactate on the other hand is the end product of anaerobic metabolism and is therefore an ideal parameter of prolonged hypoxia.

Chapters 2 and 3 show that prenatal diagnosis does help preventing the development of severe acidosis and in chapter 4 a significant correlation between preoperative lactate values and disturbed developmental outcome has been documented. Therefore a positive effect of a prenatal diagnosis of congenital heart disease on developmental outcome might be expected if larger numbers would be analyzed.

Chapter 5 concerns a retrospective study on the management and outcome of prenatally diagnosed cases of hypoplastic left heart syndrome (HLHS). At an estimated prevalence of 1 to 4 per 10.000 life births the HLHS accounts for 7 to 8% of congenital heart disease (CHD) and is the most common cause of death due to heart disease in the newborn period. Hypoplastic left heart syndrome is readily detectable before 20 weeks gestation by echocardiographic examination of the four-chamber view. It is the most serious of structural cardiac malformations diagnosed prenatally and is characterized by severe underdevelopment of the structures in the heart-aorta complex, including the left ventricular cavity and mass.

In this descriptive paper we present the experience with HLHS in the Wilhelmina Children's Hospital over a period of 13 years and compare its management strategy with that of centers in the United Kingdom (UK) and United States (US). The percentages of the intention-to-treat group are 34% (our study) versus 36% (Andrews et al.; UK). There was a slight difference in the choice of termination of pregnancy (50% vs 60%) and more so for compassionate care (16% vs 3.5%) between our study and that of the UK respectively. If we compare both European studies with the study by Allan et al. from the United States, a striking difference is encountered in the distribution of the various treatment options ($P<0.05$). In the USA study the intention-to-treat group constitutes 67% of all patients, whereas the group of parents that opt for termination of pregnancy constitutes only 13%. In 20% of all cases parents declined treatment.

Prenatal diagnosis of the HLHS provides opportunities to get patients in optimal preoperative condition when surgery is offered. It also facilitates in-depth counseling of the parents on this severe malformation.
The parents of our Dutch study population faced with the difficult decision of possible termination of pregnancy, compassionate care or surgical

strategy, choose in a minority for surgical treatment. The different parental approach to this structural cardiac anomaly may be attributed to different socioreligious opinions on the management of this type of lesion as well as to differences in counseling of the parents. Apparently clinicians and parents in Europe are more concerned with the longterm psychoneurological outcome which is grim in these patients and the prospective quality of life. This policy might well change in the future since survival rates of the Norwood procedure are improving, although the poor longterm neurophysiological outcome remains a major issue. The difference in early survival between the surgical groups with and without a prenatal diagnosis of the anomaly is likely based on the more stable preoperative clinical condition of the prenatally diagnosed patients.

Chapter 6 deals with the experience of prenatally diagnosed Ebstein's anomaly. A review of the literature on Ebstein's anomaly is performed and the cases encountered at the Wilhelmina Children's Hospital are described. While HLHS forms one extreme of the spectrum of CHD, dysplastic malformations of the tricuspid valve form the other extreme. They range from deformation of the leaflets and the tension apparatus without downward displacement (primarily described as dysplasia) to lesions in which the primary lesion is a downward displacement of the proximal attachment of the posterior and septal leaflets, known as Ebstein's malformation. The prevalence, fetal and maternal risk factors and echocardiographical features are described. Moreover, the occurrence of associated anomalies is portrayed.

Once the crucial neonatal phase is survived and pulmonary problems have been overcome, the outlook of these newborns becomes favorable and comparable to that of older children and adults in whom this diagnosis is made in later life. This is emphasized and furthermore the literature is reviewed for the intrauterine course and postnatal interventions and outcome. In our series prenatal diagnosis of isolated Ebstein's anomaly was established in four patients. Of these four fetuses two died in utero; in one case the parents opted for compassionate care and one infant is alive 9 years after operation.

We conclude that Ebstein's anomaly remains a severe and frequently fatal disorder in the fetus with gross echocardiographic abnormalities, readily detectable by routine obstetrical ultrasound. In general, the earlier the patient presents with the malformation, the poorer the prognosis. Fetal and neonatal presentation is typically associated with a dismal outcome secondary to the almost always occurring pulmonary hypoplasia. This 'early

group' constitutes a specific entity and cannot be compared with patients in whom the anomaly is detected later in life. Parental counseling of these patients therefore can not be based upon the natural history of this disease in older patients. Surgical procedures of tricuspid valve repair or replacement may be offered, but this option is almost exclusively possible in patients who are older, i.e. after the neonatal period. Unfortunately only very few patients with a prenatal diagnosis of Ebstein's disease survive the perinatal period. For some congenital heart defects (e.g. hypoplastic left heart syndrome, transposition of the great arteries and coarctation of the aorta) prenatal diagnosis will frequently lead to a better outcome. Ebstein's anomaly is an example of CHD that is easily detectable in utero because of the severity of the lesion but still has an unfavorable outcome compared to cases that present in later life.

In **chapter 7** we have investigated patients with congenital heart disease who were diagnosed prenatally in the Utrecht area and analyzed the management and outcome of this disease after prenatal detection. In addition we analyzed all patients requiring surgery for congenital heart disease in the newborn period and assessed the overlap between both groups. One-hundred-and-seventy patients with a prenatal diagnosis of congenital heart disease were included. Spontaneous intrauterine death occurred in 23 patients. Parents chose to terminate the pregnancy in 56 cases. Over half of the patients with a prenatal diagnosis (n=91) were born alive. In 29 patients parents declined treatment and 24 patients were operated on in the neonatal period. The other 38 patients underwent elective surgery after the neonatal period or did not need surgery at all. In the same period 191 patients were operated on for congenital heart disease; only 24 (13%) of them had a prenatal diagnosis of their cardiac defect and formed the overlap with the prenatal group.

Unfortunately within the surgery group of 167 patients without a previous prenatal diagnosis a mismatch existed between the efforts to diagnose the majority of congenital heart disease and the actual percentage of prenatally diagnosed cases. It is regrettable that a large number of patients had numerous prenatal ultrasound studies which were reported as normal, while the defect should have been visible on the four-chamber view. It is in this group that improvement is necessary in view of the positive effects of prenatal diagnosis on the prevention and deterioration of the acid-base-equilibrium. An increased emphasis on the evaluation fetal cardiac structures by gynecologists and echographists is required. Better training provided by pediatric cardiologists seems to be crucial to achieve this goal. A discrepancy exists between the supposed potential of the ultrasound

examination of the fetal heart and the actual situation in the Netherlands. There is room for improvement.

Rhythm disorder

Chapter 8 concerns a study which was conducted to demonstrate that prenatal diagnosis may also have beneficial effects for rhythm disorders. This study focuses on the in utero diagnosis and treatment of a specific form of fetal tachycardia as a primary condition: fetal atrial flutter (AF). Atrial flutter occurs in approximately 0.2% of all pregnancies. The atrial rate is more than 250 beats per minute with a fixed or variable AV block, resulting in a variable ventricular response.

In this multi-center study we investigated the management of a population of 44 cases diagnosed prenatally. Since the management and outcome of the AF appeared to be influenced by the presence of fetal hydrops, the study population was divided into a hydropic (n=20) and nonhydropic (n=24) group. The conversion rate to sinus rhythm in utero among the pharmacologically treated fetuses was slightly better for the nonhydropic (n=17) than for the hydropic (n=18) group with 89% (n=16) and 65% (n=11) respectively. Despite adequate treatment, recurrence of AF occurred frequently at birth, namely 24% in the hydropic group (n=4) and 11% in the nonhydropic group (n=2). More importantly fetal hydrops was associated with neurological morbidity in 4 cases (3 cerebral hypoxic-ischemic lesions and one hemorrhagic lesion) and with mortality in 3 cases.

This study shows that patients with hydrops are more difficult to treat than those without any signs of hydrops fetalis. The decision to initiate pharmacological intervention in the case of AF seems clear but can be inferred based on several factors, i.e. age at presentation, state of fetal lung maturation and existence of hydrops or associated structural heart disease. This must be weighed against possible maternal and/or fetal adverse effects inherent to the use of antiarrhythmics. In this retrospective study the drug of first choice was digoxin. Although digoxin had shown to be successful in most patients in our study, we have abandoned this drug as the drug of first choice due to the requirement of high maternal serum levels to reach therapeutic levels in the fetus. In the presence of fetal hydrops this drug has a slow and only partial transplacental transfer. The safety and efficacy of sotalol (a noncardioselective beta-adrenergic-blocking agent and its class III antiarrhythmic properties) have led to the use of this drug as the drug of first choice, especially since no recurrence of

AF was detected at birth after use of sotalol in 8 cases treated thus far. Digoxin is a second-line drug since it may have a positive inotropic effect on the compromised function of the fetal heart, besides its antiarrhythmic properties.

In conclusion a prenatal diagnosis of the arrhythmia is beneficial for the fetus as undiagnosed cases may deteriorate into a hemodynamic unfavorable situation which may lead to neurological damage or even intrauterine death. Just as in structural heart disease (chapter 4) fetuses with sustained AF at birth may be compromised requiring direct intervention at birth to restore sinus rhythm and prevent cerebral damage or neonatal death.

Diabetic pregnancies and congenital heart disease

As gravid diabetic patients form the single largest maternal referral population for prenatal cardiac investigation, we have investigated both the morphological and the physiological impact of this disease on the fetal cardiovascular system. In **chapter 9** we describe a multi-center study which aim was to study the pattern of cardiac anomalies among offspring of pregnancies complicated by type-1 diabetes mellitus. Assessment of periconceptional glycemic control, reflected by glycosylated hemoglobin (HbA1c) levels during the first trimester is also important.

We studied the incidence and the spectrum of congenital cardiac malformations among fetuses and neonates born to mothers with type-1 diabetes mellitus in two Dutch and one American populationgroups and combined our data with those reported in the literature. These combined data were compared to the incidence and pattern encountered among the offspring of unselected women from the EUROCAT Registry Northern Netherlands.

Combining the cardiac anomalies encountered in our study population with those in the literature shows that a quarter of all anomalies could be defined as conotruncal malformations (CTM): transposition of the great arteries (TGA) accounted for 49% of the CTM, followed by tetralogy of Fallot (TOF) with 25%, persistent truncus arteriosus (PTA) with 15% and double-outlet right ventricle (DORV) with 2.6%. When we compared these data with that of EUROCAT, a significant increased incidence was found for TGA, PTA, single ventricle and visceral heterotaxia. First trimester HbA1c values of diabetic pregnancies complicated by CHD were higher than those resulting in the birth of a healthy infant.

Our study reveals a high incidence of complex anomalies of laterality and looping, and of conotruncal malformations among the offspring of type-1 diabetes pregnancies. The high incidence of conotruncal septation defects suggests a profound teratogenic effect during the first weeks of gestation. These anomalies are ductal-dependent for sustained pulmonary and systemic blood flow and are particularly amenable to early medical and surgical intervention.

The data for the Netherlands show that also with only slightly increased HbA1c values, the incidence of CHD is still increased. Near normoglycemia apparently is not good enough. These children might hopefully have an improved outlook when periconceptional care in these pregnancies is further optimized but till then one should benefit from an in utero diagnosis of the CHD. In conclusion these findings stress the importance of adequate diabetes control, prenatal diagnosis of CHD and sophisticated neonatal care.

In **chapter 10** anatomically normal fetuses of women with type-1 diabetes were studied to evaluate the impact of the disease on the fetal circulation. Longitudinal data were obtained on blood flow over the AV orifices. Blood flow velocities through mitral and tricuspid valve orifices were measured and blood flow volumes were calculated and compared to those of control fetuses.

Mean and maximum temporal velocities over the fetal AV orifices and the combined ventricular output were significantly higher in the diabetic pregnancies. These changes in fetal circulation might be a compensatory reaction to the existence of a chronic hypoxemic situation caused by a relative immaturity of the placenta, with an increased distance over which oxygen diffusion has to occur from maternal to fetal side. Contrary to the control group, in the diabetic group a decrease of the ratio of right to left ventricular output did not occur in the course of gestation. This indicates that a dominant role for the right ventricle remains until the end of gestation in diabetic pregnancies. The reason for this right ventricle dominance might be the fact that more blood has to be transported to the immature placenta, for which the right ventricle is responsible and that the head of fetuses of women with diabetes is relatively smaller than the body. We conclude that these data indicate significant differences in the fetal circulation between normal pregnancy and well-controlled type-1 diabetic pregnancies and suggest the existence of a compensatory mechanism that increases cardiac output.

In conclusion, we can state that prenatal diagnosis of heart disease, both morphological and functional, may influence management of pregnancy and outcome of affected fetuses. It is the most important positive effect of prenatal diagnosis that the sequence of planned delivery in a center, equipped to treat this type of patients and the immediate installment of appropriate therapy may lead to an improved longterm outcome. Lactate levels reflecting the overall oxygen deficiency experienced seem to be a good indicator to measure this possible positive effect. Planned delivery and immediate therapy may keep lactate levels of affected fetuses below 6.1 mmol/L, providing a safe starting point for surgical intervention with better chances of a normal neurophysiological development.

The two extreme sides of the spectrum of prenatally encountered congenital heart disease described in this thesis, the hypoplastic left heart syndrome and Ebstein's anomaly, indicate that in these cases morphology might dominate outcome in a negative manner. This implies that even in the best managed pregnancies, delivery and immediate care of these patients do not assure a favorable longterm outcome.

Finally the data concerning the well-controlled diabetic pregnancies show that this maternal disease infringes on both the fetal cardiac anatomy and circulation. The higher incidence of congenital heart disease is predominantly located in the conotruncal region. The circulatory changes encountered in the structurally normal heart occur later in gestation and suggest being adaptive to ensure an increased cardiac output.

Chapter 12

Nederlandse samenvatting

Prenatale diagnostiek van hartafwijkingen

De toename van het gebruik van geavanceerde ultrasound technologie heeft het mogelijk gemaakt om een steeds groter aantal vormen van cardiale problematiek van de foetus reeds voor de geboorte te diagnosticeren. De positieve bijdrage hiervan is gelokaliseerd in het optimaliseren van het management van deze patiënten tijdens de zwangerschap, de bevalling en in de neonatale periode, teneinde ze in een zo goed mogelijke conditie aan het cardiale behandeltraject te laten beginnen. In dit promotie-onderzoek worden achtereenvolgens een aantal aspecten van deze prenatale diagnostiek beschreven.

Structurele hartafwijkingen

Aangeboren hartafwijkingen worden in toenemende mate voor de geboorte vastgesteld en vormen een zeer belangrijke groep prenataal gediagnosticeerde aandoeningen. Hoewel al het mogelijke in het werk gesteld wordt om deze patiënten een optimale behandeling te bieden, eindigt toch nog altijd een relatief groot aantal van deze zwangerschappen in een intra-uteriene vruchtdood. In dergelijke gevallen is het enige voordeel van de prenatale diagnose dat de ouders voorbereid waren op de mogelijk slechte uitkomst en dat ze geadviseerd kunnen worden met betrekking tot eventueel volgende zwangerschappen.

Daarnaast is er de groep patiënten bij wie een zeer ernstige hartafwijking voor de geboorte wordt vastgesteld en bij wie – door de ernst van de afwijking – geen vooruitzichten zijn op een aanvaardbare kwaliteit van leven na de geboorte. In zulke gevallen kunnen de ouders besluiten de zwangerschap af te laten breken. Wanneer de ouders niet voor een abortus kiezen of wanneer de diagnose van de zeer ernstige afwijking na de 24e zwangerschapsweek wordt gesteld, kunnen ze eveneens besluiten over te gaan tot een abstinerend beleid na de geboorte. In deze gevallen voorkomt de prenatale diagnostiek een langdurige en intensieve behandeling na de geboorte; een behandeling, die voor alle betrokken partijen traumatisch kan zijn.

Het belangrijkste voordeel van de prenatale diagnostiek ligt echter bij de groep die na de geboorte met spoed een chirurgische ingreep dient te ondergaan in verband met een aangeboren hartafwijking. Bij deze patiënten biedt prenatale diagnostiek de mogelijkheid om direct na de geboorte met de juiste therapie te starten, waardoor mogelijk de uiteindelijke prog-

nose gunstig beïnvloed wordt. Daarom hebben wij in **hoofdstuk 2** in een retrospectief multi-center onderzoek de invloed van prenatale diagnostiek op behandeling en uiteindelijke uitkomst bestudeerd bij patiënten met een aangeboren hartafwijking. Het optreden van een verstoring van het zuur-base evenwicht werd daarbij als uitkomstparameter gehanteerd bij patiënten met en zonder prenatale diagnose.

Eerdere studies hebben een lagere mortaliteit aangetoond bij een prenatale diagnose van een aantal goed omschreven diagnoses. Ons onderzoek heeft zich specifiek gericht op de preoperatieve conditie van een brede range van patiënten met aangeboren hartafwijkingen, waarbij werd uitgegaan van de slechtste preoperatieve waarden. In dit onderzoek werd een significant verschil in het optreden van ernstige acidose gevonden in het voordeel van patiënten met een prenatale diagnose. Zowel het preoperatieve base excess als de preoperatieve pH was significant lager in de groep waarbij de diagnose pas na de geboorte werd gesteld. In dit onderzoek was het gehele spectrum van ernstige aangeboren hartafwijkingen vertegenwoordigd. De resultaten wijzen erop dat een prenatale diagnose en aansluitend anticiperend neonataal ingrijpen ervoor kunnen zorgen dat het zuur-base evenwicht gestabiliseerd wordt en een ernstige verzuring voorkomen wordt.

De patiënten werden tevens onderverdeeld in groepen met al dan niet ductus-afhankelijke aandoeningen. Bij de groep afwijkingen, waarbij de circulatie afhankelijk was van het persisteren van de ductus Botalli, werden significante verschillen in base excess en pH gevonden in het voordeel van de prenataal gediagnosticeerde groep, terwijl bij patiënten met niet-ductus-afhankelijke aandoeningen alleen de base excess significant verschilde. Deze resultaten suggereren dat vooral de onmiddellijke toediening van Prostaglandine E1 (PGE1) in de ductus-afhankelijke groep een positief effect heeft op het voorkomen van metabole acidose. Daarnaast tonen de resultaten in de niet-ductus-afhankelijke groep dat ook bij patiënten die niet gebaat zijn bij een PGE1 behandeling, de snelle en goed gecoördineerde start van de juiste zorg een positieve invloed heeft.

Concluderend tonen de resultaten beschreven in hoofdstuk 2 een positieve invloed van prenatale diagnostiek van aangeboren hartafwijkingen op het voorkomen van ernstige acidose tijdens de preoperatieve periode. Het is te verwachten dat prenatale diagnostiek en de daarbij behorende handhaving van het zuur-base evenwicht op de lange termijn tot een betere uitkomst van deze kwetsbare patiëntenpopulatie zullen leiden met vooral een afname van de incidentie van hersenbeschadiging als gevolg.

In **hoofdstuk 3** wordt een deel van de patiëntenpopulatie uit hoofdstuk 2 opnieuw onderzocht en wordt het optreden van lactaatacidose verder uitgediept. Aangezien lactaatmetingen alleen in de Nederlandse populatie als standaard verricht werden, werden de twee Amerikaanse populaties uit het vorige hoofdstuk niet in deze studie betrokken. Er werden 209 patiënten geïncludeerd, die in de neonatale periode chirurgie nodig hadden voor hun aangeboren hartafwijking. De slechtste preoperatieve lactaatwaarden waren in de groep met een prenatale diagnose aanmerkelijk minder ernstig dan in de groep zonder prenatale diagnose, respectievelijk 3.05 ± 0.35 en 6.08 ± 0.45 mmol/L (P<0.001). De verschillen tussen beide groepen voor wat betreft base excess en pH waren niet significant. De preoperatieve lactaatwaarden waren gemiddeld 21.5 uur na opname weer normaal, terwijl dit bij de pH al na 5.3 uur en bij het base excess na 0.4 uur het geval was. Een slechtste preoperatieve lactaatwaarde van meer dan 7.5 mmol/L kwam voor bij 22% van de patiënten bij wie de diagnose na de geboorte gesteld was en bij geen van de patiënten met een prenatale diagnose (P=0.026). Extreme lactaatwaarden (>7.5 mmol/L) zijn gecorreleerd met hersenschade, neurologische complicaties en ontwikkelingsachterstand.

Titratie van bicarbonaat normaliseert vrijwel onmiddellijk de waarden van base excess en pH. Het duurt veel langer voordat de waarden van lactaat gecorrigeerd zijn. De ernst van de hypoxie en de daaruit voortkomende acidose worden dan ook het beste weergegeven door bepaling van het lactaatgehalte. Lactaatwaarden weerspiegelen de doorgemaakte hypoxie en hypoperfusie van het weefsel en hebben een grotere prognostische betekenis met betrekking tot mortaliteit en morbiditeit dan pH en base excess. De studie, die in dit hoofdstuk beschreven wordt, toont aan dat een prenatale diagnose mogelijkheden biedt om patiënten met een ernstige congenitale hartafwijking zodanig te stabiliseren dat een lactaatacidose in de preoperatieve periode voorkomen wordt. Door de onmiddellijke start van de benodigde therapie kan hierdoor mogelijk neurologische schade beperkt worden.

Aangezien de operatiemortaliteit van veel aangeboren hartaandoeningen tegenwoordig laag is, is de aandacht langzaam verschoven van korte termijn naar lange termijn resultaten, zoals het al dan niet optreden van hersenbeschadiging of van een ontwikkelingsachterstand bij kinderen met een aangeboren hartafwijking. Daarom wordt in **hoofdstuk 4** de relatie onderzocht tussen prenatale diagnostiek, preoperatieve parameters van acidose en het optreden van een ontwikkelingsachterstand op latere leeftijd. In deze studie werden 117 patiënten geïncludeerd die in de neonatale periode

chirurgie nodig hadden voor hun aangeboren hartafwijking. Vijftien van deze patiënten (13%) waren reeds prenataal gediagnosticeerd, terwijl in 102 gevallen (87%) de diagnose pas na de geboorte gesteld werd. Van al deze patiënten werden de preoperatieve waarden van lactaat, base excess en pH verzameld en werd onderzocht of er een samenhang was met het optreden van een ontwikkelingsachterstand op de leeftijd van 2 tot 8 jaar. Retrospectieve gegevens werden geëxtrapoleerd naar het Van Wiechen ontwikkelingsschema. Een ontwikkelingsachterstand werd in deze studie gedefinieerd als een achterstand in ontwikkeling van tenminste 10% op de P^{90} volgens het Van Wiechen ontwikkelingsschema. Door gebruik te maken van de verschillende parameters voor acidose werden de patiënten in groepen onderverdeeld. Met behulp van Receiver Operating Characteristic curves werden de afkapwaarden voor lactaat, base excess en pH gevonden met de beste combinatie van sensitiviteit en specificiteit.
De preoperatieve pH en base excess waren niet gerelateerd aan het optreden van een ontwikkelingsachterstand. Preoperatieve lactaatwaarden boven 6.1 mmol/L leidden daarentegen significant vaker tot een ontwikkelingsachterstand op latere leeftijd. Van de patiënten met een preoperatief lactaat boven 6.1 mmol/L kreeg op kinderleeftijd 41% te maken met een ontwikkelingsachterstand ten opzichte van 15% bij de groep met een lactaat onder 6.1 mmol/L (P=0.03; OR=3.88). In de groep waarbij de diagnose voor de geboorte werd gesteld, ontstond in 13% van de gevallen een ontwikkelingsachterstand in vergelijking met 25% in de groep waarbij pas na de geboorte de diagnose gesteld werd (P=0.50).

Concluderend was alleen een hoog lactaatgehalte gecorreleerd met een significant hogere kans op het ontstaan van een ontwikkelingsachterstand. Dat lactaat een betere voorspellende waarde heeft dan pH en base excess kan verklaard worden door het feit dat de pH snel en gemakkelijk door titratie van bicarbonaat gecorrigeerd kan worden en dat base excess behalve van de mate van verzuring ook van de Pco_2 afhankelijk is, waardoor mogelijk al aanwezige verzuring versterkt en overdreven wordt. Lactaat, daarentegen, is het eindproduct van de anaërobe verbranding en daarmee een goede parameter van doorgemaakte hypoxie.

In de hoofdstukken 2 en 3 is aangetoond dat het voor de geboorte vaststellen van een aangeboren hartafwijking leidt tot het voorkomen van verstoringen van het zuur-base evenwicht na de geboorte. In hoofdstuk 4 wordt de invloed van hoge lactaatwaarden op het ontstaan van een ontwikkelingsachterstand op latere leeftijd aangetoond. Daarmee is een gunstig effect van prenatale diagnostiek van aangeboren hartafwijkingen op het ontstaan van een ontwikkelingsachterstand aannemelijk gemaakt.

In **hoofdstuk 5** wordt de behandelingsstrategie bij een prenataal vastgesteld hypoplastisch linker hart syndroom (HLHS) beschreven. Deze afwijking wordt gekarakteriseerd door een ernstige onderontwikkeling van het linkerventrikel- en aortasysteem. Met een geschatte incidentie van 1 tot 4 per 10.000 levendgeborenen, omvat het HLHS 7 tot 8 procent van alle aangeboren hartafwijkingen en is het de meest voorkomende oorzaak van sterfte als gevolg van hartziekte in het eerste levensjaar. Het HLHS is door middel van echoscopie goed te herkennen in de eerste helft van de zwangerschap (<20 weken). Het is een van de meest ernstige vormen van hartafwijkingen die prenataal gediagnosticeerd kunnen worden.

In dit onderzoek beschrijven wij de ervaring met het prenataal vastgestelde HLHS bij patiënten die behandeld zijn in het Wilhelmina Kinderziekenhuis over een tijdsperiode van 13 jaar en vergelijken wij de verschillende behandelstrategieën met die van kinderhartcentra in het Verenigd Koningrijk (VK) en de Verenigde Staten (VS).

Het percentage kinderen, bij wie gekozen werd voor operatief ingrijpen ('intention-to-treat') bedroeg in onze studie 34 procent en dat kwam goed overeen met dat van een onderzoek in het VK (36%). De keuze voor zwangerschapsafbreking verschilde slechts in geringe mate tussen onze populatie en die van het VK (50% en 60% respectievelijk), terwijl in onze populatie vaker sprake was van een abstinerend beleid na de geboorte (16% en 3,5%). De behandelingsstrategie in het Amerikaanse onderzoek was echter aanzienlijk anders: in 67 procent van de gevallen werd daar gekozen voor een chirurgische behandeling, in 13 procent voor zwangerschapsafbreking en in 20 procent voor een abstinerend beleid.

Vroegtijdige diagnose van het HLHS schept dus niet alleen de mogelijkheid tot het verlenen van optimale perinatale zorg om de pasgeborene in de preoperatieve periode in goede conditie te houden, maar verschaft ook tijd voor advisering en begeleiding van de ouders zonder dat de medische en emotionele aspecten tijdens de acute neonatale situatie een goede beslissing in de weg staan. De ouders in onze populatie kozen in een minderheid voor een postnataal chirurgisch beleid. De verschillende benadering van deze ernstige hartafwijking kan mogelijk toegeschreven worden aan verschillen in sociale of religieuze gevoelens over het omgaan met deze aandoening, maar ook aan een andere manier van informeren en adviseren van de ouders. Blijkbaar leggen de ouders en artsen in Europa momenteel meer de nadruk op de slechte lange termijn prognose van deze kinderen en zien daarom vaker af van een operatieve behandeling. Dit kan in de toekomst

veranderen aangezien de overlevingskansen na de chirurgische 'Norwood' procedure lijken te verbeteren, hoewel de lange termijn neurologische prognose nog zeer twijfelachtig blijft.

In **hoofdstuk 6** wordt de ervaring met de prenataal gediagnosticeerde Ebstein's malformatie (EM) beschreven en worden enkele aspecten van deze aandoening nader toegelicht. De Ebstein's malformatie is een dysplastische afwijking van de tricuspidalis klep (TK), die gekenmerkt wordt door een apicale verplaatsing van de proximale aanhechting van de achterste en septale klepbladen. Naast de Ebstein's malformatie is er nog een andere – en minder ernstige – vorm van primaire dysplasie, waarbij de dysplastische afwijking van de tricuspidalis klep niet gepaard gaat met een apicale verplaatsing.

Wij beschrijven vier patiënten bij wie de Ebstein's malformatie prenataal in het Wilhelmina Kinderziekenhuis vastgesteld werd. Van deze vier kinderen stierven er twee intra-uterien, kozen de ouders in een casus voor een abstinerend beleid en is een kind 9 jaar na operatieve interventie in leven. Wij concluderen op basis van onze gegevens en van die van de literatuur dat de Ebstein's malformatie in de foetale periode een zeer ernstige en vaak letale hartafwijking is. Presentatie in utero gaat vaak gepaard met de aanwezigheid van longhypoplasie en daarom ook met een slechtere prognose. Indien de patiënt echter de cruciale neonatale periode overleeft en longcomplicaties vermeden kunnen worden, verbetert de prognose voor de pasgeborene aanzienlijk. Deze is dan zelfs te vergelijken met de prognose van kinderen en volwassenen, bij wie de aandoening op latere leeftijd werd vastgesteld.

Wanneer deze aandoening prenataal wordt vastgesteld, dan mag, bij het informeren en adviseren van ouders, het advies niet gebaseerd zijn op het beloop zoals we dat kennen bij oudere patiënten, maar dient het grote risico op sterfte in utero en in de neonatale periode aan bod te komen. Aangezien slechts enkele patiënten met een prenatale diagnose van Ebstein's malformatie de perinatale periode overleven, moet ouders duidelijk gemaakt worden dat chirurgische behandeling of vervanging van de tricuspidalisklep alleen aangeboden kan worden aan oudere kinderen die de risicovolle neonatale periode overleven. In tegenstelling tot veel andere structurele hartafwijkingen, leidt prenatale diagnostiek van Ebstein's malformatie helaas niet tot een betere overleving.

In **hoofdstuk 7** is bij de Utrechtse patiëntenpopulatie bij wie prenataal een aangeboren hartafwijking werd vastgesteld, gekeken naar de

behandelingsmodaliteiten en de uiteindelijke uitkomst. Deze populatie is vervolgens vergeleken met het totale aantal kinderen dat in de neonatale periode geopereerd werd in verband met een aangeboren hartafwijking. De bijdrage van prenatale diagnostiek op het verloop van de aandoening en op het tijdig chirurgisch aanbieden van de patiënten werd daarmee geïnventariseerd.

Honderdenzeventig patiënten met een prenataal vastgestelde aangeboren hartafwijking werden geïncludeerd. Bij 23 van hen eindigde de zwangerschap in een intra-uteriene vruchtdood en in 56 gevallen werd door de ouders besloten de zwangerschap af te laten breken. Meer dan de helft van de kinderen (n=91) werd levend geboren. Bij deze kinderen werd in 29 gevallen voor een abstinerend beleid gekozen en werden 24 patiënten in de neonatale periode geopereerd. Bij de overige 38 patiënten hoefde niet chirurgisch ingegrepen te worden. In dezelfde periode werden in totaal 191 patiënten in de neonatale periode geopereerd aan een aangeboren hartafwijking. Bij slechts 24 van hen (13%) was dus sprake van een diagnose voor de geboorte.

Helaas is er derhalve sprake van een 'mismatch' tussen de pogingen om bij zoveel mogelijk patiënten de diagnose voor de geboorte te stellen en het percentage prenataal gediagnosticeerde patiënten dat na de geboorte een operatie behoefde. Bij verreweg de meeste patiënten die geopereerd werden was de diagnose pas na de geboorte gesteld, terwijl bij een groot aantal van hen prenataal wel echoscopisch onderzoek was verricht. Doorgaans was hierbij de hartafwijking niet onderkend, terwijl deze in veel gevallen toch goed zichtbaar geweest moet zijn op het vierkamerbeeld. Eerder is reeds gewezen op de voordelen van prenatale diagnostiek van hartafwijkingen. Een grotere nadruk op eventuele cardiale problematiek van de foetus lijkt bij de opleiding van echoscopisten en gynaecologen dan ook gewenst om de grote discrepantie tussen de potentie van prenatale echoscopie van aangeboren hartafwijkingen en de huidige praktijk in Nederland te verkleinen.

In **hoofdstuk 8** wordt de betekenis van prenatale diagnostiek op het verloop van hartritmestoornissen geïllustreerd aan de hand van een specifieke ritmestoornis, de boezemflutter. Deze foetale hartritmestoornis komt voor bij ongeveer 0,2 procent van alle zwangerschappen. De frequentie van de atria (boezems) bedraagt bij deze aandoening meer dan 250 slagen/min, met een vast of variabel atrioventriculair (AV) blok, resulterend in een wisselende respons van de kamers.

In een multi-center studie evalueerden wij de behandeling van 44 kinderen bij wie de diagnose voor de geboorte gesteld was. Aangezien de behandeling en uitkomst van de boezemflutter sterk beïnvloed worden door het al dan niet aanwezig zijn van foetale hydrops, werd de studiepopulatie onderverdeeld in een hydropische (n=20) en een nonhydropische (n=24) groep. Bij 35 patiënten, waarbij werd getracht het hartritme door pharmacotherapeutisch ingrijpen te corrigeren, blijkt de conversie-ratio naar een normaal sinus ritme beter te zijn voor de nonhydropische (n=16/18; 89%) dan voor de hydropische groep (n=11/17; 65%). Ondanks zorgvuldige behandeling, vond zowel in de hydropische groep (24%) als in de nonhydropische groep (11%) een terugval in de ritmestoornis plaats rond de partus.
Drie van de hydropische kinderen overleden in de perinatale periode terwijl bij vier sprake was van ernstige neurologische morbiditeit (hypoxisch-ischemische hersenlaesie bij drie kinderen en hemorrhagische hersenlaesie bij een pasgeborene).

Dit onderzoek toont aan dat hydropische patiënten moeilijker te behandelen zijn dan patiënten zonder tekenen van hydrops foetalis. Prenatale pharmacotherapeutische interventie is vooral van belang om foetale hydrops te voorkomen. Besluit tot deze interventie is echter ook afhankelijk van factoren als zwangerschapsduur, foetale longrijpheid, de aanwezigheid van hydrops foetalis of andere structurele hartafwijkingen en (mogelijke) maternale en/of foetale bijwerkingen van anti-arrhythmica.

In dit retrospectieve onderzoek was digoxine het medicament van eerste keus. Hoewel digoxine bewezen effectief is bij de behandeling van deze foetale ritmestoornis, heeft de noodzaak van het verkrijgen van hoge, doorgaans subtoxische bloedspiegels bij de moeder om een therapeutisch effect bij de foetus te behalen, ons doen besluiten een ander medicament als eerste keus aan te raden. Dit is mede ingegeven door het feit dat digoxine in aanwezigheid van hydrops slechts langzaam en in beperkte mate de placenta passeert. Onze huidige eerste keus is sotalol. Dit is een veilig en effectief, niet-cardioselectief anti-beta-adrenergicum met klasse III anti-aritmische eigenschappen. Tot dusverre zagen wij tijdens het gebruik van sotalol bij acht patiënten geen terugkeer van de boezemflutter vóór of bij de geboorte. Digoxine wordt nog wel gebruikt als middel van tweede keus, mede vanwege het positief inotropisch effect van dit middel op het niet optimaal functionerende foetale hart.

Naar onze mening draagt tijdige prenatale diagnostiek en behandeling van deze hartritmestoornis bij tot preventie van foetale hydrops en daarmee van neurologische schade en intra-uteriene sterfte. Net als bij de

structurele hartafwijkingen hebben foetussen met boezemflutter bij de geboorte baat bij de mogelijkheid van directe interventie om het sinusritme te herstellen en daarmee hersenschade of sterfte te voorkomen.

Moederlijke diabetes en aangeboren hartafwijkingen

Zwangeren met diabetes vormen een grote verwijspopulatie voor prenatale diagnostiek van hartafwijkingen. Daarom hebben wij de invloed van deze metabole ziekte op zowel de morfologische als functionele ontwikkeling van het hart bestudeerd. In **hoofdstuk 9** beschrijven we een multi-center studie waarin we de frequentie en het spectrum van aangeboren hartafwijkingen onderzochten bij kinderen van vrouwen met type-1 (insuline afhankelijke) diabetes mellitus. Dit werd onderzocht in een Amerikaanse en twee Nederlandse populaties. Deze data werden gecombineerd met gegevens uit de literatuur. De gecombineerde gegevens werden vergeleken met de incidentie en het patroon van aangeboren hartafwijkingen bij nakomelingen van een ongeselecteerde populatie vrouwen uit de EUROCAT registratie in Noord-Nederland.

Zowel in onze studiepopulatie als in de literatuur over diabetes en zwangerschap, bleek dat een kwart van alle afwijkingen zijn oorsprong had in de conotruncale (CT) regio: transpositie van de grote vaten (TGV) vormde 49% van alle CT afwijkingen, gevolgd door tetralogie van Fallot (TOF; 25%), persisterende truncus arteriosus (PTA; 15%) en double-outlet right ventricle (DORV; 2,6%). Deze afwijkingen kwamen veel vaker voor dan in de normale populatie (EUROCAT). In geval van een hartafwijking was bij onze studiepopulatie het HbA1c – als maat van de bloedglucoseregulatie in de voorafgaande weken - in het eerste trimester significant hoger dan dat bij de overige zwangeren met diabetes.

Dit onderzoek toont een hoge incidentie van complexe hartafwijkingen van lateraliteit en looping en van conotruncale oorsprong bij kinderen van vrouwen met type-1 diabetes. De hoge incidentie van conotruncale afwijkingen suggereert een sterk teratogeen effect tijdens de eerste weken van de zwangerschap. Deze afwijkingen zijn voor een pulmonale en systemische circulatie doorgaans afhankelijk van de ductus Botalli, en daardoor is directe instelling van prostaglandine medicatie en aansluitend operatief ingrijpen vaak noodzakelijk.

De Nederlandse gegevens uit dit onderzoek tonen ook dat bij slechts

gering verhoogde HbA1c waarden, de incidentie van aangeboren hartafwijkingen reeds toeneemt. Bijna-normale HbA1c waarden zijn blijkbaar niet goed genoeg. Dit wijst er op dat de bloedsuikerregulatie rondom de conceptie nog verder verbeterd moet worden. Prenatale diagnostiek blijft echter van belang.

In **hoofdstuk 10** wordt de invloed van type-1 diabetes op de foetale circulatie bestudeerd. Bij 17 foetussen zonder structurele hartafwijkingen werden de stroomsnelheid en het volume van de bloedstroom door de mitralis en tricuspidalis openingen bepaald. De gegevens werden vergeleken met die van een controlegroep.

Bij de zwangerschappen gecompliceerd door diabetes, was zowel de gemiddelde en hoogste stroomsnelheid over de AV-kleppen, als de gecombineerde ventriculaire 'output' significant verhoogd. Deze veranderde foetale circulatie kan een compensatie zijn voor de aanwezigheid van een toestand van chronische hypoxie, die wordt veroorzaakt door de relatieve immaturiteit van de placenta, waarbij de diffusie-afstand tussen het maternale en foetale bloed groter is. Bij de controlegroep daalde de verhouding tussen de 'output' van de rechter harthelft en de linker harthelft in het verloop van de zwangerschap ten gunste van links; bij de foetussen van moeders met diabetes vond deze verandering niet plaats en bleef de verhouding constant. Dit duidt erop dat de rechter harthelft bij deze laatste groep tot aan het eind van de zwangerschap een dominante rol blijft spelen. De verklaring voor deze rechtsdominantie is tweeledig. Enerzijds is er een verhoogde bloedstroom in de richting van de immature placenta noodzakelijk, waarvoor de rechter harthelft verantwoordelijk is en anderzijds is het hoofd van kinderen van moeders met diabetes relatief klein ten opzichte van het lichaam.

Concluderend kan gesteld worden dat de foetale circulatie bij moederlijke type-1 diabetes aanzienlijk verschilt van die van ongecompliceerde zwangerschappen. De veranderingen bij diabetes berusten mogelijk op een compensatiemechanisme en op andere anatomische verhoudingen.

Als conclusie van dit proefschrift menen wij te kunnen stellen dat prenatale diagnostiek bij zowel morfologische als functionele hartafwijkingen een positieve invloed kan hebben op de behandeling en de uiteindelijke uitkomst van deze zwangerschappen. Het belangrijkste positieve effect van een prenatale diagnose betreft anticipatie op postnatale opvang: een bevalling in een ziekenhuis met een kinderhartcentrum, dat gespecialiseerd is in de behandeling van dit soort patiëntjes, waardoor onmiddellijk

met de benodigde therapie gestart kan worden. Dit leidt in het algemeen tot een betere preoperatieve conditie en in dit proefschrift werd ook een betere lange termijn ontwikkeling gevonden.

In dit proefschrift werden twee extreme vormen van aangeboren hartafwijkingen beschreven, namelijk het hypoplastisch linker hartsyndroom en Ebstein's malformatie. In beide gevallen leidt prenatale diagnostiek in ons onderzoek niet tot een betere uitkomst, aangezien de prognose van de hartafwijking momenteel te slecht is.

Tenslotte tonen de gegevens van zwangeren met type-1 diabetes, dat deze ziekte, zelfs wanneer deze goed gecontroleerd is, invloed heeft op zowel de foetale cardiale anatomie als op de foetale circulatie. De hoge incidentie hartafwijkingen bij deze groep blijkt vooral in de conotruncale regio gelokaliseerd te zijn. De circulatieveranderingen bij foetussen met een normale cardiale anatomie treden later in de zwangerschap op en lijken een compensatie te zijn om voldoende 'cardiac output' te waarborgen.

Adviezen naar aanleiding van onze bevindingen:

1 Bij het prenataal echografisch onderzoek van de foetus verdient het aanbeveling het ritme en het vierkamerbeeld van het hart te evalueren teneinde ernstige en levensbedreigende pathologie uit te sluiten.

2 Bij twijfel omtrent de aanwezigheid van een normaal hartritme of vierkamerbeeld dient de patiënt naar een derdelijns diagnostisch centrum verwezen te worden.

3 In aanwezigheid van een afwijkend hartritme of afwijkende intracardiale anatomie verdient het aanbeveling de patiënt in een centrum te laten bevallen waar directe cardiale evaluatie en behandelingsmogelijkheden aanwezig zijn.

Chapter 13

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Chapter 14

Curriculum vitae

The authors of this thesis are *Lukas Aleksander Lisowski* and *Paulus Menno Verheijen*.

Lukas was born on June 5th, 1976, in Leicester in the United Kingdom. After completion of secondary school at the Bernardinus College in Heerlen in 1994, he continued his education at the Faculty of Medicine at the University of Utrecht. In 1998 he started his scientific research at the department of pediatric cardiology at the University Medical Center Utrecht which he continued in the United States at the University of Maryland Medical System in Baltimore and Yale University in New Haven. In 1999 he went on a world trip to Australia, New Zealand and Thailand before starting his clinical internships in 2000. His clinical elective was performed at the department of orthopedics at the Academic Medical Center in Amsterdam. During his clinical internships he continued his research as a PhD study at the department of obstetrics, gynecology and neonatology. This study and the previous scientific work lead to the research articles covered in this thesis, for which he received the Talma Eykman Award in 2002. He obtained his medical degree in 2002. Because of his interest in the field of orthopedics he started a multi-center study supported by Ortomed on the treatment of anteromedial osteoartritis by the Oxford Phase 3 unicompartmental prosthesis implanted by a minimally invasive technique. In 2003 he will start his residency in general surgery as part of his training in orthopedic surgery.

Paul was born on November 29th 1974 in Wageningen, the Netherlands. From 1987 to 1993 he attended the Stedelijk Gymnasium Breda, where he obtained his diploma in 1993. After a detour of studying natural sciences and half a year of traveling through Australia and South-East Asia, he commenced his medical training at the University of Utrecht in 1994. In 1998 he started his research on prenatal diagnosis of congenital heart disease at the pediatric cardiology department of the Wilhelmina Children's Hospital. This research was continued at the University of Maryland Medical System in Baltimore and Yale University in New Haven, United States. After another half year of traveling through South-East Asia, he started his clinical internships, during which the research was continued at the department of obstetrics, gynecology and neonatology in order to complete this thesis. After a clinical elective at the department of thoracic surgery he obtained his medical degree in 2001 and started working as a resident in surgery at the Diakonessenhuis in Utrecht and Zeist. In 2002 he received the Talma Eykman Award for his research on prenatal diagnosis of cardiac pathology.