Follow-up studies in *prenatal medicine*

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Overige leden:	*Prof. Dr. M.H. Breuning* *Prof. Dr. A.A. Kaptein*

Blackbird singing in the dead of night
Take these broken wings and learn to fly
All your life
You were only waiting for this moment to arise.

Blackbird singing in the dead of night
Take these sunken eyes and learn to see
All your life
You were only waiting for this moment to be free.

Blackbird fly Blackbird fly
Into the light of the dark black night.

(Lennon / McCartney)

Aan Lex

Contents

CHAPTER 1

General introduction

The fetus in prenatal medicine

According to Medline definitions, a conceptus is an embryo until a postconceptional age of 8 weeks (or a gestational age of 10 weeks) and will then be a fetus until birth. If born viable, the person then becomes an infant. The fetus is a unique patient for several reasons. First, there is a unique relationship between the mother and her unborn child. Although the fetus has his own rights, he or she can only be treated via the mother. Therefore the purported rights of the fetus can never take precedence over that of the mother.[1] Second, despite advances in medical care there is striking little knowledge about fetal live. Questions such as does the fetus experience pain, does it have a memory, are still unanswered. Third, the accessibility of the fetus as a patient is limited. Finally, the ill fetus often displays a paucity of symptoms.

The introduction of real-time ultrasound and molecular biology in medicine, in the second part of the last century, has ushered a new era in prenatal medicine. Both diagnostic and therapeutic tools became available. Fetal medicine has evolved from interventions aimed at short term care in normal developing individuals towards interventions aimed at improving the starting-point for long-term postnatal therapy.

When asking about the prognosis of their fetus, parents are thinking of a future that lays twenty, thirty years ahead of us, and are wishing their children to be independent individuals having their own family. They know but not always realize that prenatal diagnosis may lead in some cases to the initiation of therapy and in other cases to the abstinence of further diagnostic or therapeutic interventions or even to feticide or termination of pregnancy. In order to provide effective counseling, centers for fetal medicine have an obligation to include long-term follow-up of the children that were the subject of fetal interventions for diagnosis and/or therapy. After all, there is a danger of overenthusiastic doctors that value every improvement that fetal medicine does accomplish and forget about the parents that have to care for a handicapped child. Such "dedicated" care will greatly influence the rest of their lives and that of other members of their family.

Brief history of prenatal medicine

In 1822, Jaques-Alexandre Lejumeau de Kergaradec was the first to describe the detection of the fetal heart beat by auscultation, in 1906 Cremer first described the fetal electrocardiogram from the abdominal surface of a pregnant woman.[2,3] By 1920, the first successful fetal operations on guinea pig fetuses had been performed. In the 1930s and 1940s, experimental fetal observations were done by performing operations on fetal lambs while still in utero. This experimental fetal

observations changed in the 1950s into studying the causality of fetal malformations (i.e. by interrupting the mesenteric blood supply, intestinal atresia occurred) and in the 1960s and 1970s into performing fetal surgery to simulate a variety of human congenital anomalies (congenital diaphragmatic hernia in the lamb, congenital hydronephrosis in the rabbit and lamb).[4-6] In the 1950s, Smyth described invasive electrocardiographic monitoring with an intra-amniotic electrode.[7] From the 1960s onward amniocentesis, fetoscopy, and ultrasonography, and consequently the possibility of examining the fetus clinically, genetically and biochemically were introduced. Analysis of the contents of amniotic fluid made possible the prenatal diagnosis of many inherited metabolic and chromosomal disorders and permitted assessment of fetal pulmonary maturity and the severity of fetal hemolytic disease. The era of fetal medicine had really begun.

Second trimester amniocentesis is traditionally performed around 16 weeks' gestation. Observational data from the 1970s suggested that, at this gestation, relatively large amounts of amniotic fluid (up to 20 ml) could be aspirated without significant technical difficulties. This amount of amniotic fluid was needed to yield a sufficient number of viable fetal cells to minimize the risk of laboratory failure. A major disadvantage of second trimester amniocentesis is that a final result is usually available only after 18 weeks' gestation. Such a long waiting period for a diagnosis can be very distressing for couples. Alternatively, earlier options include chorionic villus sampling and early amniocentesis. Chorionic villus sampling was first introduced in 1975.[8] It involves aspiration of placental tissue rather than amniotic fluid. Ultrasound guided aspiration can be performed using either percutaneous transabdominal or the transvaginal/transcervical approach. Currently the choice of approach and the choice of instruments tend to be based on the operator's personal preference. There is an understandable desire to perform chorionic villus sampling as early as possible. Technically, this can be done successfully as early as 6 weeks' gestation. However, a few clusters of limb reduction defects have been reported following chorionic villus sampling with a trend toward an increased incidence of these defects when chorionic villus sampling was done before 9 weeks' gestation.[9-21] Although large epidemiological follow-up studies failed to confirm this association, most clinicians delay this procedure until after 10 weeks' gestation. Early amniocentesis (9-14 weeks' gestation), introduced in the late 1980s, is technically the same as a 'late' procedure except that less amniotic fluid is removed.[22] Ultrasound needle guidance is considered to be an essential part of the procedure because of the relatively small target area. The presence of two separate membranes (amnion and chorion) until 15 weeks' gestation creates an additional technical difficulty. Only the amniotic (inner) sac should be aspirated, because the outer sac does not contain sufficient numbers of living fetal cells.

The British Professor Ian Donald (1910-1987) was the pioneer for the

utilization of ultrasound in obstetrics. Before the discovery of ultrasound, X-ray was used for fetal diagnosis. Plain X-rays yielded little information.[23] The introduction of lipofphyl/hydrophyl radiopaque materials into the amniotic fluid (amniogram) facilitated intraperitoneal transfusions but was not suitable for fetal diagnosis.

In the Netherlands, obstetric ultrasound was first developed and introduced in the early 70s in the Leiden and Utrecht University Women's Hospitals. Important for fetal diagnosis and therapy was the introduction of real-time ultrasound in the early 1980s. A milestone in prenatale medicine was achieved by William Liley. He demonstrated that severe red cell immunization, infusion of red cells in the intra-peritoneal cavity of the fetus ameliorated severe hydrops.[24]

During the 1960s two clinical methods were developed to record fetal heartbeat pattern, one based on fetal electrocardiogram (internal registration) and the other based on ultrasound (external registration). In both methods, uterine contractions were recorded simultaneously. During the 1970s, the use of cardiotocography became common practice in Western labor wards. In 1961, Erich Saling introduced the concept of blood pH measurements to fetal scalp blood sampled during labor for fetal surveillance.[25] Three years later, Saling published normal values for fetal pH and blood gas during labor and at birth.[26] Blood pH is presently accepted by many as the biochemical gold standard in fetal monitoring during labor.

The advent of echocardiography, and especially M-mode and pulsed wave Doppler ushered the field of fetal arrhythmia detection and differentiation. Robinson and Shaw-Dunn detailed the use of M-mode in the evaluation of fetal arrhythmias during the early 1970s.[27] As ultrasound technology expanded to include two-dimensional and both spectral and color Doppler modes, additional echocardiographic techniques for the identification and differentiation of fetal arrhythmias were described.

The intravascular intrauterine fetal transfusion performed by the use of fetoscopy was introduced by Rodeck in 1981.[28] Daffos *et al.* described fetal bloodsampling by ultrasound-guided percutaneous cordocentesis.[29] This method was used also for fetal intravascular transfusions and later for administering medication by cordocentesis. In the Netherlands, intraperitoneal fetal transfusion guided by X-rays started in 1965, and sonographic-guided intravascular fetal transfusion started in 1987. In 1988, Nicolini first described fetal blood sampling from the intrahepatic portion of the umbilical vein in the fetus, as an alternative procedure in cases where cord needling was unsuccessful.[30]

By the 1980s, fetal surgeons were ready for the next step, which is the correction of fetal anatomic defects.[31,32]

Prenatal medicine at the Leiden University Hospital

Leiden is the national referral center for invasive fetal therapy (intravascular fetal transfusion of red cells or platelets, fetoscopy and laser treatment in complicated monochorionic twin pregnancies). In the recent years, however, indications for treatment have been expanded and now also include non-immune fetal hydrops (caused by hydrothorax, congenital cystic adenomatoid malformations of the lung, parvo B19 infections, tachyarrhythmia) and more experimental forms of fetal treatment. Clinical research at the LUMC include minimally invasive intrauterine treatment and fetal patho-physiology in case of anemia, alloimmune thrombocytopenia and twin-to-twin transfusion syndrome.

In 1965, the first intrauterine transfusion of red cells was given to the fetus intraperitoneally because of severe red cell immunization. In 1987 the first intrauterine intravascular transfusion of red cells for anemia in alloimmunized pregnancies was performed. Intravascular transfusion of platelets in the fetus with neonatal alloimmune thrombocytopenia (NAITP) was introduced in 1989. From 1994 onwards serial fetal platelet transfusions therapy was gradually replaced by the maternal administration of high dose immunoglobulins.[33] Severe fetal anemia induced by Parvovirus B19 infection was corrected by intravascular transfusion of red cells and platelets since 1997.

In 2000, the first fetoscopic lasercoagulation of the intraplacental anastomoses in twin to twin transfusion syndrome in monochorionic twins was performed in Leiden. Intrauterine fetal shunting for lower urinary tract obstruction or congenital cystic adenomatoid malformation (CCAM) was introduced in 2002.

Counselling and guiding the parents is an important part of fetal medicine. Parents should obtain information on risks and benefits of prenatal medicine and possible alternatives. The long-term prognosis of children treated antenatally is an important part of counseling. This thesis describes the follow-up studies after prenatal diagnosis and therapy. The aim of this research is to evaluate our management in order to generate data for realistic counselling of parents.

Outline of this thesis

We describe the results of 7 studies on the outcome of children after diagnostic or therapeutic interventions during fetal life.

Section A presents follow-up studies after prenatal diagnosis.
Chapter two provides an overview of invasive prenatal diagnosis in the Netherlands during the period 1991-2000 and analyses trends. In the Netherlands, invasive prenatal diagnostic procedures have to meet Section 2 of the Special Medical Procedures Act. That act requires that each licensed center provide an annual report following a standardized format. We combined and described the annual results from all 13 centers for invasive prenatal diagnosis, with particular emphasis on indications, abnormal results, number and type of invasive procedures and terminations of pregnancy.

Chapter three presents a semi-randomized controlled trial comparing transabdominal chorionic villus sampling with amniocentesis, both performed before 14 weeks of pregnancy. It is a follow-up study on fetal morbidity and mortality and infant morbidity. First trimester amniocentesis was introduced in the late 1980s because it was thought to combine the advantage of chorionic villus sampling, namely early diagnosis, with that of mid-trimester amniocentesis, namely accuracy and safety.

In **chapter four** the outcome of pregnancies with a prenatally diagnosed central nervous system malformation is presented. The aim of this study was to evaluate the accuracy of ultrasound examination in our center, to describe the outcome of these pregnancies, and to provide information for clinicians in counseling future parents. Central nervous system malformations were most frequently detected after 24 weeks' gestation. This was a consequence of the fact that prenatal ultrasound screening for abnormalities was not routinely performed in The Netherlands.

In **chapter five** we describe our follow-up study with neurodevelopmental assessment of children born with an umbilical artery blood pH < 7. Umbilical blood pH provides good means for retrospective evaluation of obstetric efforts in preserving fetal health during birth. Normal values at birth are above 7.09 (Saling 1961) and less than 1% of children are born with a blood pH below 7.

Section B presents follow-up studies after prenatal therapy.

Chapter six describes the long-term neurodevelopmental outcome in children after twin-to-twin transfusion syndrome. Monochorionic twinning predisposes to cerebral damage due to complications caused by twin-to-twin transfusion.

Twin-to-twin transfusion syndrome occurs in approximately 15% of monochorionic pregnancies and results from shunting of blood from one twin, the donor, to the other twin, the recipient, through placental vascular anastomoses. Untreated, twin-to-twin transfusion syndrome is associated with high perinatal mortality and morbidity. Maternal and neonatal medical records of all twin-to-twin transfusion syndrome cases admitted to our center between 1990 and 1998 were reviewed. Amniodrainage had been performed in more than half of these pregnancies. Neurological and mental development at school age was assessed during a home visit in all twin-to-twin transfusion syndrome-survivors.

Chapter seven aims at evaluating long-term neurodevelopmental outcome and general health status after Parvovirus B19-induced fetal hydrops treated with intrauterine transfusion. We performed a detailed standardized general and neurological examination and age specific neurodevelopmental tests in the surviving children.

In **chapter eight** we describe the perinatal mortality and morbidity, as well as long-term neuropsychologic and cardiologic outcome of 44 fetuses with severe brady- or tachyarrhythmia. Fetal cardiac arrhythmias are diagnosed in at least 2% of pregnancies. In less than 10% of cases it concerns prolonged or incessant episodes of brady- or tachycardia. These prolonged periods of tachyarrhythmia or continuous bradyarrhythmia can lead to congestive heart failure, non-immune hydrops, and fetal or neonatal death. Episodes of heart failure may lead to permanent damage, or not. We performed a detailed standardized general, cardiac and neurological examination and age specific neurodevelopmental tests in the surviving children.

Chapter nine presents a general discussion and reflection on future perspectives.

Chapter ten summarizes the results of the presented studies.

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CHAPTER 2

Prenatal diagnosis in the Netherlands, 1991-2000: Number of invasive procedures, indications, abnormal results, and terminations of pregnancy

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Abstract

Objective To provide an overview of invasive prenatal diagnosis in the Netherlands and to analyse trends.

Methods Annual results from all centers for invasive prenatal diagnosis in the Netherlands over the period 1991-2000 were combined and described, with particular emphasis on indications, abnormal results, type of invasive procedures, and terminations of pregnancy.

Results The percentage of invasive prenatal diagnosis increased from 5% of births in 1991 to 6% in 1996 and subsequently remained level. During the study period, the number of pregnant women aged 36 and older increased by 70%, but the number of procedures performed because of maternal age remained stable. The detection rate for abnormal results was 2 to 3 % for maternal age and rose from 9 to 13 % for other indications. Other trends during the studied time period included the relative decrease of cordocentesis (-82%) and chorionic villi biopsy (-18%) in favour of amniocentesis (+48%), and a strong decrease in the number of amniocentesis procedures for increased risk of neural tube defect. In 71% of cases with abnormal results, the pregnancy was terminated.

Conclusion There was a significant decrease in the percentage of pregnant women aged 36 or older who underwent invasive prenatal diagnosis without previous screening.

Introduction

In the Netherlands, Section 2 of the Special Medical Procedures Act limits the number of centers granted a permit to perform invasive prenatal diagnostic procedures. Only 13 centers are licensed to perform invasive prenatal diagnosis: the university centers Amsterdam (two centres), Groningen, Leiden, Maastricht, Nijmegen, Rotterdam, and Utrecht, as well as 5 non-university so-called satellite clinics (Arnhem, Dordrecht, Eindhoven, Enschede and Zwolle).
The Special Medical Procedures Act covers amniocentesis, chorionic villi biopsy (transabdominal and transcervical), and cordocentesis. These procedures are performed for chromosomal or DNA-analysis, for α-foetoproteine (AFP) measurement, or for metabolic testing. Indications for invasive prenatal diagnosis are listed in **Table 1**. The act also requires that each center provide an annual report following a standardized format.

Table 1. Indications for chromosomal and or DNA-analysis in the Netherlands (Special Medical Procedures Act).

- pregnant women who have reached the age of 36 years in the 18th week of gestation
- increased risk for neural tube defect
- one of the future parents is carrier of a chromosomal abnormality
- ultrasound suspicion of fetal abnormalities
- pregnant women who have delivered a fetus or child with a chromosomal abnormalitity after a gestational age of 16 weeks
- pregnant women who had a chromosomal abnormal fetus confirmed by prenatal genotyping in a previous pregnancy
- pregnant women with an increased risk on a autosomal dominant, autosomal recessive or X-chromosomal inherited disease
- pregnant women with an inherited mitochondrial abnormality
- after abnormal result of maternal serum screening
- pregnancy after Intracytoplasmic Sperm Injection (ICSI) procedure

The Dutch Working Party on Prenatal Diagnosis has collected data relating to invasive prenatal testing in the Netherlands since 1989. This paper summarises the results from the annual reports from 1991 to 2000.[1]

Methods

The 13 licensed centers in the Netherlands annually report the numbers of

performed procedures, indications, detected abnormalities, and the number of pregnancy terminations to the Working Party on Prenatal Diagnosis, using a standard form. The annual report committee of the Working Party checks the numbers for plausibility and consistency. By referring to the Central Bureau of Statistics for data on the total annual birth rate in the Netherlands, and the age of mothers at the time of birth, the committee is able to calculate the number of women aged 36 and older in the 18th week of pregnancy quite accurately. These annual reports do not mention amniocentesis and cordocentesis performed for non-genetic diagnostic procedures in cases of fetal alloimmune anemia, uncertainty about fetal lung maturity or infectious diseases, or for therapeutic reasons (amniondrainage, intra-uterine transfusion). Non-invasive screenings, such as maternal serum testing (triple test) and nuchal translucency measurement, are also not recorded. At the time of the study period, maternal serum screening and nuchal translucency measurement for Down syndrome risk assessment were not authorized in the Netherlands. The annual reports mention the numbers of cordocenteses, but not the indications and abnormal results.

After 1995, the reports provide more detail regarding the detected abnormalities, and also whether the pregnancy was terminated or not. In cases where a pregnancy was not terminated after an abnormal test result, the mother either chose to continue with the pregnancy or was not allowed to terminate the pregnancy because of advanced gestational age at the time of diagnosis. The number of pregnancy losses after an invasive procedure is not mentioned in the annual reports. In 1997, the term "other chromosomal abnormality" was defined more precisely in order to exclude some common variants, that may have been reported by some centers and not by others in the previous years. At the same time, the fetus was adopted as the base measure rather than the pregnant woman.

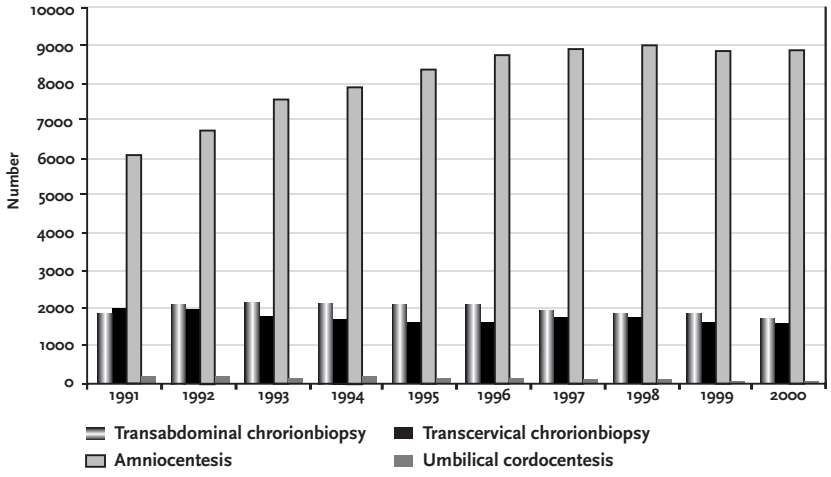
Chi-square linear-by-linear association (SPSS inc., Chicago, Illinois, USA) was used for trend analysis between the years 1991-2000.

Results

The mean annual number of invasive procedures was 11 839, with a minimum of 10.126 in 1991 and a maximum of 12 574 in 1997. This means that around 6% of the approximately 200.000 children born each year in the Netherlands during the study period underwent invasive prenatal diagnosis. **Figure 1** shows the annual number of amniocenteses, chorionic villi biopsies (transcervical and transabdominal), and cordocenteses. The number of amniocenteses increased from 6059 in 1991 to 8977 in 1998 (+ 48%), the number of chorionic villi biopsies decreased from 3985

in 1992 to 3257 in 2000 (-18%) and the number of cordocenteses decreased from 186 in 1991 to 33 in 2000 (-82%).The decrease in both chorionic villi biopsies and cordocentesis is statistically significant (p<0.001).

Figure 1. Overview of prenatal diagnostic procedures 1991-2000.



Maternal age was the indication for 72% of the amniocenteses and chorionic villi biopsies. The other indications for prenatal invasive testing are listed in **Table 2**. The total number of women aged 36 and older who underwent invasive prenatal testing increased during the study period from 7058 to 8878 **(Table 2)**, an increase of 25.8%. However, the number of pregnant women aged 36 and older (at the 18th week of gestation) increased far more during the study period, from 15.140 to 25.730 **(Figure 2)**, an increase of 69.9%.

Figure 2. Overview of prenatal diagnostic procedures 1991-2000.

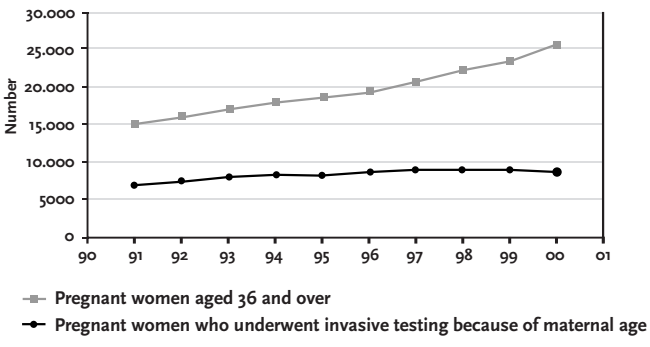


Table 2. Amniocentesis and Chorionic villi biopsy 1991-2000. Shown is the number (%) of women (1991-1996) and fetus (1997-2000)

Indication	Year 1991		1992		1993		1994		1995		1996		1997		1998		1999		2000		1991-2000	
Maternal age	7058	(71.0)	7692	(72.0)	8149	(71.2)	8444	(72.3)	8339	(69.2)	8751	(70.8)	9156	(73.3)	9118	(73.1)	8954	(73.3)	8878	(73.3)	84539	(72.0)
Increased risk for neural tube defect	1066	(10.7)	932	(8.7)	920	(8.0)	839	(7.2)	738	(6.1)	537	(4.3)	374	(3.0)	363	(2.9)	304	(2.5)	261	(2.2)	6334	(5.4)
Parent carrier of a chromosomal abnormality	139	(1.4)	145	(1.4)	144	(1.3)	144	(1.2)	139	(1.2)	169	(1.4)	159	(1.3)	168	(1.3)	179	(1.5)	164	(1.4)	1550	(1.3)
Ultrasound abnormality <24 weeks*	434	(4.4)	501	(4.7)	625	(5.5)	645	(5.5)	496	(4.1)	518	(4.2)	604	(4.8)	594	(4.8)	631	(5.2)	715	(5.9)	5763	(4.8)
Ultrasound abnormality >24 weeks*									344	(2.9)	378	(3.1)	270	(2.2)	302	(2.4)	307	(2.5)	354	(2.9)	1955	(2.6)
Previous child/fetus with a chromosomal abnormality	315	(3.2)	362	(3.4)	388	(3.4)	375	(3.2)	416	(3.4)	394	(3.2)	354	(2.8)	365	(2.9)	407	(3.3)	381	(3.1)	3757	(3.2)
DNA- examination	160	(1.6)	132	(1.2)	185	(1.6)	210	(1.8)	191	(1.6)	243	(2.0)	248	(2.0)	255	(2.0)	270	(2.2)	267	(2.2)	2161	(1.8)
Metabolic examination	62	(0.6)	55	(0.5)	32	(0.3)	17	(0.1)	36	(0.3)	32	(0.3)	48	(0.4)	48	(0.4)	28	(0.2)	27	(0.2)	385	(0.3)
Serum screening	187	(1.9)	202	(1.9)	282	(2.5)	383	(3.3)	740	(6.1)	796	(6.4)	606	(4.9)	619	(5.0)	574	(4.7)	537	(4.4)	4926	(4.2)
Other	519	(5.2)	656	(6.1)	720	(6.3)	619	(5.3)	604	(5.0)	537	(4.3)	671	(5.4)	647	(5.2)	556	(4.6)	531	(4.4)	6060	(5.2)
Total	9940		10677		11445		11676		12043		12355		12490		12479		12210		12115		117480	

Average percentage of multiple pregnancies in pregnant women who underwent prenatal testing is 3%.

*From 1991 to 1994 ultrasound abnormalities were not categorized in gestational age.

The percentage of pregnant women aged 36 and older who underwent an invasive prenatal test because of maternal age significantly (p<0.001) decreased from 46 to 34%. The percentage of procedures performed because of 'increased risk of neural tube defect' significantly (p<0.001) decreased during the study period from 10.7 to 2.2% **(Table 2)**. The percentage of procedures with the indication 'abnormal result at serum screening' rose from 1.9% in 1991 to 6.4% in 1996 and dropped to 4.4% in 2000. For the indication 'abnormalities on fetal ultrasound,' the percentage rose from 4.4 to 8.8%.

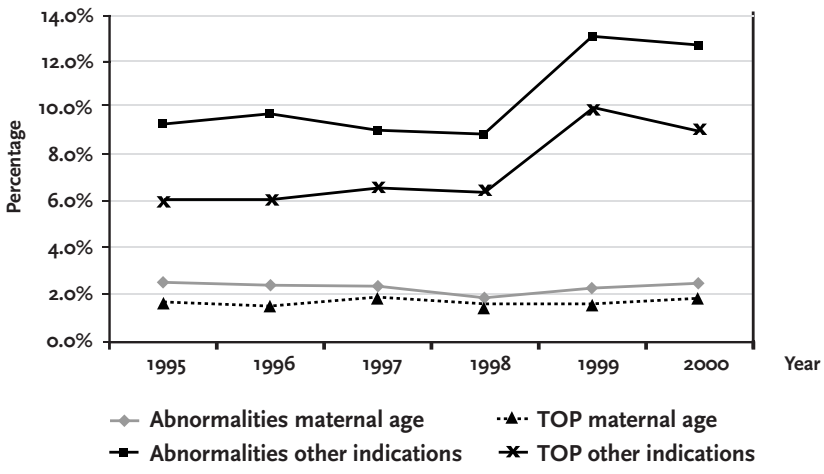
The average percentage of abnormal test results was 4.7%, increasing from 3.6% in 1991 to 5.4% in 2000. The total number of abnormalities detected as a result of invasive prenatal diagnostic procedures increased from 362 in 1991 to 638 in 2000. The number of abnormal test results and terminations of pregnancy during the 6 year period from 1995 to 2000 are listed in **Table 3**, according to the main indication for invasive prenatal testing. An average of 70.8% of the pregnancies with abnormal results was terminated **(Table 3)**.

Table 3. Abnormal results and termination of pregnancy at invasive prenatal testing, 1995-2000.

Indication	Procedure		Abnormal result		Termination of pregnancy	
	N	%	N	%	N	%
Maternal age	53 196	(72.2)	1259	(2.4)	923	(73.3)
Increased risk of neural tube defect	2577	(3.5)	37	(1.4)		
Parent carrier of a chromosomal abnormality	978	(1.3)	160	(16.4)		
Ultrasound abnormality <24 weeks	3558	(4.8)	990	(27.8)		
Ultrasound abnormality >24 weeks	1955	(2.7)	335	(17.1)		
Previous child/fetus with a chromosomal abnormality	2317	(3.1)	45	(1.9)	1522	(69.3)
DNA-examination	1474	(2.0)	379	(25.7)		
Metabolic examination	219	(0.3)	37	(16.9)		
Serum screening abnormal	3872	(5.3)	130	(3.4)		
Other	3546	(4.8)	82	(2.3)		
Total	73692		3454	(4.7)	2445	(70.8)

The percentages of abnormalities found as a result of invasive testing varied significantly according to indication, from 1.4% for 'increased risk of neural tube defect' and 2.4% for 'maternal age', to 25.7% for 'increased risk of DNA-abnormalities' and 27.8% for 'ultrasound abnormalities <24 weeks.' While the percentage of abnormal test results for the indication 'maternal age' remained fairly constant throughout the study period, it rose considerably for the other indications after 1998 **(Figure 3)**. The number of terminations of pregnancies because of fetal abnormality increased during the study period, but the percentage remained constant **(Figure 3)**.

Figure 3. Percentage abnormal test results at invasive prenatal testing 1995-2000, shown per indication



The number of different DNA abnormalities for which prenatal diagnostic procedures were performed increased from 41 in 1995 to 100 in 2000. The total number of DNA abnormalities that were detected also increased, from 55 in 1995 to 72 in 1999 **(Table 4)**. The most frequent DNA abnormalities were cystic fibrosis, fragile-X, myotonic dystrophy (Steinert), Huntington's disease, Duchenne muscular dystrophy, spinal muscular atrophy type 1 (Werdnig-Hoffmann) and adrenogenital syndrome. The most frequently diagnosed chromosomal abnormalities were trisomy 21, trisomy 18, triploidy, Turner's syndrome (45,X), and Klinefelter's syndrome (47,XXY) **(Table 4)**.

Table 4. Detected abnormalities and termination of pregnancy after invasive prenatal testing 1995-2000.

Diagnosis	Number of diagnosis; number of terminations of pregnancy (%) in the year						
	1995	1996	1997	1998	1999	2000	1995-2000
trisomy 21	156;137 (88)	149;127 (85)	165;145 (89)	166;148 (89)	164;149 (91)	189;162 (86)	989;868 (88)
trisomy 18	72;53 (74)	83;59 (71)	73;59 (81)	72;56 (78)	98;82 (84)	98;85 (87)	496;394 (80)
trisomy 13	18;13 (72)	17;13 (17)	29;23 (79)	26;21 (81)	26;23 (88)	29;25 (86)	145;118 (81)
45,X	37;22 (59)	23;15 (65)	33;22 (67)	28;23 (82)	46;35 (76)	48;33 (69)	215;150 (70)
47,XXX	5;1 (20)	8;0 (0)	14;5 (36)	13;6 (46)	11;3 (27)	3;3 (100)	54;18 (33)
47,XXY	6;5 (83)	25;9 (36)	16;7 (44)	11;2 (18)	17;9 (53)	16;5 (31)	91;37 (41)
47,XYY	4;0 (0)	4;2 (50)	3;0 (0)	6;0 (0)	6;1 (17)	3;1 (33)	26;4 (15)
Triploidy	11;4 (36)	14;11 (78)	32;23 (72)	15;12 (80)	24;20 (83)	14;14 (100)	110;84 (76)
DNA-abnormalities	55;49 (83)	67;60 (89)	59;50 (85)	63;50 (79)	72;68 (94)	65;54 (83)	381;331 (87)
other chromosomal abnormality	123;43 (35)	158;50 (32)	71;34 (48)	65;33 (51)	119;38 (32)	120;36 (30)	656;234 (36)
Neural tube defect	58;44 (76)	34;20 (59)	35;25 (71)	22;17 (77)	31;26 (84)	45;41 (91)	225;173 (77)
Metabolic abnormality	29;6 (21)	7;2 (28)	7;6 (86)	7;4 (57)	8;8 (100)	8;8 (100)	66;34 (52)
Total	574;377 (66)	589;368 (62)	537;399 (74)	494;372 (75)	622;462 (74)	638;467 (73)	3454;2445 (71)

Discussion

Thanks to the centralisation of procedures, and the annual reports of the Working Party on Prenatal Diagnosis, the precise number of invasive prenatal diagnostic procedures performed in the Netherlands is known; in addition, the indications, the number of abnormal test results, and the number of terminations of pregnancy because of fetal abnormality are also known. There was a slight rise in the total number of pregnant women who underwent invasive prenatal diagnosis during the study period: from 5% of births in 1991 to 6% in 1996. After that, the percentage remained at the same level. Almost three-quarters of the procedures were performed because of 'maternal age,' and this number remained fairly stable during the study period. An interesting finding was that the number of pregnant women aged 36 and older increased by 70% in the study period, whereas the number of women who underwent invasive testing increased by only 26%.
The percentage of abnormal test results was highly dependent on the indication for the procedure. The percentage varied from 1.4% for 'increased risk of neural tube defect' and 2.4% for 'maternal age,' to 25.7% for 'increased risk for DNA abnormalities' and 27.8% for 'abnormalities on fetal ultrasound'.

In 1999, the number of terminations of pregnancy because of fetal abnormality was 1.8% of the total number of registered terminations of pregnancy in the Netherlands (www.stisan.nl).[2] It is estimated that around 150 children with spina bifida, encephalocele or anencephaly, and 210 children with Down syndrome (trisomy 21) were born in the Netherlands in 1998, after 24 weeks' gestation.[3,4]

Many numbers remained remarkably constant between 1991 and 2000. Nevertheless, on closer consideration, several interesting trends can be observed. The first trend is an 82% decrease in the number of cordocenteses and an 18% decrease in chorionic villi biopsies. The most plausible explanation for this is that women choose amniocentesis more often because they consider it a safer procedure. The relative decrease in the use of chorionic villi biopsy compared to the use of amniocentesis is probably because of the slightly higher risk of miscarriage, and probably also because of reports in the literature of a possible relation between chorionic villi biopsy and transversal limb defects if the test is performed early in pregnancy (<10 weeks).[5,6] It is currently assumed that there is no relation between limb defects and chorionic villi biopsy performed after 10 weeks of pregnancy.[7] In addition, some centers changed their policy in favour of amniocentesis during the study period, because 1-2% of pregnant women receive an indistinct result from chorionic villi biopsy and then have to undergo a second procedure (generally amniocentesis).[8-10] Therefore, several centers advise performing amniocentesis instead of chorionic villi biopsy, when there is a low probability of an abnormal result. In recent years, amniocentesis interphase fluorescence in situ hybridisation (FISH) for the most frequent trisomies has also been increasingly preferred in

cases with a high a priori risk (e.g., abnormality fetal ultrasound) because it gives a quick result for certain trisomies.[11] As interphase FISH is performed on non-dividing cells in amniotic fluid, a time-consuming cell culture is not necessary. Before interphase FISH became available, a quick result could only be obtained by examination of metafases in fetal blood or chorionvilli in uncultured material. The decrease in cordocentesis is obviously explained by the introduction of fast results from the interphase FISH.

The second trend is the decrease in the number of amniocenteses performed for detecting neural tube defects. While around 11% of all procedures in 1991 were performed because of high risk of neural tube defect, by 2000 the percentage was close to 2%. The explanation for this spectacular decrease is obvious: when there was an increased risk of neural tube defect, a detailed ultrasound was performed, frequently combined with serum testing, which provides equal sensitivity without the risk of a miscarriage.[12]

The third trend is the decrease from 46 to 34%, of pregnant women who underwent an invasive procedure because of 'maternal age.' This trend can be explained by the rise of (non-invasive) prenatal screening at 15-17 weeks gestation by means of the triple test, and screening by means of nuchal translucency measurement at 11-14 weeks gestation, though the Population Screening Act does not authorize either of these tests.[13,14] From the annual reports of the National Institute of Public Health and Environment (RIVM) and the University Hospital Groningen, which together process >90% of all triple tests in the Netherlands, we know that the percentage of pregnant women who underwent a triple test rose from 1.6% in 1991 to 2.8% in 1999. The RIVM data show that half of these pregnant women were older than 36 years.[15] In the last 6 years of the study period, more prenatal diagnostic procedures were performed because of abnormal serum screening test results.[15] In 1991, 1.9% of all procedures were performed because of 'abnormal test result after serum screening', whereas in 1996 this percentage was 6.4% and in 2000 it was 4.4%. The number of pregnant women who underwent a nuchal translucency measurement was not registered in the Netherlands, but members of the Dutch Working Party on Prenatal Diagnosis estimate that the percentage went from <1% in 1996 to between 8% and 10% in 2002. An increasing number of pregnant women 36 years and older resort to invasive procedures only when prenatal screening indicates a higher risk.[15] This double screening (maternal age and nuchal translucency or serum screening) is more effective than screening for maternal age only. This explains why the increased number of pregnant women 36 years and older did not lead to an increase of invasive testing, but still led to a higher number of detected abnormalities. Prenatal screening in the first trimester by means of nuchal translucency measurement, combined with first trimester maternal serum screening and other ultrasound observations, is an inevitable evolution.[16] The literature indicates that the percentage

of detected Down syndrome cases is 85% when prenatal screening is performed after combined first trimester screening compared to 30% when screening is only done for maternal age only, assuming that the 5% of pregnant women with the highest risk undergo an invasive procedure.[17] Even if only the 1% of pregnant women considered at the highest risk by first semester screening undergo an invasive procedure, it is anticipated that 72% of fetuses with Down syndrome would still be detected.[17] As soon as prenatal screening is authorized in the Netherlands (and this is expected to take place in 2007), a nationwide registration system will start, providing an integrated report on the effects of maternal serum testing, first- and second trimester detailed ultrasound, invasive prenatal diagnosis, and pregnancy outcome.

Conclusion

Invasive prenatal testing is well organized in the Netherlands. Annual reports on invasive testing are consistent, and the total number of procedures in the study period was stable. There was a clear decrease in the number of pregnant women 36 years and older who chose invasive testing without prior prenatal screening. There was also a clear increase in the number of detected fetal abnormalities. We expect this trend to continue: the number of non-invasive testing will increase, the number of invasive procedures will decrease, and the number of detected fetal abnormalities will increase.

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CHAPTER 3

Amniocentesis before 14 completed weeks as an alternative to transabdominal chorionic villus sampling: a controlled trial with infant follow-up

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Abstract

Objective A (semi-) randomized controlled study with long-term follow-up was conducted to compare the effects of transabdominal chorionic villus sampling and early amniocentesis on fetal mortality and child morbidity.

Methods Women requesting early prenatal diagnosis for advanced maternal age were allocated to early amniocentesis or transabdominal chorionic villus sampling either by randomization or, if they declined randomization, by their own choice.

Results Of the 212 women who entered the study, 117 were randomized, 70 chose early amniocentesis and 25 chose transabdominal chorionic villus sampling. Overall, 130 women underwent early amniocentesis and 74 underwent transabdominal chorionic villus sampling at a median gestation of 12 weeks. Two women were excluded because of fetal death before the procedure. Mosaic karyotypes were found in 5.4% of the early amniocenteses and in none of the chorionic villus samples.
All unintended fetal losses occurred after early amniocentesis with a frequency of 6.2 per cent (95% confidence interval: 2.7% to 11.8%). Talipes equinovarus was only observed after early amniocentesis with a frequency of 3.1% (95% confidence interval: 0.8% to 7.7%).

Conclusion We conclude that chorionic villus sampling remains the method of choice if prenatal diagnosis is needed in the first trimester of pregnancy.

Introduction

First trimester amniocentesis was introduced in the late 1980s because it was thought to combine the advantages of early diagnosis, as seen with chorionic villus sampling, with those of accuracy and safety offered by mid-trimester amniocentesis. Further advantages of early amniocentesis (EA) could result from early detection of spina bifida by measurement of amniotic fluid alpha-fetoprotein levels and, in multiple pregnancy, from more reliable karyotyping than can be achieved with transabdominal chorionic villus sampling.[1-4] Rapid detection of common fetal trisomies in uncultured amniocytes could make the concept of EA even more attractive.[5-8]

EA also gained considerable support from studies suggesting an increased incidence of terminal limb defects after chorionic villus sampling.[9-21]

However, assumptions that one method is superior to another cannot be validated merely by observational data. This is exemplified by the reports of the randomized controlled trials which compared chorionic villus sampling and midtrimester amniocentesis.[22-23]

In 1991, Byrne *et al*. reported that the diagnostic accuracy of early amniocentesis was comparable with, rather than superior to, transabdominal chorionic villus sampling (TA-CVS).[24] They proposed a randomized design to evaluate the merits of both procedures without limiting the patient's choice. We adapted this study design insisting on a complete and long-term follow-up of infants for up to one year after prenatal diagnosis.

Methods

Study setting

Before starting this study, about 500 midtrimester amniocenteses and 350 chorionic villus samplings were performed annually at Leiden University Hospital. All procedures were done by four clinicians, all of whom having at least two years experience with both procedures. Most experience with chorionic villus sampling related to transcervical rather than transabdominal sampling. The feasibility of EA and subsequent chromosome analysis were assessed in women scheduled for termination of pregnancies. Having encountered no difficulties with these procedures, approval for a randomized study design comparing TA-CVS with EA was obtained from the institutional ethical committee. Both procedures, EA and TA-CVS, were considered to be experimental procedures as opposed to mid-trimester amniocentesis and transcervical chorionic villus sampling, which were considered to be standard care options. Women attending too late for TA-CVS or EA, those undergoing prenatal diagnosis for reasons other than maternal age,

women with multiple pregnancies, and those requesting either one of the standard procedures were not included in the study. All women received written information and counselling on all of these options.

Allocation

Study participants were offered either randomization to TA-CVS or EA, or a choice between TA-CVS or EA, if they declined the highly recommended randomization. A formal process of selfrandomization was offered so as to incorporate an element of choice and enhance participation in the randomized part of the study.

The self-randomization process was conducted as follows: before the preparatory ultrasound examination, a sequentially numbered randomization envelope was opened. This envelope contained two identical smaller, sealed, opaque envelopes and an adhesive label stating 'affix me to the envelope that is not chosen before opening any envelope'. The small envelopes each contained a self-adhesive card one of which indicated 'early amniocentesis', and the other 'chorionic villus sampling'. Both cards also carried an identical code number. The woman was asked to choose one of the small envelopes and open it after the 'affix me' label had been put on the other envelope. Once the card was attached to the woman's medical record, she was offered the opportunity to open the other envelope to satisfy her that she had had a 50% chance of obtaining either procedure. The original randomization envelope together with all of its contents (except for the card attached to the patient's records), were returned to the randomization procedure supervisor. Thereupon the woman was considered to have been adequately randomized and ready for diagnosis and follow-up by the 'intention to treat' approach.

Women who declined randomization were allocated to EA or TA-CVS according to their own choice.

If ultrasound examination at the time of the intended procedure showed evidence of fetal death, no procedure was performed; these women were not formally entered into the study. If ultrasound examination suggested that the allocated method (either by randomization or by choice) would be too difficult (e.g., posterior placenta in a retroverted uterus), the woman was advised to undergo an alternative procedure. In some cases, the alternative was the other experimental procedure (EA or TA-CVS) than the one to which she had been allocated. In others, it was one of the standard options (transcervical chorionic villus sampling or mid-trimester amniocentesis).

Procedures

All procedures were performed by one of the four experienced operators. Both EA and TA-CVS were carried out by transabdominal, ultrasound guided, free-hand technique. For EA, the amniotic cavity was punctured with a 22-gauge needle and

11 ml of fluid was aspirated, the first ml being discarded. Care was taken to avoid puncture of fetus and placenta. For TA-CVS, the skin was infiltrated with local anaesthetic. A 20-gauge needle was introduced into the placenta and moved five to 10 times within the placental tissue, while negative pressure was applied by manual aspiration (±10 ml) through a 20 ml syringe. Care was taken to avoid puncture of the amniotic membrane. After the procedure, patients were advised to avoid undue exertion during the remainder of the day.

Samples consisted of either 10 ml of amniotic fluid or five to 25 mg of chorionic villi, all of which were examined at the cytogenetics laboratory. Amniotic fluid cells were cultured in duplicate in Amniomax-C100 (Life Technologies, Breda, The Netherlands) and Chang A (Tech Gen International, Veldhoven, The Netherlands) medium. Chromosome preparations were harvested and GTG-banded according to standard techniques. TA-CVS preparations included both short-term (48 hours) and long-term cultures.

Follow-up

Outcomes were assessed on three occasions: six weeks after the procedure, at birth and, finally, when the infant was between six and nine months old (approximately one year after the procedure). At the first follow-up, women were offered a comprehensive fetal ultrasound examination and were asked to complete a questionnaire on how they had experienced the method that they had received. They were also asked about complications such as bleeding, pain, fluid loss and about the interval between the test and receipt of the results.

Follow-up at birth consisted of a pregnancy outcome form completed either by the woman or by one of her caregivers.

One month before the long-term follow-up, parents received a reminder asking renewed permission to screen the infant at six months of age in the home environment. At the home visit, the mother was questioned about the paediatric history and infant development. If the baby had been hospitalized, or received medical treatment, further details were sought from the caregivers. The child was also examined for the presence of congenital anomalies and tested with the Dutch version of the Denver Developmental Screening Test.[25] DDST is designed for children aged from two weeks to six years and covers four areas of development: personal/social, fine motor adaptive, language and gross motor development. The test results are scored as normal, questionable or abnormal. All home visits were conducted by one of us who had received four months training in paediatric dysmorphology and neuropsychology for this purpose.

End of study

A publication of Nicolaides *et al.* which indicated a higher incidence of fetal loss after EA than after TA-CVS and our own prospective data collection prompted a

review 1 1/2 years after starting the study.[26-28] The combined information was submitted for advice to our institutional ethical committee which recommended immediate termination of patient recruitment.

Data analysis

Data were analysed at three different levels. Firstly, we compared the women randomized according to the group to which they had been allocated i.e., 'intention to treat' analysis. Secondly, we compared the women who had been allocated to EA with those allocated to TA-CVS on the basis of their own choice. A third analysis was based on the procedure that had been carried out: EA or TA-CVS. Confidence intervals were calculated using the CIA software.[29]

Results

A total of 212 pregnant women were recruited to the study. Two of them (one randomized to TA-CVS and one randomized to EA) did not participate because fetal death was detected at the time of randomization and before any procedure was undertaken. Of the remaining 210 women, 115 agreed to be randomized: 55 were randomized to EA and 60 to TA-CVS. The remaining 95 women declined randomization with 70 of them choosing EA and 25 TA-CVS **(Table 1)**. A different procedure than the one allocated was performed in 17 cases (eight per cent). In total, 130 women underwent EA and 74 women underwent TA-CVS **(Table 1)**.

Table 1. Comparison between the procedures allocated and the procedures received.

	Procedure received				
Procedure allocated	**EA**	**TA-CVS**	**TC-CVS**	**MA**	**Total**
Randomized to EA	54	---	---	1	55*
Randomized to TA-CVS	7	50	3	---	60*
Womens' choice for EA	67	2	1	---	70
Womans' choice for TA-CVS	2	22	1	---	25
Total	130	74	5	1	210

EA = Early amniocentesis; TA-CVS=transabdominal chorionic villus sampling;
TC-CVS = transcervical chorionic villus sampling; MA=mid-trimester amniocentesis.
*Excluding one woman with fetal death diagnosed upon randomization.

Characteristics of the pregnancies at the time of the procedure are summarized in **Table 2**. The groups showed no differences in terms of maternal age, smoking, vaginal bleeding, obstetric history, gestational age at sampling and placental localization.

Table 2. Maternal characteristics and ultrasound findings of the 212 pregnancies at the time of allocation

	Procedure allocated				Procedure received	
	Random. EA	Random. TA-CVS	Choice EA	Choice TA-CVS	EA	TA-CVS
Number of pregnancies	56	61	70	25	130	74
Mother						
Mean age in year	37.8	37.9	38.3	38.1	39.1	37.8
Current smoker	11 (19.6)	12 (19.7)	11 (15.7)	3 (12.0)	22 (16.9)	15 (20.3)
Vaginal bleeding	0 (0)	4 (6.6)	3 (4.3)	1 (4.0)	4 (3.1)	4 (5.4)
Obstetric history						
First pregnancy	12 (21.4)	9 (14.7)	10 (14.5)	5 (20.0)	26 (20.0)	10 (13.5)
Previous miscarriage	17 (30.4)	19 (31.1)	16 (22.9)	10 (40.0)	32 (24.6)	25 (33.8)
Fetus						
Median gestational age in completed weeks (range)	12 (11-14)	12 (11-14)	12 (11-13)	12 (11-13)	12 (11-14)	12 (11-14)
Median crown-rump length (range)	63 (50-79)	60 (48-83)	61 (47-84)	60 (45-70)	62 (47-84)	60 (45-83)
Placenta						
Anterior (%)	29 (51.8)	22 (36.1)	29 (41.1)	15 (60.0)	54 (41.5)	39 (52.7)
Posterior (%)	22 (39.3)	30 (49.1)	26 (37.1)	9 (36.0)	56 (43.0)	27 (36.5)
Fundal (%)	3 (5.3)	7 (11.5)	7 (10.0)	--	10 (7.7)	6 (8.1)
Lateral (%)	2 (3.6)	1 (1.6)	3 (4.3)	1 (4.0)	5 (3.8)	1 (1.3)
Unknown (%)	--	1 (1.6)	5 (7.1)	--	5 (3.8)	1 (1.3)

Random. = randomized to; choice = womens' choice for; EA = early amniocentesis; TA-CVS = transabdominal chorionic villus sampling

All cytogenetic abnormalities are shown in **Table 3**. Among the 210 fetuses, there were two distinctly abnormal karyotypes (one 47,XY,+13 and one 47,XXY). The former pregnancy with fetal Patau syndrome was terminated and the latter pregnancy with fetal Klinefelter syndrome ended in a spontaneous miscarriage. A further six showed an aberrant karyotype but a normal phenotype; two of these were balanced translocations and a further one proved to be a false-positive result. These cases will be discussed in relation to sampling technique below.

Table 3. Cytogenetic abnormalities

Karyotype	Procedure allocated	Procedure received	Follow-up
***Mosaicism* [number of cells]**			
A: 45,X[1]/46,XY[26]/47,XXY[11] C: 46,XY[33]/47,XYY[1]	Choice EA	EA	Confirmed (cord blood at birth)
A: 46,XX[22] C: 46,XX,t(2;13)(q;q)[30]	Choice EA	EA	Normal (MA), both parents normal Karyotype
A: 46,XX[46]/47,XY,+8[4] C: 46,XX[35]	Choice EA	EA	Normal (MA)
A: 46,XX[35] C: 46,XX[22]/47,XY,+22[6]	Random. EA	EA	Normal (MA)
A: 46,XY[27]/47,XY,+21[3] C: 46,XY[39]/46,XY,+i(21q)[1]	Random. EA	EA	Normal (MA)
A: 46,XY[13]/46,XX[9] C: 46,XY[22]/46,XX[6]	Choice TA-CVS	EA	Normal (cord blood at birth)
A: 46,XX[17] C: 46,XX[15]/46,XX,t(2;5)(q23;q23)[15]	Choice EA	EA	Normal (MA)
Normal chromosome variant			
46,XY,inv(9)	Choice EA	EA	No further examinations
46,XY,s+	Choice TA-CVS	TA-CVS	No further examinations
46,XY,9qh+	Random. TA-CVS	TA-CVS	Mother is carrier
46,XX,t(5;6)(p14;q25)	Choice EA	EA	Confirmed (cord blood at birth)
46,XX,t(9;18)(q32;q21)	Choice TA-CVS	TA-CVS	Father is carrier
False-positive abnormal karyotype			
46,XY,inv(16)(p;q)	Random. TA-CVS	TA-CVS	Normal (MA)
Abnormal karyotype			
47,XXY	Choice EA	EA	Confirmed (miscarriage tissue)
47,XY,+13	Choice EA	EA	Conformed (abortion tissue)

A=cultured in Amniomax; C=cultured in Chang; EA=early amniocentesis;
TA-CVS=transabdominal chorionic villus sampling;
MA=mid-trimester amniocentesis; random.=randomized to; choice=womens' choice for.

Outcome in the randomized cohort (intention to treat analysis)

Of the 55 women randomly assigned to EA, 54 underwent EA, but only 50 of the 60 allocated to TA-CVS underwent TA-CVS. Of the remaining 10 women, seven had EA and three received transcervical chorionic villus sampling because of anticipated technical problems **(Table 1)**, which could suggest that technical feasibility is better for EA than for TA-CVS.

Chromosomal mosaicism was found in two women in the EA group and one false-positive diagnosis was obtained in the TA-CVS group **(Table 3)**.
Five fetal losses occurred in the randomized groups, three among women allocated to EA and two among those allocated to TA-CVS. All of these losses related to fetuses with normal karyotypes and all occurred after EA **(Table 4)**.

Table 4. Characteristics of cases with unintended fetal loss after invasive prenatal diagnosis

Case	Allocation by	Procedure allocated	Procedure received	CRL before procedure	CRL at fetal death	Fetal karyotype	Remarks
1	Womans' choice	EA	EA	54	70	46,XX	Vaginal loss of amniotic fluid 1 day after EA
2	Womans' choice	EA	EA	50	50	47,XXY	
3	Randomization	EA	EA	54	130	46,XX	
4	Randomization	EA	EA	60	60	46,XX	Neonatal death of previous child
5	Randomization	EA	EA	55	55	46,XX	History of two previous fetal losses. Vaginal blood loss from eight weeks onwards in current pregnancy
6	Randomization	TA-CVS	EA	59	59	46,XY	
7	Randomization	TA-CVS	EA	65	120	46,XY	Maternal enteritis at the time of EA
8	Womans' choice	EA	EA	74	130	46,XX(96%)/ 47,XX, +8(4%)	Second trimester amniocentesis (normal karyotype 46,XX) one week before fetal death

EA = Early amniocentesis; TA-CVS = transabdominal chorionic villus sampling; CRL = fetal crown-rump length.

Major congenital anomalies occurred in two cases (one in each group) and malformations overall occurred in 16 cases, five of whom had been randomized to EA **(Table 5)**.

Table 5. Congenital anomalies

		Procedure allocated				Procedure received	
	Total	Random. EA	Random. TA-CVS	Choice EA	Choice TA-CVS	EA	TA-CVS
Number of births	201	52	58	66	25	121	74
Major congenital anomalies							
Talipes equinovarus							
Unilateral	2	1	--	1	--	2	--
Bilateral	2	--	1	1	--	2	--
Spina bifida aperta	1	--	--	--	1	--	1
Minor congenital anomalies							
Pylorus hypertrophy	2	--	1	--	1	--	2
Preauricular skin tags	1	1	--	--	--	1	--
Aplasia cutis congenita	1	1	--	--	--	1	--
Partial syndactyly toes	6	--	4	1	1	2	4
Simian crease	8	2	2	4	--	6	2
Vesico-urethral reflux	1	--	--	--	1	--	1
Haemangioma fructosum	14	--	7	6	1	5	8
Hypospadia	1	--	1	--	--	--	1
No follow-up after birth	--	--	--	--	--	--	--
No home visit	9	1	1	2	5	4	4

Random. = randomized to; choice = womens' choice for; EA = early amniocentesis; TA-CVS = transabdominal chorionic villus sampling

Outcome among women allocated to their treatment of choice

Of the women choosing either EA or TA-CVS, the large majority (70 out of 95) opted for EA and for most of them (67 out of 70), this procedure was implemented **(Table 1)**. Of the 25 opting for TA-CVS, 22 underwent TA-CVS **(Table 1)**.

Chromosomal mosaicism was detected in four of the women who had chosen and received EA and in one of the women who had chosen TA-CVS. But, this latter woman had also undergone EA because TA-CVS had been anticipated to be too difficult **(Table 3)**.

Three fetal losses were noted among the women who had chosen their own procedure. All of these occurred in women choosing and receiving EA **(Table 4)**.

Major congenital anomalies occurred in two pregnancies allocated to EA and in one allocated to TA-CVS. In total, congenital malformations occurred among 13 of the 70 women (18.6%) opting for EA and in five of the 25 (20%) opting for TA-CVS **(Table 5)**.

Outcome related to treatment received

As indicated above, a sizeable proportion of women did not receive the procedure to which they had been assigned either by choice or by randomization. As it is likely that outcome relates more to the procedures performed than to those to which the women were allocated, we also conducted an analysis based on the actual procedure received. This analysis indicated that out of 85 women assigned to TA-CVS, as many as 13 (15.3%) underwent another procedure while of the 125 assigned to EA only four (3.2%) underwent another procedure, a difference of 12.1 per cent (95% confidence interval: 3.8% to 20.3%).

Multiple needle insertions were needed in 6.2 per cent of the women receiving EA and in 41.9% of the women receiving TA-CVS; a difference of 35.7% (95% confidence interval: 23.8% to 47.7%) **(Table 6)**.

After EA, 96.5% of the women waited more than two weeks for their cytogenetic results; whilst after TA-CVS, only 18.2% waited that long. The mean culture time for TA-CVS was 2.5 days for the short-term culture, and 8.0 days for the long-term culture. For EA the mean culture time was 13.8 days for the Amniomax culture and 15.6 days for the Chang culture.

Of the women who underwent EA, 5.2% complained of severe pain during the procedure against 9.0% of those who underwent TA-CVS. Vaginal blood loss within four weeks after the test was reported by 2.6 per cent of the women after EA and by none after TA-CVS. Loss of amniotic fluid was reported in 3.5% after EA and in none after TA-CVS.

Of the women who underwent EA, 97.4% would choose the same prenatal test if they became pregnant again compared with 93.9% who underwent TA-CVS.

All seven cases of chromosomal mosaicism detected in early pregnancy

occurred among the 130 women undergoing EA. Six of these seven cases showed a normal karyotype on subsequent investigations **(Table 3)**.

Table 6. Procedural characteristics and cytogenetic findings

		Procedure allocated				Procedure received	
	Total	**Random. EA**	**Random. TA-CVS**	**Choice EA**	**Choice TA-CVS**	**EA**	**TA-CVS**
Number of women	210	55	60	70	25	130	74
Procedure							
Single insertion (%)	171	50 (90.9)	35 (58.3)	68 (79.1)	18 (72.0)	122 (93.8)	43 (58.1)
Sampling failure (%)	5	1(1.8)	2 (3.3)	2 (2.9)	--	2 (1.5)	3 (4.0)
Cytogenetic findings							
Normal karyotype (%)	187	51 (92.7)	56 (93.3)	60 (85.7)	20 (80.0)	116 (89.2)	65 (87.8)
Mosaicism (%)	7	2 (3.6)	--	4 (5.7)	1 (4.0)	7 (5.4)	--
Normal chromosome variant (%)	5	--	1 (1.7)	2 (2.9)	2 (8.0)	2 (1.5)	3 (4.0)
False-positive abnormal karyotype (%)	1	--	1 (1.7)	--	--	--	1 (1.4)
Abnormal karyotype (%)	2	--	--	2 (2.9)	--	2 (1.5)	--
Culture failure (%)	3	1 (1.8)	--	--	2 (8.0)	1 (0.8)	2 (2.7)
Complications							
Extra first trimester prenatal test performed (%)	3	--	2 (3.3)	--	1 (4.0)	1 (0.8)	2 (2.7)
Extra second trimester prenatal test performed (%)	12	4 (7.3)	2 (3.3)	5 (7.1)	1 (4.0)	8 (6.2)	4 (5.4)

Random. = randomized to; choice = womens' choice for; EA = early amniocentesis;
TA-CVS = transabdominal chorionic villus sampling

All eight cases of unintended fetal loss occurred among women having received EA, irrespective of whether they had been randomized to EA, had chosen EA or had received EA because of anticipated technical difficulties after allocation to TA-CVS **(Table 6)**. Unintended fetal loss thus occurred in 6.2% of women after EA (95% confidence interval: 2.7% to 11.8%).
It appeared that congenital malformations occurred less frequently after EA (15.7 per cent) than after TA-CVS (25.7%) **(Table 5)**; but this difference of -10 per cent (95% confidence interval: -21.9% to 1.9%) did not reach conventional levels of statistical significance. All four cases of talipes, however, were observed after EA **(Table 5)**, a frequency of 3.1% (95 per cent confidence interval: 0.8% to 7.7%). Two of these cases were seen after transient amniotic fluid leakage.

None of the 192 infants who were visited at home, had abnormal results on the Denver Developmental Screening Test. Nine infants were not visited at home: due to either parental refusal (three cases) or because they had left The Netherlands (six cases).

Discussion

Since 1987, several uncontrolled series of early amniocentesis have been published.[30-58] When combined, these studies relate to results of EA in well over 10,000 women. As to fetal loss after the procedure, most of these reports claim good or excellent results, with very few unintended fetal losses. The first few controlled reports have been far less encouraging however, despite the fact that they used study designs that are still prone to bias, such as historical (Shulman *et al.*, 1994) and matched (Crandall *et al.*, 1994) controls, losses after EA were greater than with alternative methods for prenatal diagnosis.[59,60]
Nicolaides *et al.*, using the same study design that we used, found an unintended fetal loss rate of 5.3% after EA, compared with 2.2 per cent after TA-CVS.[26-27]
In the randomized part of their study, loss rates after EA were 5.9% and after TA-CVS 1.2%.

Whilst one may question whether it was justified to stop our study at the time it was stopped and before obtaining more conclusive results, it would seem that the disadvantages of EA outweigh its advantages. The advantages of EA appear to be related to its technical feasibility, which seems to be greater than for TA-CVS, at least at the beginning of the learning curve. In our study, we could detect no other advantages except that severe pain occurred slightly less frequently after EA than after TA-CVS. Chromosomal mosaicism was encountered exclusively after EA. The need for a repeat test was similar to that after TA-CVS.

Unintended fetal demise was substantially more frequent after EA than after TA-CVS (6.2%; 95% confidence interval: 2.7% to 11.8%), as was talipes

equinovarus of which all four cases were seen after EA (3.1%; 95% confidence interval: 0.8% to 7.7%).

In the appreciation of the women, EA appears to score roughly similar to TA-CVS. If anything, EA may even score slightly better in the women's appreciation. Cause and effect are not readily discerned though, because the large majority of the women who opted for a specific procedure, rather than being randomized, chose EA in preference to TA-CVS.

Conclusion

We conclude that either EA should no longer be offered, as is the case in our institution, or it should be offered in the context of a randomized trial by those who feel that the case for and against is less clear than we suggest.

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CHAPTER 4

Outcome of children with prenatally diagnosed central nervous system malformations

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Abstract

Objective To study the outcome of pregnancies with a prenatally diagnosed central nervous system (CNS) malformation.

Methods Leiden University Medical Center is a tertiary referral center for fetal ultrasound and invasive prenatal diagnosis. Maternal and neonatal records of prenatally diagnosed CNS malformations were retrospectively reviewed over a 6-year period (1993–1998). Information on current development of surviving children was obtained by contacting the care-giving pediatric neurologist.

Results During the study period 124 fetuses were diagnosed with a CNS malformation. Data on pregnancy and delivery were available for 118 pregnancies Additional malformations were present in 47% of fetuses (55/118). A total of 46% of pregnancies (54/118) were terminated, and 15% (18/118) ended in spontaneous intrauterine death. A total of 39% of pregnancies (46/118) resulted in live birth, and 29 of the infants were still alive at the age of 3 months. One child was lost to follow-up, one infant died at the age of 4 months, and two children died at the age of 3 years. Psychomotor development of the remaining 25 children was normal for five, slightly disabled for seven, moderately disabled for five and severely disabled for eight.

Conclusion Due to the high rate of termination of pregnancy and to the frequent association with other anomalies, the survival rate of pregnancies in which a CNS defect had been diagnosed prenatally was only 25%. More than 50% of surviving children were moderately or severely disabled.

Introduction

Congenital central nervous system (CNS) malformations are relatively common and account for a substantial proportion of miscarriages, stillbirths and infant deaths.[1,2] Moreover, these malformations are an important cause of long-term morbidity in children. Prenatal detection of CNS malformations has substantially improved in the last decade. After diagnosing a CNS anomaly prenatally, sonographers and obstetricians have to counsel the parents, who, after receiving the bad news, are confronted with difficult decisions, which may involve the option of terminating the pregnancy.[3-7] In order to give clinicians some guidance during counselling, we aimed to review the number and type of CNS anomalies that were detected prenatally in our center and to describe the outcome of these pregnancies. We also wanted to know which factors influenced the decisions made by the parents (for example, gestational age at the time of diagnosis, type of CNS malformation and whether or not additional anomalies were found). Furthermore, we wanted to evaluate the accuracy of ultrasound examination in our center. Finally, we were interested in the long-term outcome of survivors, because such information may be particularly helpful in counselling future parents.

Methods

In The Netherlands, fetal anomaly scans are not part of routine prenatal care. Detailed ultrasonography is only performed when there is an increased risk of fetal anomaly based on family history, maternal illness or medication, or complications during pregnancy. Leiden University Medical Center is a tertiary referral hospital for prenatal anomaly scanning. All prenatal ultrasound examinations in this hospital are performed by experienced sonographers and reported in a database. We reviewed this database for all pregnancies with CNS malformations detected between 1 January 1993 and 31 December 1998. We excluded 19 cases with choroid plexus cysts, because these cysts either disappeared spontaneously before birth (n = 15) or the fetus died due to other causes (n = 4). The remaining malformations were classified into seven groups: (1) spina bifida, (2) anencephaly, (3) encephalocele, (4) hydrocephaly, (5) holoprosencephaly, (6) Dandy-Walker malformation and (7) other CNS anomalies.

Malformations were also classified as: (a) isolated, (b) associated with a chromosomal disorder or (c) associated with other anomalies but with a normal karyotype. Isolated malformations included cases with abnormalities developing in sequence from the primary malformation. For example, spina bifida with hydrocephaly and pes equinovarus or holoprosencephaly with facial abnormalities were classified as isolated malformations. We reviewed clinical records of both

mother and child for information on pregnancy, delivery and neonatal period. If extra information was required, we contacted the referring gynecologist in order to complete our data. A clinical geneticist routinely examined all infants as well as fetuses after termination of pregnancy (TOP) or intrauterine death after 16 weeks. Current clinical information at the time of completion of this study was obtained by contacting the pediatric neurologists involved in the care of the surviving children. We based our estimation of mental and motor development on medical information and for some of the older children on their school performance. Because of the large variation in age between the children and the frequency of serious abnormalities, we could not perform a standardized test.

Results

In the 6-year study period, 4,470 pregnancies were screened for congenital anomalies in our center. Mean maternal age in the study group was 30 years. Indication for ultrasound was, first, an increased risk of fetal anomaly already known before the beginning of the pregnancy (Group 1: for example, a congenital anomaly in a previous child) or, second, an increased fetal risk because of pregnancy complications (Group 2: for example, polyhydramnios in the current pregnancy). The mean gestational age in Group 1 (n = 2,731) was 20 weeks, and in Group 2 (n = 1,739) 28 weeks. In 580 cases (116 in Group 1 and 464 in Group 2) a fetal anomaly was diagnosed. A CNS malformation was diagnosed in 2.8% of pregnancies (124/4,470), but we only had information on pregnancy and delivery for 118 cases. Ten of these 118 were multiple pregnancies (two triplets and eight twins) but in each of these pregnancies only one fetus had a congenital CNS malformation. The mean age of the 118 women at the time of delivery was 30 years (range, 18–43 years). Karyotyping was performed prenatally in 70 cases and postnatally in eight cases. In 40 cases the parents chose not to undergo karyotyping. A total of 46% of fetuses (54/118) were male and 49% were female (58/118). In six unkaryotyped cases, four with anencephaly, one with holoprosencephaly and one with encephalocele, the sex remained undetermined after TOP (five cases between 12 and 17 weeks) or fetal death (one case at 12 weeks). The mean gestational age at the time of diagnosis was 28 weeks (range, 12–42 weeks). A total of 43% of CNS malformations (51/118) were diagnosed before 24 weeks and 57% (67/118) after 24 weeks' gestation. When the CNS malformation was diagnosed before 24 weeks, only 24% of mothers (12/51) chose to continue the pregnancy, whereas 78% of mothers (52/67) continued their pregnancy when the malformation was diagnosed after 24 weeks.

Table 1 lists the CNS malformations diagnosed at the time of ultrasound examination. Closure defects of the neural tube (spina bifida, anencephaly and

encephalocele) were the most common finding (51%), followed by hydrocephaly without spina bifida (26%). Holoprosencephaly (8%) and Dandy-Walker malformation (7%) were less common. Other malformations (the remaining 8%) were microcephaly (one diagnosed as Pena Shokeir syndrome) (n = 4), enlarged cisterna magna (n = 3), enlarged third ventricle in association with Pena Shokeir syndrome (n = 1) and isolated agenesis of the corpus callosum (n = 1). In 53% of fetuses (63/118), the CNS malformation appeared to be isolated. In the remaining 47% of fetuses (55/118) there were additional abnormalities: 17 chromosomal abnormalities (five trisomy 18, three trisomy 13, three translocations, two deletions, two triploidy, one tetrasomy and one Turner syndrome), six prenatally undetected CNS malformations and 32 other anatomical anomalies (e.g. anomalies of the heart, kidney, diaphragmatic hernia and syndromes such as Pena Shokeir syndrome, Goldenhar syndrome and Meckel–Grüber syndrome). None of the fetuses with a CNS malformation in combination with a chromosomal disorder survived longer than 3 months after birth. In the majority of cases (37/55) additional anomalies were so serious that they determined the outcome of pregnancy. Only 20% of fetuses (11/55) with a CNS malformation in combination with additional anomalies and only 30% of fetuses (18/63) with an isolated CNS malformation survived beyond 3 months after birth.

Table 1. Classification of 118 pregnancies with prenatally diagnosed central nervous system malformations

Main CNS malformation on prenatal ultrasound	Isolated CNS malformation	In combination with abnormal karyotype	In combination with other malformations	Total
Spina bifida	16*	3	7	26
Anencephaly	24†	-	-	24
Encephalocele	1	1	8	10
Hydrocephaly	11	5	15	31
Holoprosencephaly	3	4	3	10
Dandy - Walker	4	3	1	8
Other	4	1	4	9
Total	63	17	17	118

*All fetuses with isolated spina bifida had associated anomalies (e.g. hydrocephaly, hindbrain herniation, pes equinovarus) or ultrasonographic markers ('lemon' or 'banana' sign).[20]
†Three fetuses with anencephaly also had spina bifida. CNS, central nervous system.

Table 2 lists the outcome of the 118 pregnancies according to the type of CNS malformation. TOP was performed in 46% of pregnancies (54/118). In 13% of pregnancies (15/118) TOP was performed after 24 weeks, because it was decided that the fetus had an abnormality that was not compatible with life or would cause severe handicap with inhumane suffering. All these fetuses, except those with anencephaly and one fetus with rachischisis totalis, had serious additional (non-CNS) anomalies. Spontaneous intrauterine death occurred in 15% of pregnancies (18/118). Eventually, 46 pregnancies resulted in live births and 25% of the infants were still alive at the age of 3 months (45% of all pregnancies without TOP). Of the 17 infants who died in the first 3 months after birth, 14 died in spite of therapeutic interventions. In three cases (diagnosed with spina bifida, hydrocephaly and Pena Shokeir syndrome, respectively) the parents declined therapeutic interventions.

Table 2. Classification of 118 pregnancies with prenatally diagnosed central nervous system malformations

	TOP		Intrauterine death		Live born		
Ultrasound findings	**<24 weeks**	**>24 weeks**	**Ante-partum**	**Intra-partum**	**Died <3 months**	**Alive after 3 months**	**Total**
Spina bifida	8	3	2	1	4	8	26
Anencephaly	13	6	1	1	3	--	24
Encephalocele	7	1	1	--	--	1	10
Hydrocephaly	8	2	3	1	2	15	31
Holoprosencephaly	2	1	3	2	2	-	10
Dandy - Walker	1	2	1	-	3	1	8
Other	--	--	1	1	3	4	9
Total (n (%))	39(33%)	15(13%)	12(10%)	6(5%)	17(14%)	29(25%)	118(100%)

TOP, termination of pregnancy.

In 12 cases, listed in **Table 3**, diagnosis after birth differed from prenatal ultrasound diagnosis. In nine cases the abnormalities turned out to be more extensive than prenatally suspected, whereas in three cases they turned out to be less extensive. In all cases the medical intervention (if any) remained justified. Difficulties in the prenatal diagnosis of CNS malformations occurred predominantly with spina bifida, with posterior fossa anomalies and with corpus callosum agenesis.

Table 3. Data from 12 children in whom antepartum diagnosis differed from postpartum diagnosis

Gestational age at diagnosis (weeks)	**Diagnosis before birth**		**Diagnosis after birth**		
	CNS anomaly	***Other anomalies***	***CNS anomaly***	***Other anomalies***	***Outcome***
23	Spina bifida (S3-S4)	Growth restriction	Spina bifida not confirmed	Low-set ears, abnormal appearance	Intrauterine death at 25 weeks
25	Microcephaly, encephalocele	Large VSD, single umbilical artery, unbalanced translocation (46,XX;t(1;3))	Microcephaly, epidermal cyst	Tetralogy of Fallot, unbalanced translocation (46,XX;t(1;3))	TOP
19	Hydrocephaly	Growth restriction, oligohydramnios triploidy (69,XXX)	Spina bifida (L3-L4)	Triploidy (69,XXX), micrognathia, cheilo-gnathopalatoschisis, polydactyly, horseshoe kidney, pes equinovarus	Intrauterine death at 27 weeks
30	Hydrocephaly	None	Hydrocephaly	Walker Warburg syndrome Lissencephaly, eye and skeletal malformations, muscle dystrophy	Died at 3 years due to pneumonia
33	Hydrocephaly, agnesis of the corpus callosum. Suspicion of spina bifida and pes equinovarus	None	Hydrocephaly	None	Alive
34	Hydrocephaly	None	Hydrocephaly	Goldenhar syndrome: palatoschisis, anal atresia, deafness	Alive
40	Hydrocephaly	None	Spina bifida (cervical myelo-meningocele)	None	Alive
25	Suspicion of Dandy-Walker malformation	VSD with overriding aorta, trisomy 13, growth restriction	Holoprosencephaly	VSD with overriding aorta, trisomy 13, palatoschisis, abnormal hands and feet	TOP (severe maternal pre-eclampsia)
32	Dandy-Walker malformation or arachnoidal cyst	Fluid collection in the neck	No Dandy-Walker malformation or cyst	Hydrops fetalis	Died 3 weeks after birth
34	Suspicion of Dandy-Walker malformation	Hyperechogenic kidneys, possibly polycystic kidney disease	Dandy-Walker malformation not confirmed	Hyperechogenic kidneys, trisomy 13	Died 2 days after birth
34	Dandy-Walker malformation, partial vermis aplasia	None	Hypoplasia right cerebellar hemisphere	None	Alive
31	Agenesis of the corpus callosum	None	Head circumference > 98th percentile	None	Alive

CNS, central nervous system; TOP, termination of pregnancy; VSD, ventricular septal defect.

Table 4. Outcome of 29 children who survived the first 3 months after birth

Gestation at diagnosis (weeks)	Diagnosis postpartum	Gestation at birth (weeks)	Age at follow-up (years)	Mental disabilities	Motor disabilities
35	Spina bifida (L3-S2)	37	6	+ (Special school)	++ (Wheelchair-bound)
27	Spina bifida (occipital meningocele)	35	5.5	N	+ (Walks independently)
39	Spina bifida (L2-S2)	40	4	+++	+++
29	Spina bifida (L2-S2)	37	4	+	+++ (Wheelchair-bound)
37	Spina bifida (Th12-L1)	41	4	N	+++ (Wheelchair-bound)
40	Spina bifida (cervical myelomeningocele. Prenatally diagnosed as hydrocephaly)	40	3	N	+++ (Wheelchair-bound)
17	Spina bifida (L5-S2 (fetal valproate syndrome)	40	3	+	+ (walks independently) with callipers)
24	Spina bifida (L5-S1)	37	2	N	+ (Walks independently)
15	Spina bifida (L5-S1)	39	1	N	N
20	Encephalocele	35	Died at 3 years (cause unknown)	+++	+++
33	Hydrocephaly	37	7	N	+ (Walks independently)
35	Hydrocephaly	40	5	++ (severe deafness)	N
34	Hydrocephaly (Goldenhar syndrome)	38	4	++ (severe deafness)	++ (Walks with aid a few steps)
39	Hydrocephaly, camptodactyly	39	4	+++	+++ (Tetraparesis)
30	Hydrocephaly (Walker Warburg syndrome)	38	Died at 3 years due to pneumonia	+++	+++
39	Hydrocephaly	40	3	N	N
29	Hydrocephaly	35	3	N	+++ (Diplegia)
34	Hydrocephaly, corpus callosum agenesis	37	2.5	+	+ (Walks independently)
30	Hydrocephaly	31	2.5	N	+ (Walks independently)
27	Hydrocephaly, partial corpus collosum	33	2	+++ (Blind)	+++
36	Hydrocephaly	37	2	N	N
26	Hydrocephaly, partial corpus callosum	37	2	++ (Severe deafness)	+ (Walks independently)
31	Hydrocephaly, anal atresia, syndactyly	36	Died at 4 months due to pneumonia	+++	+++
26	Enlarged cisterna magna prenatally normalizing and postpartum not confirmed	40	7	N	N
30	Microcephaly	40	3	+++	+++
30	Microcephaly	39	2	++	++
34	Hypoplasia right cerebellar hemisphere (prenatally diagnosed as Dany-Walker malformation)	37	1.5	+	+
31	Head circumference >98th percentile (prenatal suspicion of corpus callosum agenesis)	38	0.5	N	N
30	Hydrocephaly		37	Lost to follow-up	

N, normal development; +, slightly disabled; ++, moderately disabled; +++, severely disabled.

Table 4 lists the 29 infants surviving more than 3 months, classified according to diagnosis after birth. One child was lost to follow-up after 3 months. The duration of follow-up of the remaining 28 children varied from 6 months to 7 years. Two children with encephalocele and hydrocephaly, respectively, died at the age of 3 years, and one child with hydrocephaly died at the age of 4 months. Of the remaining 25 children, five had normal psychomotor development, seven were slightly disabled, five were moderately disabled, and eight were severely disabled. Normal development was seen in one child with sacral spina bifida, two with hydrocephaly, one with prenatally suspected corpus callosum agenesis and one with prenatally suspected posterior fossa anomaly. The two latter anomalies were, however, not confirmed after birth.

Discussion

We have described a cohort of fetuses diagnosed with CNS abnormalities at our center. More than half of the prenatal diagnoses were made after 24 weeks' gestation. This is a consequence of the fact that prenatal ultrasound screening for abnormalities is not routinely performed in The Netherlands. In 90% of cases prenatal ultrasound examination provided a complete and correct diagnosis. In 8% of cases additional, prenatally undetected, abnormalities were found after birth, and in 2% the abnormalities were found to be less extensive than prenatally suspected. In 51% of cases closure defects of the neural tube were found, and 26% of cases were diagnosed as hydrocephaly without spina bifida. CNS abnormalities are very frequently associated with secondary anomalies; in our study all spina bifida cases had hindbrain herniation, hydrocephaly, or pes equinovarus and many cases of holoprosencephaly had facial abnormalities. Moreover, 45% of fetuses with CNS abnormalities in our study were found to have additional anomalies, or an abnormal karyotype. After the diagnosis was made, 46% of pregnancies were terminated and another 29% resulted in fetal or neonatal death. None of the fetuses with an abnormal karyotype, anencephaly or holoprosencephaly survived. More than 50% of the surviving children remained moderately or severely disabled, and only 4% of the initial cohort had normal psychomotor development.

The major reasons for the low survival rate of fetuses with CNS anomalies in our study are the high rate of TOP as well as the frequent coexistence of additional anomalies. Previous studies have also found a high rate of additional (CNS or other) anomalies. Aletebi and Fung described 15 fetuses with posterior fossa anomalies, seven of which were found to have additional anomalies.[8] Ecker *et al.* found that 86% of fetuses with posterior fossa anomalies had additional malformations.[9] Den Hollander *et al.* found that 50% of fetuses with ventriculomegaly had additional anomalies.[10] Kölble *et al.* described ten fetuses

with prenatally diagnosed Dandy-Walker malformation.[11] Postnatally, Dandy-Walker malformation was confirmed in all cases, but additional malformations, not diagnosed prenatally, were found in seven cases.

The Netherlands is one of two countries in the European Union where neither routine ultrasound screening for fetal anomalies nor maternal serum screening are implemented. A recent report from the Dutch Health Council again advised against prenatal ultrasound screening.[12] This restrictive policy clearly explains why so many CNS anomalies in our study were detected after 24 weeks. In the Netherlands, TOP is prohibited after 24 weeks' gestation, unless detected anomalies are considered to be incompatible with postnatal life or would cause severe handicap with inhumane suffering. The advanced gestational age at the time of detection probably explains why, compared to other European countries, a smaller percentage of pregnancies with CNS anomalies were terminated.[9,13-15] Forrester and Merz studied the various factors influencing the decision to perform TOP and found that 65% of pregnancies with prenatally diagnosed neural tube defects were terminated.[13] Hassed *et al.* reported on 25 families faced with a CNS anomaly that was considered lethal.[14] Only two of the families elected to continue the pregnancy. Ecker *et al.* described 99 pregnancies with prenatally diagnosed posterior fossa anomalies.[9] A total of 50% of these pregnancies were terminated. Cornel *et al.* also found that the percentage of TOP in prenatally diagnosed neural tube defects in The Netherlands was relatively low compared to other European countries.[15] Based on these studies, it seems likely that individual parents would benefit from the introduction of routine second-trimester fetal ultrasound in The Netherlands. Most of the discrepancies between prenatal and postnatal diagnosis in our study concerned non-CNS anomalies that were not detected with prenatal ultrasound. However, in two cases with multiple anomalies, closure defects of the neural tube were missed, and in two cases with hydrocephaly, prenatally suspected spina bifida was not confirmed after birth. Other false-positive diagnoses concerned posterior fossa anomalies and agenesis of the corpus callosum. Isaksen *et al.* reported reliability rates similar to those found in our study.[16] They compared prenatal ultrasound and postmortem findings in 124 fetuses and infants with CNS anomalies and found complete concordance in 89% of cases. Den Hollander *et al.* described 42 cases with prenatally diagnosed fetal ventriculomegaly and found complete concordance in 28 cases, more extensive anomalies in ten, and less extensive anomalies in four cases.[10]

Of course, the prognosis for surviving children depends on their specific anomaly. In our study the children most likely to survive were those with spina bifida and hydrocephaly. Out of nine survivors with spina bifida, five had normal mental development and four could walk independently. Their development depended mainly on the level of the lesion. Out of 13 survivors with hydrocephaly, five had normal mental development, and seven could walk independently.

Overall, the children with isolated hydrocephaly were less disabled than those with additional anomalies. Mulder *et al.* described the outcome of 67 fetuses with a CNS anomaly.[17] Only 1/25 fetuses with spina bifida survived, and this child was severely retarded at the age of 2 years. Out of three survivors with hydrocephaly, one child was moderately retarded and two developed normally. Den Hollander *et al*. found normal psychomotor development in 12/26 surviving children with prenatally diagnosed ventriculomegaly.[10] Lipitz *et al.* found normal neurological outcome for 25/26 fetuses with isolated, borderline unilateral ventriculomegaly.[18] Twining *et al.* studied 38 cases of fetal ventriculomegaly.[19] They found that fetuses with isolated ventriculomegaly had an 80% chance of survival and a 50% chance of normal development. Aletebi and Fung found some degree of cognitive, neurosensory or psychomotor delay at follow-up in 4/5 survivors with prenatally diagnosed posterior fossa abnormalities.[18] In general, our findings concur with those of previous studies.

Conclusion

We conclude that prenatal diagnosis of CNS malformations is fairly reliable and that the prognosis of affected fetuses is generally poor. Due to the high rate of TOP and to the frequent association with other anomalies, the survival rate was only 25% in our study. More than 50% of surviving children were moderately or severely disabled.

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CHAPTER 5

Follow-up of children born with an umbilical arterial blood pH < 7

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Based on: Am J Obstet Gynecol 1995;173:1758-64

Abstract

Objective We performed neurodevelopmental assessment in children born with an umbilical artery pH < 7.

Methods All infants born with an umbilical artery pH < 7 from a 19-month period were retrieved from the obstetric database. Obstetric, neonatal, and pediatric records were reviewed. At an age of 1 to 3 years, children were visited at home for semi-structured questioning of the mother and a Denver Developmental Screening Test of the child.

Results During the study period 1614 umbilical artery pH measurements were entered in the database. Thirty (1.9%) were < 7. From this group 23 infants were admitted to the neonatal intensive care unit, and 8 of them required intubation. Twenty-eight children survived the neonatal period. Three children experienced an episode of mild hypertonia. One child had a mild motor developmental delay.

Conclusion Babies born with an umbilical artery pH < 7 are at great risk to experience considerable short-term morbidity. Those who leave the neonatal intensive care unit without major problems have good outcomes, and pessimism in counselling their parents is unwarranted.

Introduction

Umbilical artery pH is considered to be an objective measurement, reflecting the baby's condition at the time of birth. In many countries this measurement is part of quality control programs in obstetric care and may be used in cases of litigation. This pH value correlates well with fetal scalp blood pH immediately before delivery and with capillary blood pH of the baby immediately after birth.[1] During pregnancy umbilical artery pH averages 7.37 (SD 0.03). Published normal and pathologic values after delivery are listed in **Table 1.**[1-15] The lower statistical limits of normal umbilical artery pH values (mean - 2 SD) in this table range from 7.02 to 7.18. An umbilical artery pH < 7 is well below this range and has been suggested before to be the most realistic cutoff for pathologic acidemia at birth.[16, 17]

Table 1. Umbilical artery pH values reported in literature

Source	No. of deliveries	Mean umbilical artery pH	Lower statistical limit of normal umbilical artery pH (mean - 2 SD)
Saling [1] (1964)	77*	7.25	7.09
Kubli *et al.* [2] (1972)	3,317	–†	< 7.10 (5%)
Römer *et al.* [3] (1976)	3,804	7.27	7.10
Huisjes and Aarnoudse [4] (1979)	852	7.20	7.02
Sykes *et al.* [5] (1982)	899	7.20	7.04
Eskes *et al.* [6] (1983)	4,667	7.23	7.09
Yeomans *et al.* [7] (1985)	146*	7.28	7.18
Low [8] (1988)	4,500	7.26	7.13
Ruth and Raivio [9] (1988)	106*	7.29	7.15
Ramin *et al.* [10] (1989)	1,292*	7.28	7.14
Thorp *et al.* [11] (1989)	1,694*	7.24	7.10
Fee *et al.* [12] (1990)	13,601	7.27	–†
Miller *et al.* [13] (1990)	147*	7.27	7.15
Römer and Wesseler [14] (1991)	2,549	7.27	7.13
Vintzileos *et al.* [15] (1992)	243*	7.28	7.14
This study	1,614	7.21	7.03

*Selected population (uncomplicated pregnancy and delivery).
†Values not reported by authors.

Low umbilical artery pH values tend to be viewed with a pessimism similar to that for low Apgar scores. Several authors have pointed out that pediatricians and obstetricians tend to be unrealistically pessimistic about the prognosis of infants born with low Apgar scores.[18, 19] The same applies to low umbilical artery pH values, although umbilical artery acidemia at birth is seldom associated with poor neurologic outcome.[9, 12, 20] Dijxhoorn *et al.* concluded that most neonatal neurologic abnormalities must be caused by other factors.[21] Definitions of acidemia, however, differ among studies, and follow-up is often rather selective. Realistic counselling of parents as to what to expect in the long run is therefore difficult. To provide a rational basis for such counselling we conducted a follow-up of all infants born in our unit with an umbilical artery pH < 7 and studied their developmental outcome at age 1 to 3 years.

Methods

Routine measurement of both venous and arterial umbilical pH was introduced for all births at Leiden University Hospital in April 1991. A segment of the cord 10 to 30 cm long is doubly clamped and kept at room temperature. Blood gas and pH are measured within 30 minutes after birth, with a Corning 178 (Medfield, Mass.) analyzer. This analyzer, located next to the delivery rooms, is tested twice a day to verify its reliability.

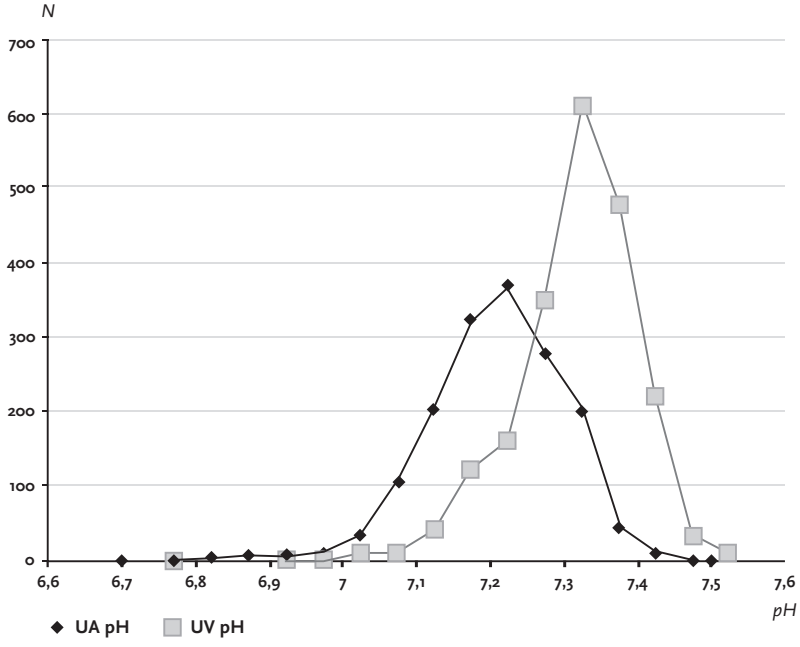
Data were entered in our obstetric database. The database was searched for umbilical artery pH values < 7 of all babies born alive, of at least 24 weeks' gestation, and without apparent congenital anomalies for the period up to December 1992. Obstetric and neonatal records of these mothers and babies were reviewed.

With approval of the protocol by the hospital's ethical committee, family physicians were contacted by letter to explain the aims and nature of the study. After consultation with the family physician, the parents were sent an explanatory letter asking their permission to review all medical records and their cooperation for screening the children in their home environment. At the subsequent home visit a history was taken from the mother, concentrating on her birth experience and development of the child. The child was examined with the Dutch version of the Denver Developmental Screening Test (DDST). The DDST is designed for children aged 2 weeks to 6 years and covers four areas of development: personal social, fine motor adaptive, language, and gross motor development. The test results are scored as normal, questionable, or abnormal. All home visits were performed in January and February of 1994 by one of the authors (HTCN) who had received 3 months' intensive training in pediatric neurology and neuropsychology for this purpose.

Results

During the 19-month study period 2,536 babies were born in the department. Umbilical vein and umbilical artery pH, respectively, were available for 81% and 64% of them. Mean umbilical vein pH was 7.31 (SD 0.09), and mean umbilical artery pH was 7.21 (SD 0.09) **(Fig 1)**. Mean arteriovenous difference was 0.11 (SD 0.06).

Figure 1. Frequency distribution of umbilical vein (UV) and umbilical artery (UA) pH values measured between April 1991 and December 1992 at the Obstetric Department of Leiden University Hospital.



Thirty (1.9%) of the 1,614 babies with recorded umbilical artery pH values had a value < 7. Umbilical artery pH at birth and 5-minute Apgar score of these babies showed only a weak correlation (r = 0.45) **(Fig. 2).** The obstetric data of the 30 babies are summarized in **Table 2**. Mean umbilical artery blood pH in this group was 6.91 (range 6.70 to 6.99). Mean umbilical artery base deficit in this group was 16.85 (range 11.4 to 26.5). Nine of the 30 babies (30%) were preterm (< 37 weeks), but only one of them was very preterm (< 32 weeks) whereas 6 (20%) were postterm **(Table 2)**. All neonates except one (case 15) with a birth weight of 2,380 g at 38 weeks were of appropriate weight for gestation. In 20 of the 30 infants fetal distress was suspected on the basis of an abnormal fetal heart

rate pattern or fetal scalp acidemia during delivery. Two babies were born after emergency cesarean section because of complications during cordocentesis for suspected fetal thrombocytopenia. In both cases a cord hematoma was seen after birth. In one (case 10, maternal idiopathic thrombocytopenia) the fetal platelet count was 164,000/µ1. In the other (case 14, alloimmune thrombocytopenia on the basis of human platelet antigen-la) the fetal platelet count during the procedure was 32,000/µ1.

Figure 2. Correlation between umbilical artery (UA) pH at birth and 5-minute (5') Apgar score in 30 infants born with an umbilical artery pH < 7. Umbilical vein (UV) pH was < 7 in 7 cases.

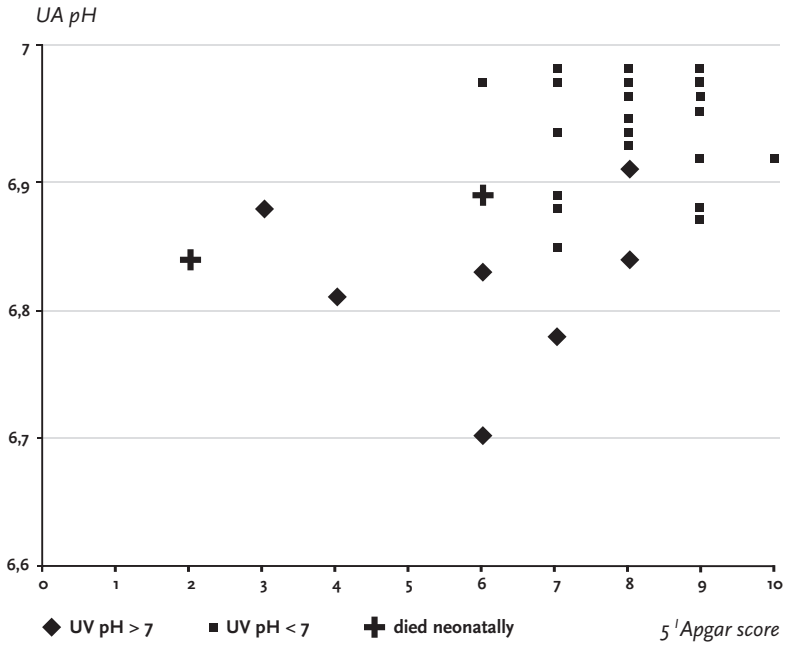


Table 2 (next page) also shows neonatal and pediatric data of these 30 children.[22] Of the 23 infants admitted to the neonatal intensive care unit, 8 required intubation and artificial ventilation. Because of clear signs of severe neurologic damage, artificial ventilation was discontinued in 2 neonates. They both died shortly thereafter. Of the 28 survivors, 25 could be visited at home. For 3 of the infants the parents gave permission to retrieve all medical information but declined a home visit. Reasons for refusal were excessive medical contacts (case 7), feelings of resentment (case 12), and not given (case 18). The medical records of all 3 explicitly mentioned normal neurologic development at the ages of 14 (case 7), 26 (case 12), and 29 (case 18) months, respectively.

The ages of the children at the home visits ranged from 14 to 33 months. Twenty-three infants performed the DDST well and scored a normal test result. One child (case 24) displayed a mild motor developmental delay. Her test result was scored as questionable. Another child (case 9) refused to perform some items of the fine motor adaptive tasks. Her test result was scored as questionable, but she was tested shortly afterward by a pediatrician and then performed the test in a normal manner. None of the children had results scored as abnormal.

Three children had experienced an episode of mild hypertonia. Febrile convulsions had occurred in 3 children, in two of them more than once. In both cases neurologic examination and electroencephalographic findings showed no abnormalities.

The semi structured interview of the 25 mothers visited at home resulted in the following assessments. Twenty-one were aware of the fact that an Apgar score was given, and 19 could explain the main principles of the score. Only 4 knew, before they received our request to participate in this study, that umbilical artery pH measurement was routinely performed. Nineteen of 25 mothers believed that their babies did not have a good start in life.

Discussion

We studied a complete cohort of children with severe acidemia at birth defined as an umbilical artery pH < 7. There was considerable short-term morbidity: 77% were admitted to the neonatal intensive care unit and 27% required artificial ventilation. Two of the 30 children died in the neonatal period. In a follow-up of the 98 survivors we found no major abnormalities at age 1 to 3 years. During their first years of life, 4 of the 28 (14%) surviving children demonstrated minor abnormalities: three had episodes of mild hypertonia, and one had a mild motor developmental delay as detected by the DDST. This incidence is comparable to the 21% incidence of mild motor abnormalities found by Low *et al.* in the first year after uneventful birth.[23] We do realize, however, that the DDST is only a screening test and that subtle forms of brain damage may not be discovered by this test.

Table 2. Obstetric, neonatal, and pediatric data

Case No.	Obstetric						Neonatal		
	Gestational age (compl. weeks)	UA pH	UV pH	Obstetric risk factors	Suspicion of fetal distress	Mode of delivery	NICU Admittance	Length of intubation (hr)	Clinical signs of encephalopathy[22]
1	32	6.88	6.94	Preeclampsia, abruptio placentae	+	CS before labor	+	72	–
2	33	6.91	6.95	Uterine rupture	+	CS during labor	+	6	–
3	34	6.89	7.03	Diabetes mellitus	+	CS before labor	+	–	–
4	35	6.78	6.80	Abruptio placentae	+	CS before labor	+	1	Sarnat I
5	36	6.70	6.75	Abruptio placentae	+	CS before labor	+	–	–
6	36	6.88	7.31	–	–	Spontaneous	–	–	–
7	36	6.92	7.23	–	–	Spontaneous	–	–	–
8	36	6.98	7.37	PROM; breech	+	Extraction	+	–	–
9	36	6.99	7.28	Rh isoummunization; Breech	+	Extraction	+	–	–
10	37	6.92	7.08	Complication at cordocentesis	+	CS before labor	+	3	–
11	37	6.99	7.20	Breech	–	Extraction	+	–	–
12	38	6.81	6.94	PROM	–	Vacuum extraction	+	–	Sarnat I
13	38	6.84	–	Abruptio placentae	+	CS before labor	+	100	Sarnat III
14	38	6.89	7.31	Complication at cordocentesis	+	CS before labor	+	14	Sarnat III
15	38	6.99	7.04	PIH	+	Trial of vacuum extraction; CS during labor	+	3	–
16	39	6.84	6.90	Meconium	–	Spontaneous	+	–	–
17	39	6.94	7.23	Breech	+	Extraction	+	–	–
18	39	6.96	7.01	HELLP	–	Spontaneous	–	–	–
19	39	6.98	7.14	-	+	Spontaneous	–	–	–
20	40	6.85	7.17	Intrapartum version of oblique lie	+	CS during labor	+	70	–
21	40	6.94	7.04	PROM; meconium	+	Vacuum extraction	+	–	–
22	41	6.83	6.99	No progress	+	Vacuum extraction	+	–	Sarnat I
23	41	6.99	7.10	CPD; meconium	+	CS during labor	+	–	–
24	41	6.99	7.28	–	–	Vacuum extraction	–	–	–
25	42	6.89	7.02	Epileptic convulsions during pregnancy	–	Vacuum extraction	+	–	–
26	42	6.89	7.14	Breech	+	Extraction	+	–	Sarnat I
27	42	6.94	7.06	Breech; meconium; cord prolapse	+	CS during labor	+	–	Sarnat I
28	42	6.95	7.29	No progress	–	Vacuum extraction	–	–	–
29	42	6.97	7.27	Meconium	+	Spontaneous	–	–	–
30	42	6.99	7.08	–	–	Spontaneous	+	–	–

UA, umbilical artery; UV, umbilical vein; NICU, neonatal intensive care unit; plus sign, present; minus sign, absent; CS, cesarean section; N, normal result; PROM, premature rupture of membranes;

Neonatal				Pediatric		
Pulmonary problems	Renal or liver dysfunction	Antibiotic Treatment	Other neonatal complications	Medical history	Age at test (mo)	DDST
Hyaline membrane disease, grade III	–	+	Bradycardia	Febrile convulsions; systolic murmur	31	N
–	–	+	Hypoglycemia	–	25	N
–	–	–	Myocardial hypertrophy	Delayed bonding	17	N
Wet lung	+	–	Leukopenia; hypoglycemia	Pyloromyotomy	19	N
–	+	–	–	Hypertonia; febrile convulsions	28	N
–	–	–	–	–	31	N
–	–	–	–	Inguinal hernia; amblyopia	–	–
–	–	–	Jaundice	–	21	N
–	–	–	Exchange transfusion	Myocardial hypertrophy	24	Q
Wet lung	–	–	–	–	32	N
–	–	–	Jaundice	–	32	N
–	–	+	–	–	–	–
Pneumothorax	+	+	Hypovolemic shock; convulsions; died 100 hr postpartum			
–	+	+	Generalized hypotonia; died 18 hr postpartum			
–	–	–	Jaundice	Hypertonia	26	N
Wet lung	–	–	–	Otitis media; pulled elbow	33	N
–	+	–	Brain scan; frontal flaring	Normal brain scan	21	N
–	–	–	–	Single febrile convulsion	–	N
–	–	–	–	Hyperactive	28	N
Meconium aspiration	–	+	–	–	25	N
–	+	+	Sepsis; meningitis	–	24	N
–	+	–	–	Bronchial asthma	19	N
–	–	–	Single umbilical artery	Atopy; hypertonia	17	N
–	–	–	–	Obstipation	14	Q
–	–	–	Jaundice; hypoglycemia	–	24	N
–	–	+	–	–	29	N
–	–	–	Hypertonia	Sacral dimple	16	N
–	–	–	–	–	14	N
–	–	–	–	–	30	N
–	–	–	–	–	18	N

Q, questionable result; PIH, pregnancy induced hypertension; HELLP, hemolysis, elevated liver enzymes, low platelet count; CPD, cephalopelvic disproportion.

We searched the literature for follow-up studies on children born with severe acidemia. In the studies by Ruth and Raivio and Dijxhoorn *et al.* no major motor or cognitive deficits were found among children born with umbilical artery pH < 7.[9,24] The number of infants with pH < 7 studied in these reports was extremely small and follow-up ranged from 1 to 12 months. Fee *et al.* studied 15 children and Dennis *et al.* studied 27 children born with an umbilical artery pH < 7.05.[12,20] These children were followed up at age 1 to 2 years and age 4 to 5 years, respectively. None of these children were reported to have major deficits. Goodwin *et al.*, however, reported major abnormalities among 10 of 29 infants born with an umbilical artery pH < 7.[25] In their study umbilical artery pH measurement was selectively done in cases of fetal distress or neonatal depression. Follow-up was restricted to those infants with abnormal examination results at hospital discharge. There was no follow-up of infants who were normal at discharge from the neonatal intensive care unit.

Low *et al.* conducted two follow-up studies on children born with metabolic acidosis, defined as buffer base <34 mEq/L.[23,26] In a first study 37 infants without neonatal encephalopathy were selected.[23] At follow-up one child had a major motor handicap caused by a traumatic intercurrent event during childhood. They found no other children with major motor or cognitive deficit in the study group. In a second study the same authors evaluated another 37 infants.[26] Five of these had major motor deficits at age 1 year and 2 of these 5 infants also were mentally retarded. In contrast to the findings in the former study, almost half of the infants included in this study had documented newborn encephalopathy. Three of the 5 infants with major deficits had severe newborn encephalopathy with coma or multiple seizures.

Conclusion

Umbilical artery pH measurement is not superfluous. It has actual value in selecting those babies that are in need of extra neonatal care, and it also provides good means of retrospectively evaluating our obstetric efforts in preserving fetal health during birth. The results of our study indicate, however, that umbilical artery pH measurement after birth is not predictive of serious developmental delay, unless it is accompanied by clinical evidence of hypoxic encephalopathy. This seems only logical, since this measurement remains no more than a snapshot of the situation. In addition to the degree of acidosis, the duration of acidemia undoubtedly plays a role. To summarize our results we would state that if a neonate born with severe acidemia shows no severe neurologic abnormalities in the newborn period, pessimism in counselling the parents concerning the future psychomotor development of their child is unwarranted.

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CHAPTER 6

Long-term neurodevelopmental outcome in twin-to-twin transfusion syndrome

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Abstract

Objective To determine the long-term neurodevelopmental outcome in children after twin-to-twin transfusion syndrome (TTTS).

Methods Maternal and neonatal medical records of all TTTS-cases admitted to our center between 1990 and 1998 were reviewed. Neurological and mental development at school age was assessed during a home visit in all TTTS-survivors.

Results A total of 33 pregnancies with TTTS were identified. Four couples opted for termination of pregnancy. All other pregnancies were managed conservatively, 18 (62%) with serial amnioreductions and 11 (38%) without intrauterine interventions. Mean gestational age at delivery was 28.6 (range: 20-37) weeks. Perinatal mortality was 50% (29/58). Birth weight of donor twins was less than recipient twins ($p<0.001$). Systolic blood pressure at birth was lower in donors than in recipients ($p=0.023$) and donors required more frequently inotropic support postnatally than recipients ($p=0.008$). The incidence of hypertension at birth was higher in recipients than in donors ($p=0.038$). Abnormal cranial ultrasonographic findings were reported in 41% (12/29) of the neonates. All long-term survivors ($n = 29$) were assessed during a home visit. Mean gestational age at birth of the surviving twins was 31.6 (range: 25-37) weeks. Mean age at follow-up was 6.2 (range: 4-11) years. The incidence of cerebral palsy was 21% (6/29). Five out of six children with cerebral palsy had an abnormal mental development. The incidence of cerebral palsy in the group of survivors treated with serial amnioreduction was 26% (5/19). Four children were born after intrauterine fetal death of their co-twin: two of them had cerebral palsy.

Conclusion The incidence of adverse neurodevelopmental outcome in TTTS-survivors is high, especially after intrauterine fetal death of a co-twin.

Introduction

Cerebral palsy is estimated to occur seven times more often in twins than in singletons.[1] The higher relative risk for cerebral damage is not only attributable to the higher incidence of premature birth and low birth weight in twins compared to singletons. Monochorionic twinning predisposes to cerebral damage due to complications caused by twin-to-twin transfusions.[2] Twin-to-twin transfusion syndrome (TTTS) occurs in approximately 15% of monochorionic pregnancies and results from shunting of blood from one twin, the donor, to the other twin, the recipient. The donor becomes hypovolemic and oliguric, whereas the recipient becomes hypervolemic and polyuric.[3] The management of TTTS remains a significant challenge in perinatal medicine, and the perinatal mortality rate in untreated TTTS is reported to be 75-100%.[4,5] Treatment of TTTS with serial amnioreductions or with laser coagulation of placental vascular anastomoses has decreased the perinatal mortality rate to an average rate of approximately 40%.[6-8] Nevertheless, the morbidity in surviving twins, which includes mainly neurological, cardiovascular and renal complications, remains high.[3] Cerebral white-matter lesions have been reported to occur antenatally in up to 35% of TTTS-survivors.[9] To date, few studies have reported long-term neurodevelopmental outcome in TTTS. The incidence of cerebral palsy and global developmental delay in surviving twins varies from 4% to 23%.[10-15] However, in most studies, follow-up of the surviving twins did not extend beyond a mean age of 2 years corrected for prematurity. Assessment at school age is essential since neurological handicaps and mental retardation may only become evident several years after birth.[16-18] The main purpose of our study was to evaluate long-term neurodevelopmental outcome in school-aged twins after TTTS.

Methods

We identified all cases of TTTS who were admitted at our center from January 1990 to December 1998. Written information on the aims of the study was sent to the parents of all surviving twins. Parents were asked for consent to examine their children. Neurological outcome was assessed in all children by a single pediatrician during a home visit. Neurological outcome was defined as abnormal when evidence of cerebral palsy was found. Cerebral palsy was classified as diplegia, hemiplegia, quadriplegia, dyskinetic or mixed. We estimated the level of mental development of the children according to their school performance. School entry in the Netherlands starts at four years of age. All children with learning disabilities due to mental retardation or behavioral problems are referred to a school for special education. For the purposes of the study, children in mainstream education with

or without special assistance were considered to have a normal mental development, whereas children who needed special education as well as children one or more grades below the appropriate school-level for their age were considered to have an abnormal mental development.

Diagnosis of TTTS was reached according to the following prenatal ultrasound criteria: 1.) monochorionicity established by absence of a "twin peak" sign and the presence of a thin dividing membrane, 2.) oligohydramnios (deepest vertical pocket < 1cm) in the twin sac of one fetus and 3.) polyhydramnios (deepest vertical pocket > 8cm) in the twin sac of the other fetus. During the study period, the standard treatment at our centre for TTTS was serial amnioreduction. Monochorionicity was confirmed after delivery.

The following obstetrical data were extracted from the medical charts: gestational age at the time of diagnosis, number of therapeutic amnioreductions and total volume of amniotic fluid removed, intrauterine death, gestational age at delivery and mode of delivery. We also recorded the stage of TTTS on admission.[19] In short, staging according to Quintero has five stages: stage I, bladder of donor twin still visible; stage II, anuria of donor twin; stage III, critically abnormal Doppler studies; stage IV, hydrops; stage V, death of one or both twins.[19] The following neonatal data were extracted: birth weight, Apgar score at 5 minutes, arterial blood pressure on admission measured with Dinamap, hematocrit on day 1 of life. Growth discordance between recipient and donor was calculated by dividing the difference in birth weights by the birth weight of the recipient twin. Hypotension or hypertension at birth was defined as a systolic blood pressure respectively below the 3rd or above the 97th percentile for gestational age.[20] We also recorded the use of inotropic support during the stay in our nursery. Neonatal cranial ultrasound findings were reviewed, such as periventricular leukomalacia (PVL) (grade classification according to de Vries *et al.*), intraventricular hemorrhage (IVH) (grade classification according to Volpe *et al.*), porencephalic or parenchymal cysts, subependymal pseudocysts, ventriculomegaly and lenticulostriate vasculopathy.[21,22] Other significant neonatal problems were also reviewed, including transient tachypnea of the newborn, respiratory distress syndrome, chronic neonatal lung disease, patent ductus arteriosus, necrotising enterocolitis, renal failure, hydrops fetalis, retinopathy of prematurity and congenital malformation.

Analysis of the TTTS group according to whether the twins were donor or recipient was performed in order to detect eventual differences in perinatal mortality and morbidity as well as differences in long-term outcome. Results of categorical variables were compared using Fisher's exact test, whereas continuous normally distributed variables were examined with paired Student's *t* test. Chi-squared test for trend was used in evaluate the relationship between the stage of TTTS and outcome. A probability-value <0.05 was considered to indicate statistical significance. Analysis was performed with SPSS software (version 10; SPSS, Inc., Chicago, Illinois, USA).

Results

Obstetric results:

During the 8-year study period, 33 multiple pregnancies (31 twins and 2 triplets) with TTTS were admitted to our center. The mean gestational age at the time of diagnosis was 22.4 (range: 15-28) weeks. The Quintero stage at admission was I in nine cases, II in eight cases, III in ten cases, IV in three cases and V in three cases. Four couples opted for termination of pregnancy. In the remaining 29 pregnancies, intrauterine death of both twins occurred in 38% (11/29) of the pregnancies. In four pregnancies, one twin survived while the co-twin died in utero. Caesarean delivery was performed in 9 (31%) of the 29 pregnancies. The mean gestational age at delivery was 28.6 (range: 20-37) weeks. Serial amnioreduction was performed in 18 (62%) of the 29 TTTS-pregnancies. Mean gestational age at birth of the group of twins treated with serial amnioreduction was 31.3 weeks (range: 28-35). The median number of amnioreductions per case was 1 (range: 1-7) and the mean amount of amniotic fluid removed 2 litres (range: 0.5-15) per pregnancy. Amnioreduction was not performed in the remaining 15 pregnancies either due to intrauterine death of one or both twins at presentation (n = 7), because the patient opted for termination of pregnancy (n = 4), because of mild TTTS (Quintero stage I) (n = 3), or due to imminent delivery (n = 1). We found a direct relationship between stage of TTTS and mortality rate (P = 0.042) as well as stage of TTTS and adverse outcome (cerebral palsy or death) (P = 0.015) **(Table 1)**. Cases, in which parents opted for termination of pregnancy (n = 4) and, cases with stage V (n = 3) of TTTS were not included in this analysis.

Table 1. Mortality rate and adverse outcome (cerebral palsy or death) by stage of TTTS

Stage	Death*	Cerebral palsy or Death†
I	31% (5/16)	37% (6/16)
II	33% (4/12)	42% (5/12)
III	61% (11/18)	83% (15/18)
IV	67% (4/6)	67% (4/6)
Total	46 % (24/52)	58 % (30/52)

Values are percentages (n/N)
Cases in which parents opted for termination of pregnancy (n = 4) and cases with stage V (n = 3) of TTTS were not included in this analysis.
*Chi-squared test for trend = 4.1, df = 1, P = .042
†Chi-squared test for trend = 5.9, df = 1, P = .015

Table 2. Mortality and morbidity rates in donor and recipient twins

	Donor (n=29)	Recipient (n=29)	P-value
Intrauterine fetal death	41.4% (12/29)	48.3% (14/29)	NS
Neonatal death	17.6% (3/17)	0% (0/15)	NS
Overall perinatal death	51.7% (15/29)	48.3% (14/29)	NS
Cerebral Palsy	17% (3/17)	17% (3/17)	NS

Values are percentages (n/N)
Cases in which parents opted for termination of pregnancy (n = 4) were not included in this analysis.
NS, not significant.

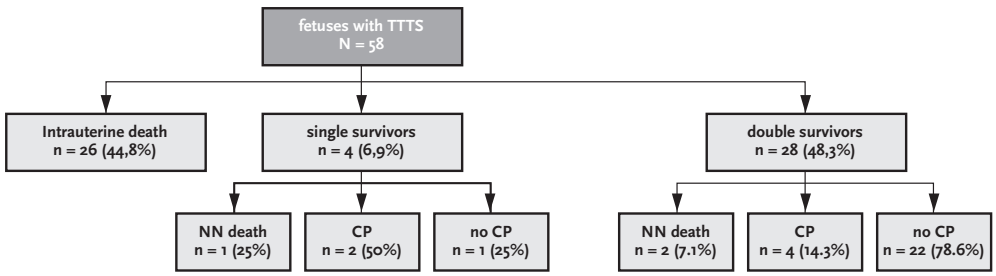
Neonatal results:

Thirty-six (55%) fetuses were male, 30 (45%) were female. The overall perinatal survival rate was 50% (29/58) and in the subgroup treated with serial amnioreduction, 53% (19/36). Neonatal death occurred in 3 infants, all donor twins, and was caused by terminal renal failure (n =1), *Escherichia coli* sepsis (n = 1) and severe respiratory distress syndrome (n = 1). There was no difference in overall perinatal mortality between donor and recipient twins **(Table 2)**. The mean birth weight in donors was 1,016 g (range: 220-2,740), whereas the mean birth weight in recipients was 1,291 g (range: 310-2,790). The difference in birth weight between donors and recipients was significant (P < 0.001). Eight of the 17 donors (47%) were also small for gestational age as compared to none of the recipients (P = 0.003). The mean birth weight discordance between life born recipients and donors was 24% (range: 2%-41%). The median Apgar score at 5 minutes was 8 (range: 4-10). There was no significant difference in Apgar score between donors and recipients. The mean hematocrit at birth in donors was 48.2% (range: 28-68) and in recipients, 51.8% (range: 39-66). The difference in hematocrit between donors and recipients was not significant. The mean systolic blood pressure at birth in donor twins was 45.6 (range: 30-60) mmHg and in recipients 61.8 (range: 44-94) mmHg. The difference in systolic blood pressure at birth between donors and recipients was significant (P = 0.023). Eight of the 17 donors (47%) also required inotropic support as compared to only one of the recipients (p = 0.008). Hypertension at birth was found in 27% (4/15) of the recipients, but in none of the donors (P = 0.038). Renal failure occurred in two neonates, both of whom were donor twins. One of them died of terminal renal failure, the other child requires hemodialysis. Fetal hydrops was found in two twins at delivery (6%). One of them was a recipient twin. The other case of fetal hydrops occurred in a donor after the co-twin died in utero and was due to severe fetal anaemia

(hemoglobin value of 4.5 g/dL) probably after acute blood loss into the dead co-twin through the vascular anastomoses. An intrauterine blood transfusion raised the hemoglobin to 13 g/dL. The donor twin was born a few days later and was still hydropic. The incidence of respiratory distress syndrome was 31% (10/29 neonates). The incidence of chronic lung disease was 10% (3/29 neonates). Patent ductus arteriosus was found in 25% (8/32) of the neonates. Necrotising enterocolitis was diagnosed in 9% (3/32) of the neonates. None of the neonates had retinopathy of prematurity or congenital malformations.
We found no significant differences in neonatal morbidity between donors and recipients. Abnormal cranial ultrasonographic findings were found in 12 of the 29 neonates (41%) in whom a scan was performed (IVH grade I-II: 4 neonates, unilateral IVH grade III with intraparenchymal echodensity: 2 neonates, bilateral IVH grade III with intraparenchymal echodensity: 1 neonate, PVL grade I: 3 neonates, ventriculomegaly: 3 neonates, lenticulostriate vasculopathy: n=1).
In 3 neonates no cranial ultrasound scan was performed. We found no significant differences in abnormal ultrasonographic findings between donors and recipients.

Long-term outcome:
We were able to follow-up all 29 surviving twins during a home visit. The derivation of the surviving population is shown in a flow diagram in **Figure 1**.

Figure 1. Outcome of 58 fetuses in 29 pregnancies with TTTS.



Cases in which parents opted for termination of pregnancy (n = 4) were not included in this analysis.
NN, neonatal ; CP, cerebral palsy

The mean gestational age at birth of the surviving twins was 31.6 (range: 25-37) weeks and the mean age at follow-up was 6.2 (range: 4-11) years. The incidence of cerebral palsy was 21% (6/29) (spastic quadriplegia: n = 2, spastic diplegia: n = 3, spastic hemiplegia: n = 1).

The incidence of cerebral palsy in the group treated with serial amnioreduction was 26% (5/19 infants). Five children with cerebral palsy had abnormal mental development, and one child with left spastic hemiplegia had a normal mental development. All children with abnormal mental development needed special education. Both infants with quadriplegia were severe mentally retarded. Data regarding the 6 surviving twins with abnormal neurodevelopmental outcome are listed in **Table 3**. In the group of children without cerebral palsy or abnormal mental development, 22% (5/23) of the children had a mild speech delay and required speech therapy. All of these children were kept in mainstream education with special assistance from a teacher or remedial teaching.

Table 3. Data of the 6 surviving twins with adverse neurodevelopmental outcome

Case	Twin	Number of amino-reductions (n)	GA at birth (wk)	Birth weight (g)	Neonatal cranial ultrasound findings	Age at follow-up (y)	Neurologic outcome	Abnormal mental outcome	Other morbidity	Outcome of co-twin
1	Recipient	3	28	780	PVL I, ventriculomegaly	10 1/2	Quadriplegia	Yes	CLD	NN death
2	Recipient	3	29	1206	PVL I	10	Diplegia	Yes	NEC	IU death
3	Donor	7	32	930	Normal	9 1/2	Quadriplegia	Yes	renal failure	Normal
4	Donor	1	35	1064	Normal	6	Diplegia	Yes	none	Normal
5	Donor	4	32	1330	Normal	4 1/2	Diplegia	Yes	NEC	IU death
6	Recipient	0	25	801	IVH III + IPE	4	Hemiplegia	No	CLD	NN death

GA, gestational age; PVL, periventricular leukomalacia; CLD, chronic lung disease; NN, neonatal; NEC, necrotising enterocolitis; IU, intrauterine; IPE, intraparenchymal echodensity

Four survivors were born after intrauterine death of their co-twin: one of them died in the neonatal period due to sepsis caused by *Escherichia coli*, two survivors have cerebral palsy and only one survivor has a normal outcome.
The incidence of adverse long-term neurodevelopmental outcome in twins whose co-twin died in utero was 67% (2/3 children). The incidence of adverse long-term neurodevelopmental outcome in twins who were both born alive was 15% (4/26). The difference in neurodevelopmental outcome between survivors whose co-twin died in utero compared with twins who were both alive at birth was not significant, probably because study numbers were too small.

Gestational age at birth as well and birth weight were not associated with a significantly higher incidence of adverse neurodevelopmental outcome. We found

no significant difference in long-term neurodevelopmental outcome between donors and recipients. In the neonatal period, IVH grade I-II was diagnosed in four neonates. All of them have a normal long-term psychomotor outcome. One neonate had a bilateral IVH grade III with intraparenchymal echodensity and died in the neonatal period of terminal renal failure. Two neonates from the same pregnancy had a unilateral IVH grade III with intraparenchymal echodensity. One of them died two days after birth of multi-organ failure. Its co-twin had a right-sided IVH grade III with intraparenchymal echodensity and has now spastic hemiplegia on the left side. PVL grade I was diagnosed in 3 neonates. Two of them have an abnormal long-term neurodevelopmental outcome. One of them also had ventriculomegaly but has only mild symptoms (mild speech and motor delay) without further signs of cerebral palsy or abnormal mental development. Another child with ventriculomegaly died two days after birth. The neurodevelopmental outcome of the recipient twin with lenticulostriate vasculopathy was normal.

Discussion

We analysed the perinatal mortality and morbidity in TTTS. We report a high perinatal mortality rate (50%) in TTTS, which emphasizes the critical nature of this disease. The perinatal mortality rate in the group that was treated with serial amnioreduction was slightly lower (47%), and comparable to previously published mortality rates in pregnancies treated similarly.[6-8] We also found a direct relationship between stage of TTTS and mortality rate and between stage of TTTS and adverse outcome (cerebral palsy or death), which confirms the prognostic significance of the Quintero staging classification. Regarding the neonatal findings, this study shows a significant difference in systolic blood pressure at birth between donors and recipients. Hypertension at birth in recipients has been reported previously, and is theoretically more consistent with increased afterload rather than increased preload after volume overload.[23] Increased afterload may result from a higher endothelin-1 level in recipients.[24] Abnormal cranial ultrasonographic findings were found in 41% of the neonates who underwent cranial ultrasonography. Denbow *et al.* reported an even higher incidence, 58%, whereas Hecher *et al.* reported a lower incidence (range: 6% to 18%, depending on the type of antenatal therapy) of abnormal cranial ultrasound findings.[8,9] However, the definition of abnormal ultrasound findings in the study of Hecher *et al.* did not include IVH grades I and II.

The main objective of our study was to evaluate the long-term neurodevelopmental outcome in TTTS. We report a high incidence (21%) of cerebral palsy and abnormal mental development in surviving twins with TTTS. This is the first study in which all TTTS survivors were at least 4 years of age at

follow-up. Since the incidence of adverse neurodevelopmental outcome is positively correlated to the duration of follow-up, it is important to continue follow-up until school age.[17;18] The incidence of cerebral palsy and abnormal mental development is similar to most previous publications on long-term neurodevelopmental follow-up. Haverkamp et al. found a 23% incidence of severe psychomotor retardation in combination with cerebral palsy in a cohort of 40 survivors of TTTS who were followed until a mean age of 24 months.[13] Cincotta *et al.* found a 22% incidence of cerebral palsy and global developmental delay in 23 surviving twins who were followed to at least 2 years of age corrected for prematurity.[12] In a smaller study of 14 TTTS survivors who were followed until 2 years of age, Seng *et al.* report a lower incidence (14%) of cerebral palsy with mental retardation.[11] However, the inclusion criteria for TTTS of Seng *et al.* were not based on prenatal ultrasound findings, but rather on postnatal inter-twin hemoglobin and birth weight differences. Other studies, including our study, have shown that the recipient does not necessarily have a higher hemoglobin or a higher hematocrit than the donor. Reaching the correct diagnosis of TTTS is no longer guaranteed by these postnatal criteria. Therefore, some of their patients may not have been affected by TTTS, which would also explain the exceptionally high survival rate (88%) in their study. Mari *et al.* also report a much lower incidence (5%) of cerebral palsy in a cohort of 42 surviving twins who were at least 2 years of age at last follow-up.[10] However, one infant in their cohort had multilocular encephalopathy but was lost to follow-up. Another infant died at 6 months of age of respiratory as well as neurological complications. Whether this child also had cerebral palsy is not clearly mentioned. Most importantly, the rate of neonatal deaths in their study was high, 16% (8/51 infants). One half of these neonatal deaths occurred in children who were born at 24 and 25 weeks of gestation. The incidence of neurodevelopmental disability in children who were born at 24 and 25 weeks gestation is reported to range from 12% to 45%.[25] Two other neonates who died in their study were reported to have abnormal cranial ultrasound findings (respectively, brain infarction and IVH). Therefore the suspected incidence of cerebral palsy in the study of Mari *et al.* could be higher. In all three neonatal deaths reported in our study, major abnormal cranial ultrasound findings were found (bilateral IVH grade III with intraparenchymal echodensity, n=1; unilateral IVH grade III with intraparenchymal echodensity, n=1; ventriculomegaly, n=1). Therefore, the incidence of cerebral palsy in our study would most certainly have been higher had these three neonatal deaths not occurred. Mari *et al.* also found that survivors who were born after 27 weeks of gestation had an excellent long-term outcome. In our study, 5 of the 6 survivors with adverse neurodevelopmental outcome were born after 27 weeks of gestation. However, because our study was not a case-control study, we could not conclude whether cerebral palsy was prematurity related or TTTS related. We found that

adverse neurodevelopmental outcome was associated with intrauterine fetal death of a co-twin. This result supports previously published findings in which a higher incidence of serious neurological morbidity was found in survivors after death of a co-twin.[3,26,27] The major cause of cerebral white-matter damage in surviving twins whose co-twin died in utero is acute cerebral ischemia due to acute exsanguination of the surviving twin into the low-resistance vascular system of the moribund or dead twin through the vascular anastomoses.[3]

In all previously reported long-term follow-up studies, TTTS pregnancies were treated with serial amnioreduction. In our study, the incidence of adverse neurodevelopmental outcome in twins with TTTS treated with serial amnioreduction was also high (26%). Recent reports suggest that laser ablation therapy of placental vascular anastomoses may be associated with a lower incidence (4-9%) of cerebral palsy in surviving twins compared to serial amnioreduction.[14,15]

Conclusion

To assess whether cerebral palsy in TTTS is treatment related, the results of the first randomised control trial (www.eurofoetus.org) that compared both laser ablation therapy and serial amnioreduction must be awaited. Considering the high incidence of adverse neurodevelopmental outcome in TTTS, we recommend that all surviving twins undergo thorough follow-up visits.

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CHAPTER 7

Long-term outcome after fetal transfusion for hydrops associated with parvovirus B19 infection

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Abstract

Objective To evaluate neurodevelopmental status of children treated with intrauterine red blood cell and platelet transfusion for fetal hydrops caused by parvovirus B19.

Methods Maternal and neonatal records of all intrauterine transfusions for congenital parvovirus B19 infection in our center between 1997 – 2005 were reviewed. Congenital B19 virus infection was confirmed by the presence of parvovirus B19-specific IgM or parvovirus B19 DNA in fetal blood samples. All children underwent a general pediatric and neurological examination. Primary outcome measure was neurodevelopment status (developmental index by Bayley Scales of Infant Development or Snijders-Oomen test). Secondary outcome measure was general health status of surviving children.

Results A total of 25 IUT sessions were performed in 24 hydropic fetuses. Median fetal hemoglobin concentration, platelet count, and blood pH before intrauterine transfusions were 4.5 g/dL (range 2.4- 11.4 g/dL), 79 x 10^9/L (range 37-238 x 10^9/L) and 7.36 (range 7.31-7.51), respectively. Sixteen survivors aged 6 months to 8 years were included in the follow-up study. Eleven children (68%) were normal and 5 children (32%) demonstrated a delayed psychomotor development with a suboptimal neurological examination (mild delay n=3, severe delay n=2). Neurodevelopmental status did not correlate with pre-intrauterine transfusion hemoglobin, platelet, or blood pH values. Growth and general health status were normal in all. Two children had minor congenital defects.

Conclusion Neurodevelopmental status was abnormal in 5 of 16 survivors and was not related to the severity of fetal anemia and acidemia. We hypothesize that fetal parvovirus B19 infection may induce central nervous system damage.

Introduction

The incidence of parvovirus B19 (B19V) infection among seronegative pregnant women is around 2.4%.[1] Vertical transmission occurs in 33-51% of cases of maternal infection.[2,3] Fetal infection is fatal in 9% of the cases.[4] Fetal death occurs in more than half of the B19V cases with severe fetal anemia and hydrops.[3,5-11] Management of B19V infection with intrauterine red blood cell and platelet transfusions significantly reduces the mortality and morbidity of B19V infection.[12-16] However, severe fetal anemia or a prolonged hydropic state may also lead to delayed neurodevelopment in surviving children.[17,18] B19V has also been associated with cases of prenatal stroke, leading to significant neurodevelopmental delay in surviving patients.[19-21]

Few data are available concerning long-term neurodevelopmental outcome of patients surviving hydrops treated with intrauterine transfusions. Four groups studied the outcome in survivors of severe anemia due to red cell alloimmunization treated with intrauterine transfusions. The percentage of children with disabilities ranged from 4.5% to 10.5%.[14,15,22,23] However, fetal hemolytic disease may not be fully compared to B19V-induced fetal hydrops.

Dembinski *et al.* reported normal neurodevelopmental outcome in 20 survivors after B19V-induced fetal hydrops treated with intrauterine transfusions.[24] However, 11 other children in their series were lost to follow-up. Three children who received intrauterine transfusions for B19V described in two reports also had normal developmental outcome.[8,10]

The main objective of our study was to evaluate the neurodevelopmental status of children who survived fetal hydrops caused by B19V and treated with intrauterine transfusions. Primary outcome measure was the neurodevelopmental status of surviving children. We also studied the correlation between neurodevelopmental outcome and the severity of fetal anemia, thrombocytopenia and acidemia. Secondary outcome measure was the general health status of surviving children.

Methods

The Department of Obstetrics of the Leiden University Medical Center is the national referral center for intravascular fetal transfusion in the Netherlands. We searched our database for all intrauterine transfusions performed between December 1997 and December 2005 for cases of fetal hydrops and B19V infection. Fetal hydrops was defined as excess fluid in two or more cavities of the fetal body. Diagnosis was confirmed by the presence of B19V-specific IgM or B19V DNA in fetal blood samples. Fetal blood samples were assessed for hemoglobin

concentration (g/dL), platelet counts (x 10^9/L) and pH before and after intrauterine red blood cell and platelet transfusion. In all cases, blood samples were drawn to exclude chromosomal abnormalities. The amount of transfused blood necessary to correct for fetal anemia was calculated on the basis of the initial hematocrit and the estimated fetal weight according to the protocol by Rodeck *et al.*.[20] Results are depicted as percentages of the estimated fetal blood volume (120 mL/kg estimated fetal weight) in **Table 1.**

Table 1. Maternal, fetal and neonatal characteristics of the study population.

	Normal development at investigation (n=11)	Abnormal development at investigation (n=5)
Maternal age at intrauterine transfusions (y)	28 (19-36)	28 (24-32)
Gravidity	3 (1-4)	2 (1-3)
Parity	2 (0-3)	1 (0-2)
Maternal symptoms		
Fever	3	1
Skin rash	2	1
Arthralgia	3	4
Fetal movements		
Normal	3	2
Reduced	8	3
Gestational age at infection (wk)	17 (14–25)	14 (10-23)
Gestational age at intrauterine transfusions (wk)	22 (20–27)	20 (18-28)
Hemoglobin before intrauterine transfusions (g/dL)	5.4 (2.4-11.0)	4.4 (2.4-4.9)
Hemoglobin after intrauterine transfusions (g/dL)	12 (9.7–13.9)	11.8 (9.7-18.7)
pH before intrauterine transfusion	7.3 (7.3-7.4)	7.4 (7.3-7.5)
pH after intrauterine transfusion	7.3 (7.2-7.4)	7.3 (7.2-7.4)
Platelets before intrauterine transfusion (x 10^9)	54 (37-238)	102 (79-137)
Transfused volume of fetal blood volume (%)	27 (6 - 42)	20 (17-87)
Birth weight (g)	3145 (2145-4160)	3170 (2890-3340)
Gestational age at birth (wk)	39 (32 - 41)	40 (37-41)
Current age (y)	4 (0.5 - 8.0)	4 (0.4-8.0)
Intelligence quotient scores	104 (86-132)	76 (26-84)

Data are presented as median (range) or n.

The Institutional Review Board of the Leiden University Medical Center approved the follow-up study and all parents gave written informed consent for their children. A trained examiner assessed neurodevelopmental outcome using tests validated for each age category. The Bayley Scales of Infant Development (Second Edition-Dutch version :BSID-II-NL) was used for infants 1 to 42 months of age.[25,26] It is made up of three separate scales (mental scale, motor scale, and behavioral rating). Mental and motor scale scores are converted to a mental developmental index and a psychomotor developmental index with a mean of 100 and a standard deviation (SD) of 15. Normal limits are defined as mental developmental index and psychomotor developmental index values between 85 and 114. A score of 70-84 indicates a mild and a score <70 a severe delay. For children at 2.5 to 7 years of age, the revised Snijders-Oomen Non-Verbal Intelligence Test–Revised (2.5-7) was used.[27] This test consists of six basic subtests (Categories, Mosaic, Puzzles, Patterns, Situations and Analogies). Scores are calculated as performance scale and reasoning scale. Raw subtest scores are standardized with population and age-specific scores with a mean value of 100 and a SD of 15. The Snijders-Oomen Non-Verbal Intelligence Test-Revised has been validated for Dutch and Belgian children.

Data on parental ethnicity, education and socio-economic status were recorded. A pediatrician performed a standardized general examination, including weight, height and head circumference to evaluate growth using age-specific percentiles, and a standardized neurological examination.[28,29] A recent medical history was taken from the parents or caretakers.

Statistical analysis was performed by SPSS statistics (version 12 SPSS inc., Chicago, Illinois, USA). A P-value of < .05 was considered to indicate statistical significance. Results are depicted as median value and range. The correlation between neurodevelopmental status and fetal hemoglobin values, blood pH, and platelet counts was explored using separate linear regression analyses.

Results

We retrospectively evaluated the occurrence of maternal symptoms of B19V infection in the 16 mothers of children tested at 0.5 to 8 years of age. Symptoms occurred at a median gestation of 17 weeks (range 10- 25 weeks). In one case the timing of symptoms could not be determined. All women experienced general malaise, 4 (25%) had fever for 2-3 days, 7 (43%) noted generalized arthralgia, and 3 (18%) had a skin rash. Three women (18%) reported two or more symptoms. Seven women (43%) experienced no symptoms at all and were referred because of a suspected B19V contact during pregnancy.

Fourteen women became infected through contact with children who had fifth disease, either their own children or children at school or a daycare center.

In two cases, the source of infection could not be identified. Eleven women (68%) reported reduced fetal movements during clinical infection. Treatment by intrauterine transfusions invariably resulted in an immediate and persistent increase of fetal movements.

During the study period, 690 intrauterine transfusion procedures were performed at our center. Twenty-five intrauterine transfusion procedures (3.5%) were performed in 24 fetuses to correct B19V-induced hydrops and anemia. One fetus received two intrauterine transfusions. One fetus died during the intrauterine transfusion session, six died in utero after intrauterine transfusion sessions, and one infant died at birth (mortality rate: 33%). Sixteen of the 24 fetuses survived and all children were available for investigation at follow-up.

Maternal, fetal, and neonatal characteristics are depicted in **Table 1**. In two cases, hemoglobin concentrations after intrauterine transfusion could not be determined due to needle displacement. Fetal blood pH measurements were obtained in 12 cases. All available blood pH values were within the normal range before and after intrauterine transfusions.

One infant was born at 32 weeks of gestation by spontaneous preterm delivery. There were no signs of acute intrauterine infection and antenatal fetal heart rate monitoring was normal. He was ventilated for respiratory distress syndrome and recovered clinically with normal development at follow-up. All other infants were delivered at 37 or more weeks of gestation. One infant was small for gestational age with a birthweight of 2,340 grams at 37 weeks of gestation, the other infants had a normal birthweight. Fifteen infants had a 5-minute Apgar score higher than 7. One infant had a 5-minute Apgar score of 4, but neurodevelopment was normal at follow-up.

Physical examination demonstrated a cardiac murmur in one child with a clinically insignificant mitral valve insufficiency and a corrected hypospadia in another child. No other signs of dysmorphology were detected in these children. All other children were normal on examination. Weight, length, and head circumference were all within normal limits for age.

Tests for neurodevelopment were performed in the outpatient clinic (n=13). One child was tested in the home situation because of inability to travel. Two children had recently been evaluated extensively elsewhere because of possible neurodevelopmental delay. Parents consented to retrieval of all clinical data, but declined visiting our clinic for repeat investigation.

Seven children were tested with the Snijders-Oomen Non-Verbal Intelligence Test–Revised and nine with the BSID-II-NL test. Snijders-Oomen Non-Verbal Intelligence Test–Revised IQ scores and BSID-II-NL mental scores were within the normal range in 11 children (68%). These children all had a normal neurological examination. The medical history of one child suggested a delayed motor development, but neurological examination and developmental testing revealed

no abnormalities. He was later diagnosed with the Buschke-Ollendorff syndrome, an autosomal dominant disease consisting of osteopoikilosis and disseminated connective tissue nevi of elastic type, not associated with congenital B19 infection.

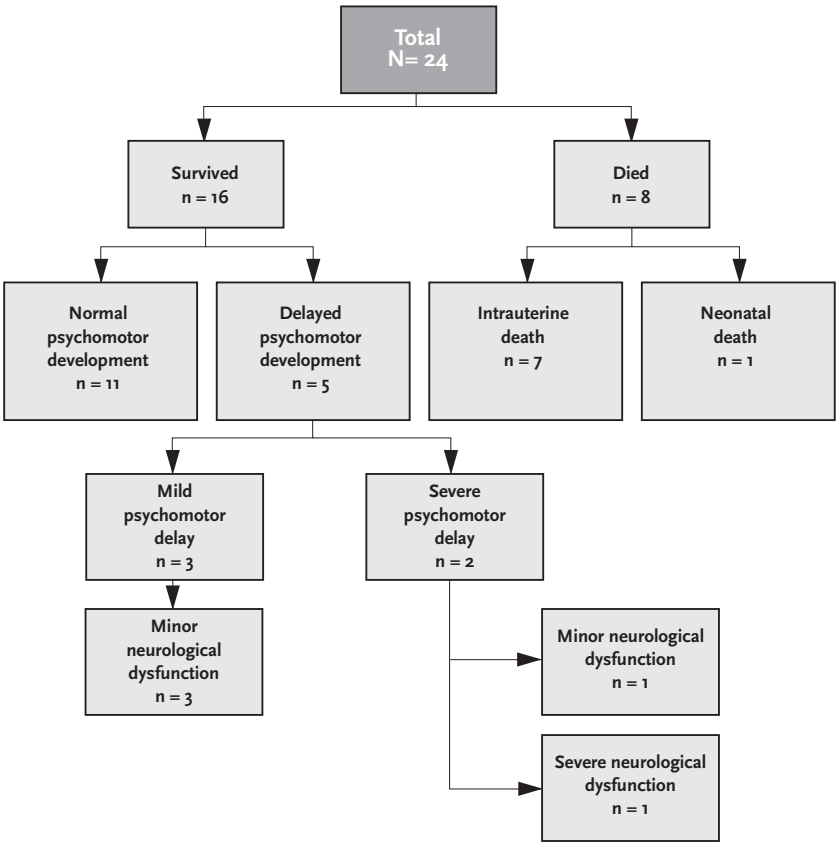
Table 2. Details of the 5 children with mild to severe neurodevelopmental delay.

Child	Current Age (y)	Sex	Gestational Age at Intrauterine Transfusion (wk)	Pre-Intrauterine Transfusion Hemoglobin (g/dL)	Pre-Intrauterine Transfusion Platelets (x 10^9/L)	Pre-Intrauterine Transfusion pH	Transfused Volume of Fetal Blood Volume (%)	Gestational Age at birth (wk)	Birth Weight (g)	DQ/IQ score (95% Confidence Interval)
1	1.5	Female	18	4.0	128	7.41	19	41	3,155	PDI:84 (87-97)
2	3.2	Male	20	5.0	87	7.35	17	40	3,175	MDI:76 (75-87)
3	7	Male	22	8.3	76	7.36	6	37	2,340	IQ:80 (107-117)
4	0.5	Female	23	4.5	79	7.51	24	40	3,170	MDI:55 (55-78)
5	7.5	Male	28	5.0	137	7.32	87	37	3,340	IQ:26 (107-117)

DQ: developmental quotient; IQ: intelligence quotient; MDI: mental developmental index; PDI: psychomotor developmental index.

Five children (32 %) had a developmental score indicating delay. Three children had a mild delay (children 1-3 in **Table 2**). Two children had a severe developmental delay (children 4 and 5 in **Table 2**). All five children demonstrated signs of a neurological deficit on examination. One child had marked hypotonia of the lower extremities, two children experienced delayed development of fine motor coordination, and one child suffered from marked hypertonia and hyperreflexia of the upper extremities suspect of developing diplegia. One of the two children with severe developmental delay (child 5) had strabismus convergens, ataxia and generalized hypotonia. Additional laboratory and metabolic investigations were unremarkable, but a cerebral magnetic resonance imagining (MRI) scan demonstrated atrophy of the cerebellar vermis.

Figure 1. Psychomotor and neurological outcome in the study group.



Neurodevelopmental outcome data are depicted in **Figure 1**, details are presented in **Table 2**. Using repeated linear regression analysis, no statistically significant correlations were found between neurodevelopmental status and fetal pre-intrauterine transfusion hemoglobin levels (r 0.059; 95% confidence interval [CI] -8.0 to +9.8, P=.834), intrauterine pH (per 0.1 unit: r 0.209; 95% CI -47.5 to +26.5; P=.537), or pre-intrauterine transfusion platelet counts (r 0.184; 95% CI -0.450 to +0.082; P=.159).

Discussion

The objective of this study was to evaluate long-term neurodevelopmental outcome and general health status of children who experienced fetal hydrops due to

intrauterine B19V infection. All children had been treated by intrauterine transfusions. Neurodevelopmental status was abnormal in one-third of the survivors of B19V infection. This is in contrast to the findings of the only other published large series of long-term follow-up in these patients. Dembinski and colleagues reported a good clinical outcome after intrauterine transfusions for B19V-induced hydrops.[24] However, they had a high loss to follow-up as only 20 out of 31 children (65%) were seen for testing. We agree with Wolke *et al.* that the chances for adverse outcome are generally much higher in the group that is initially lost to follow-up.[30] Miller *et al.* described long-term outcome after parvovirus B19 infection in 427 pregnancies with 367 surviving infants, of whom 129 were followed up at 7- 10 years of age by sending questionnaires to obstetricians and general practitioners.[8] Only seven fetuses in this series developed fetal hydrops, and only 3 of them survived, of whom 2 underwent an intrauterine transfusion. These 2 survivors had a good neurodevelopmental outcome. Rodis *et al.* investigated 108 children with congenital B19V infection and 97 controls at a median age of 4 years.[10] Significant delays in motor, speech, or language development or significant attention deficits requiring special education were observed in 7.4% of the children in the study group versus 7.2% in the controls, cerebral palsy was detected in one patient of the study group.[10] However, this study included only one hydropic fetus and outcome was assessed by sending a questionnaire to the caretakers.[10] We consider it a strength of our study that all children were individually investigated and tested for neurodevelopmental status.

Our findings on the association of B19V with congenital anomalies are similar to those of previous reports. Miller *et al.* described a case of ventricular septum defect and an earlier cohort study reported hypospadias.[8,4] We detected a case of mitral valve insufficiency and a case of hypospadias. Although some case reports suggest a possible teratogenic effect of B19V, a clear association of maternal B19V infection with congenital defects has not been proven.[31-33] This is further supported by normal growth and general health status in our study population. Dembinski *et al.* reported a higher incidence of preterm births (9 out of 20 children) compared to our report (1 of 16 births) and an average number of 4 intrauterine transfusions.[24] In contrast, all fetuses in our study received one intrauterine transfusion, except for one who received 2 intrauterine transfusions. The higher frequency of intrauterine transfusions in the group of Dembinski *et al.* may explain the increase in the number of preterm deliveries.[24] Average duration of gestation and hemoglobin levels at intrauterine transfusion were similar in both reports. We did not find any correlation between fetal hemoglobin levels, fetal blood pH, or pre-intrauterine transfusion platelet counts and neurodevelopmental status, but this may be due the limited sample size. The wide confidence intervals in the regression analyses confirm that the small number of study subjects is a limiting factor in this study.

One of our patients with a severe developmental delay had an abnormal MRI scan with atrophy of the cerebellar vermis. This is an interesting finding as two experimental studies on fetal B19V infection report cerebellar hypoplasia and ataxia as principal adverse outcomes.[34,35] Clinical studies have confirmed the presence of cerebellar lesions on MRI scans after congenital B19V infection and support the possibility of prenatal stroke in these infants.[19,36,37] We were not able to perform imaging studies in the other children as this was beyond the scope of this study. Future investigations should focus on the possibility of central nervous system damage after congenital B19V infection, especially in the presence of clinical symptoms or developmental delay.

Conclusion

Severe fetal hydrops may be prevented by timely referral and treatment of B19V infection during gestation. Because neurodevelopmental outcome is not clearly related to the severity of fetal anemia and acidemia, we speculate that fetal B19V infection may induce central nervous system damage.

Acknowledgements

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CHAPTER 8

Fetal arrhythmia and long-term outcome

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Submitted

Abstract

Objective To evaluate perinatal mortality, morbidity, long-term neurodevelopmental and cardiologic outcome of fetuses with severe tachy- or bradyarrhythmia.

Methods Follow-up study of 44 fetuses diagnosed with fetal cardiac arrhythmia between January 1990 and December 2005. Neurodevelopmental assessment included neurologic evaluation and assessment of developmental status by the Snijders-Oomen Non-Verbal Intelligence Test-Revised or the Dutch version of the Bayley Scales of Infant Development- Second Edition according to age. Cardiological assessment included clinical evaluation and electrocardiography.

Results Between January 1990 and December 2005, 44 fetuseses were diagnosed with sustained fetal tachy- or bradyarrhythmia: 28 with supravenricular tachycardia (SVT), 7 with atrial flutter (AF) and 9 with atrioventricular block (AVB). The incidence of cardiac anomalies was 18%. Hydrops was seen in 42-50%. Direct or transplacental fetal antiarrhythmic medication was given in 76% of cases. In the SVT group, 19 children needed medication postpartum. In 14/22, the arrhythmia ceased within the first year of life. In the SVT and AF group mortality was 6%. In 21% of these cases, Wolff Parkinson White (WPW) syndrome was diagnosed. Mental scores were normal in all survivors. Of the seven cases of AVB included in the follow-up there is no survivor. The other two cases were lost for long-term follow-up, but their medical records noted pacemaker therapy in one and mental retardation in the other.

Conclusion In conclusion, mortality in SVT and AF patients in our study was 6%, but mental scores were normal in all survivors. Twenty-one per cent of survivors had WPW syndrome. Prognosis in AVB patients was poor.

Introduction

Fetal cardiac arrhythmia is best defined as an irregular cardiac rhythm that results in a fetal heart rate outside the normal range (100-160 beats/minute).
Fetal arrhythmias are common in clinical practice, with a frequency ranging from 1% to 3% of all pregnancies. Most of these arrhythmias reflect transient, isolated ectopic beats. However, sustained episodes of tachy- or bradyarrhythmia do occur and, if not treated appropriately, these can lead to congestive heart failure, hydrops, fetal or neonatal demise, or severe neurologic morbidity in survivors.[1-7]

The most common forms of fetal tachycardias are supraventricular tachycardia (SVT), atrial flutter (AF), or sinus tachycardia. The majority of fetal SVTs are atrioventricular re-entrant tachycardias (AVRT) involving an accessory atrioventricular myocardial pathway. Other mechanisms of SVT, including atrial and junctional ectopic tachycardia, or ventricular tachycardia are rare, each constituting less than 1% of fetal arrhythmias. More than three quarters of cases of fetal bradycardia is caused by complete atrioventricular block (AVB). AVB in the absence of structural heart disease is mostly autoimmune mediated by maternal anti SS-A/SS-B antibodies. In general, complete AVB with complex congenital heart disease such as left isomerism has a very poor prognosis. Other, less frequent causes of bradycardia include sinus bradycardia, advanced second-degree AVB, prolonged QT interval syndrome, and fetal toxicity.

Ultrasound diagnosis of fetal arrhythmia offers the possibility of prenatal therapy. If indicated, antiarrhythmic drugs can be given directly to the fetus or via the mother in order to obtain a therapeutic plasma concentration in the fetus. In SVT, digoxin is the most commonly used drug. There is no consensus regarding second line antiarrhythmic treatment if digoxin therapy fails. In first and second degree AVB, transplacental steroid treatment may reduce the effects of inflammation and fibrosis of the conduction system caused by maternal antibodies. In AVB cases with extremely low ventricular rates transplacental treatment with sympathomimetic agents such as terbutaline or salbutamol can be given to increase atrial and ventricular rates. Elective delivery by cesarean section can be performed in the third trimester of pregnancy to start direct neonatal therapy (antiarrhythmic drugs, radiofrequency catheter ablation or pacemaker therapy).

The goal of pre- and postnatal treatment of fetal tachycardia is to achieve sinus rhythm or to reduce the fetal heart rate in order to prevent heart failure or death. In several reports, neurological morbidity has been linked to fetal tachycardia. Neurologic morbidity may result from dysfunction of cerebrovascular autoregulation in hemodynamically compromised fetuses.[8] In most cases of fetal tachycardia, medication can be stopped within months after delivery. However, in cases of fetal SVT, particularly involving accessory atrioventricular pathways, recurrences can be expected later in life. In the literature, we found strikingly little information regarding

long-term follow-up of major fetal arrhythmias.

The aim of this study was to evaluate perinatal mortality and morbidity as well as long-term neurolodevelopmental and cardiologic outcome of fetuses with severe tachy- or bradyarrhythmia diagnosed at our center.

Methods

Patients

Leiden University Medical Center is a tertiary fetal referral center. We searched both our antenatal and neonatal databases for infants with in utero cardiac arrhythmia, diagnosed between January 1990 and December 2005. In this time period the management protocol included complete work up with ultrasound examination and consultation of the pediatric cardiologist. Fetal ultrasound included detailed anatomic imaging of the fetal heart to diagnose or exclude cardiac defects. For the assessment of the cardiac rhythm and the origin of the ectopic beats we used M-mode evaluation of the atrial and ventricular walls, as well as visualization of blood flow within the cardiac chambers and the outflow tract with pulsed Doppler flow.

Fetal Diagnosis and Therapy

Supraventricular tachycardia (SVT) as a result of atrioventricular reentrant tachycardia (AVRT) was diagnosed if there was a 1:1 atrioventricular conduction observed with a short VA interval at a rate of 200 to 300 beats/min. Atrial flutter (AF) was diagnosed when the atrial rate was 300-450 beats/min. Ventricular rates in AF depended on the degree of AV conduction block, usually 200-300 beats/min. The highest (peak) fetal heart rate was noted to give an indication of the severity of the tachycardia. Tachycardias that were present more than 50% of the time during the ultrasound examination were defined as "persistent", and if tachycardia lasted less than 50% of the time it was classified as "intermittent". AVB was classified as 2nd degree or complete AVB based on M-mode registrations. Fetal hydrops was defined as a fluid collection visible on ultrasound in two or more cavities of the fetal body (generalized edema, ascites and pleural or pericardial effusions).[9] Maternal serum antibody titers (anticardiolipin antibodies, anti SS-A/Ro and anti SS-B/La) were obtained in case of a heart block.

Antiarrhythmic therapy was started when arrhythmias were sustained or associated with hemodynamic compromise at <34 weeks of pregnancy. After 34 weeks, such cases were delivered. A baseline electrocardiography of the mother was obtained before the treatment started and maternal cardiac monitoring was conducted during the loading period to detect early signs of toxicity. During the study period, the following drugs were used: digoxin, sotalol, flecainide, amiodarone and adenosine. Digoxin was administered to the mother in adjusted doses to

maintain a maternal serum therapeutic level of 1 to 2 ng/mL (loading dose 2 x 0.75 mg, maintenance 0.25-0.5 mg, maximum 0.75 mg/daily). Flecainide (200 mg to 400 mg daily) and sotalol (dose: 2 times daily 80-160 mg) were used as secondary agents. Amiodarone was administered by combined direct fetal intravenous and maternal oral and intravenous route. Direct fetal amiodarone therapy consisted of amiodarone on the basis of estimated fetal weight (10 mg/kg). In some cases adenosine was given intravenously as direct fetal therapy just before the amiodarone therapy (dose 0.1 mg/kg). Drugs to treat AVB were given to the mother: ritodrine (intravenously 9 mg/hour), dexamethasone (4 mg daily) and fenoterol (intravenously 150 μgram/hour).

Follow-up

Obstetric and neonatal records were reviewed. With approval of the protocol by the institutional review board of the Leiden University Medical Center, family physicians were contacted by letter to explain the aims and nature of the study. After consultation with the family physician, the parents were sent an explanatory letter asking their permission to review all medical records and their cooperation for testing the children. The neurodevelopmental and cardiological status was assessed from June - August 2006. The parents were asked to fill out the Dutch translation of the Child Behaviour Check List (CBCL), a validated questionnaire for the assessment of behavioural/ emotional problems. At the subsequent consultation the child was examined by a pediatric cardiologist and a psychologist. Neurologic examination was performed by a pediatrician. Cardiologic examination included medical history, physical examination and electrocardiography (ECG). Additional studies, i.e. 24 hour-Holter monitoring, exercise test and echocardiography were performed if children were symptomatic.

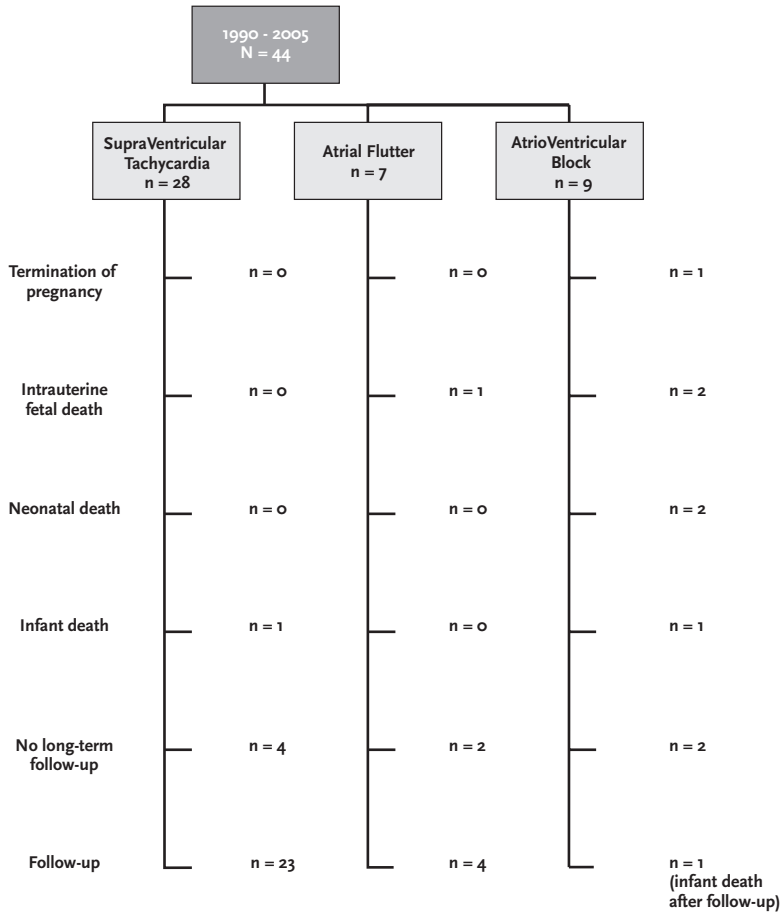
In the children aged 6 months to 30 months, the Dutch version of the Bayley Scales of Infant Development- Second Edition (BSID-II-NL) was used to test 3 scales of neurodevelopment (mental scale, motor scale and behavioral rating).[10,11] Mental scales are converted to a mental developmental index (MDI) with a mean of 100 and standard deviation of 15. Motor scales are converted to psychomotor developmental index (PDI) with mean 100 and standard deviation 15. The normal limits are defined as MDI and PDI values between 85-114. Values of 70-84 are defined as mildly delayed performance. A score of < 69 is defined as significantly delayed performance. In the children aged 2.5-16 years the intelligence scores were assessed with the Snijders-Oomen Non-Verbal Intelligence Test-Revised (SON-R 2.5-7 and SON-R 5.5-17).[12] Scores are calculated as performance scale (SON-PS) and reasoning scale (SON-R). Raw subtest scores are standardized with population and age specific scores with a mean value of 100 and a SD of 15. The SON-R has been validated for Dutch and Belgian children. Total test scores are depicted as IQ-scores with confidence intervals.

Results

Study population characteristics

During the 16-year study period, 44 pregnancies were referred to our center because of sustained fetal tachy- or bradyarrhythmia. **Figure 1** shows the overall outcome of the 44 fetuses with arrhythmia.

Figure 1. Overall outcome of 44 fetuses with arrhythmia.



Perinatal characteristics of the study population are presented in **Table 1**.

Table 1. Characteristics of the study population (N = 44), by type of arrhythmia.

Type of arrhythmia	SupraVentricular Tachycardia (n = 28)	Atrial Flutter (n = 7)	AtrioVentricular Block (n = 9)
Median maternal age in years (range)	28 (20-39) A	31 (24-39)	32 (28-36)
Median maternal gravidity (range)	2 (1-6) **A**	1 (1-4) **B**	2 (1-3)
Median maternal parity (range)	1 (0-4) **A**	0 (0-3) **B**	1 (0-1)
Median number of previous abortions (range)	0 (0-3) **A**	0 (0) **B**	0 (0-1)
Percentage of male fetuses (n)	60.7 (17)	42.9 (3)	57.1 (4) **C**
Median gestational age at diagnosis of arrhythmia in weeks (range)	29 (18-40) **B**	30 (24-38) **C**	23 (12-37) **B**
Median peak/slowest Fetal Heart Rate in beats per minute (range)	247 (200-400) **A**	237 (200-250) **B**	55 (45-70)
Percentage of fetal hydrops (n)	42.3 (11) **A**	- **C**	50.0 (4) **B**
Median duration of fetal hydrops in days since diagnosis (range)	7 (1-30) **A**	-	24 (1-50)
Percentage of antenatal therapy (n)	61.5 (16) **A**	50.0 (3) **B**	33.3 (3)
Median duration of antenatal therapy in days (range)	56 (12-95) **B**	49 (43-96)	33 (12-93)
Mode of delivery: vaginal / VE-FE / cesarean: n	19 / 1 / 7 **A**	4 / 1 / 1 **B**	7 / - / 2
Median gestational age at birth in weeks (range)	38 (30-42) **A**	37 (36-38) **C**	36 (30-40) **D**
Median birth weight in grams (range)	2993 (1547-3965) **A**	3282 (2530-4726) **B**	2704 (2300-3470) **D**
Median Apgar score (range) 1'	9(1-10) **B**	7 (3-9) **C**	8 (0-9) **D**
5'	10 (7-10) **B**	9 (6-10) **C**	8 (3-10) **D**
10'	10 (8-10) **C**	9 (6-10) **E**	8 (4-10) **F**
Median umbilical artery pH (range)	7.29 (7.10-7.43) **D**	7.29 (7.10-7.35) **C**	7.32 (7.12-7.41) **D**

VE-FE = Vacuum or Forcipal Extraction. Data are complete or % of missing or ignored values is indicated: **A**) ≤10; **B**) 10-20; **C**) 20-30; **D**) 30-40; **E**) 40-50; **F**) 50-60.

This study included no fetuses with ventricular tachycardia. The median gestational age at the time of diagnosis was 29 weeks for SVT (range 18-40), 30 weeks for AF (range 24-38) and 23 weeks for AVB cases (range 12-37). The mechanism of SVT was atrioventricular reentrant tachycardia in all cases. Hydrops at the time of diagnosis was present in 42% of SVT-cases. There were no fetal deaths in the SVT group and one termination of pregnancy (TOP) for trisomy 21 in the AF group. One infant in

the SVT group with cardiomyopathy and encephalopathy due to hydroxyglutaric aciduria died at the age of 5 months.
The AVB cases consisted of complete AVB (n=7) and 2nd degree AVB (n=2) and hydrops was present in 50% of the cases. Two of 9 cases had auto-immune associated AVB, 5 had complex congenital heart malformations and 2 had a severe form of long QT syndrome (LQTS 8 or Timothy syndrome). In the AVB group were 3 fetal deaths and 4 postnatal deaths **(Table 2)**. One case of infant death in the AVB group occurred after our follow-up.

Table 2. Details on cases of tachy- or bradyarrhythmia leading to fetal or infant death.

Type of arrhythmia	Complementary diagnosis	Outcome
SVT	D2-hydroxyglutaric aciduria induced cardiomyopathy	Died at age 5 months
AF	Trisomy 21	Intrauterine fetal death
AVB		TOP at 23 weeks
AVB	Left isomerism	TOP at 19 weeks
AVB	Corrected transposition of the great arteries, pulmonal stenosis	Intrauterine fetal death
AVB	Maternal Sjögren syndrome	Pacemaker, died at 20 months
AVB	Endocardial fibroelastosis	Pacemaker, died at age 2 days
AVB	Long QT syndrome	Pacemaker, died at age of 29 days
AVB	Long QT syndrome	Pacemaker, implantable cardioverter defibrillator, surgery, died at the age of 2 years

SVT = SupraVentricular Tachycardia; AF = Atrial Flutter; AVB = AtrioVentricular Block;
TOP = Termination of pregnancy

Drug therapy

Clinical data and details of drug therapy of all 19 cases of tachyarrhythmia in which prenatal drug therapy was applied are presented in **Table 3**. During antiarrhythmic therapy, sinus rhythm was achieved in 7/9 (77%) of non hydropic and in 6/8 (75%) of hydropic tachycardia fetuses **(Table 3)**. There is a trend towards multidrug therapy in the more recent years. Clinical data and details on drug therapy in the 3 cases of prenatally treated bradyarrhythmia are presented in **Table 4**. Pregnancies in these 3 cases were terminated by elective cesarean.

Table 3. Clinical data on cases of tachyarrhythmia in which prenatal drug therapy was applied.

Year	Type of tachyar-rhythmia	Continuous or intermittent	presence of fetal hydrops	Maternal and direct fetal drug therapy	Conversion Yes/No (after number of days of therapy)
1992	SVT	continuous	yes	D→F→D→cs	no
1994	SVT	continuous	yes	D + K	unknown
1994	SVT	intermittent	no	D	yes (66)
1997	SVT	Intermittent	no	D	unknown
2002	SVT	intermittent	no	D	yes (16)
2001	SVT	continuous	no	D	yes (4)
1996	SVT	intermittent	yes	S	yes (7)
1997	AF	intermittent	no	S	no
1997	SVT	intermittent	no	S	yes (19)
1998	AF	intermittent	no	D→D + S	yes (14)
1998	SVT	continuous	yes	S→S + D→D + F	yes (5)
1998	SVT	continuous	yes	S→D + F→F	yes (5)
1999	SVT	intermittent	yes	F→F + D	yes (5)
2000	SVT	intermittent	no	D→D + F→F	yes (4)
2002	SVT	continuous	yes	F→F + D→Ad(cc) + Am(cc) + Ad(cc) + Am(iv/o)→Am(iv) + D(iv)	yes (19)
2003	SVT	intermittent	yes	D + F→D + S →Am(cc/iv/o)→Am(cc/iv/o)→cs	no
2004	SVT	intermittent	no	F	yes (1)
2004	AF	continuous	no	F→F + D →cs	no
2004	SVT	intermittent	yes	D + F→Ad(cc) + Am(cc/iv/o)	yes (12)

SVT = SupraVentricular Tachycardia; AF = Atrial Flutter; cs = elective preterm delivery by Cesarean Section; iv = intravenous; cc = cordocentesis; o = oral; D = Digoxin; F = Flecanaide; K = Kinidine sulphate; S = Sotalol; Ad = Adenosine; Am = Amiodarone.

Table 4. Clinical data on 3 cases atrioventricular block in which drug therapy was applied.

Year	Fetal heart rate	Fetal hydrops	Maternal and direct fetal drug therapy	Outcome
1996	45 beats/ minute (3° block)	no	Dexamethasone → Dexamethasone + Ritodrine → elective delivery (37 weeks)	Died 1.5 years after delivery
2001	48 beats/ minute (3° block)	yes	Ritodrine → elective delivery by cesarean section (30 weeks)	Died 2nd day after birth
2005	45 beats/ minute (2° block)	yes	Fenoterol →elective delivery by cesarean section (34 weeks)	Mental retardation, cardiomyopathy, pacemaker

Table 5. Short term outcome of the study population (N=40)

Type of arrhythmia	Supra Ventricular Tachycardia (N=28)	Atrial Flutter (N=6)	Atrio Ventricular Block (N=6)
Neonatal arrhythmia (%)	22 (78)	4(67)	6 (100)
unknown	1 (4)	-	-
Neonatal ward admission (%)	25 (89)	6 (100)	6 (100)
[Duration in days (Standard Deviation)]	[12(15)]	[9(6)]	[21(16)]
Unknown	1	-	-
Neonatal anti-arrhythmic therapy (%)	19 (86)	4 (67)	6(100)
Medication	17	1	-
+electric cardioversion	-	2	-
+accessory pathway ablation	2	1	-
+ pacemaker implantation	-	-	5
+implantable cardioverter-defibrillator	-	-	1
Neonatal death	-	-	2
Infant death	1	-	1

Short-term follow-up

Neonatal data are presented in **table 5**. The incidence of cardiac anomalies in the study population was 18% (8/44). More details on these cardiac anomalies are given in **Table 6**. Neonatal arrhythmia was seen in all AVB fetuses and in 67% of AF-fetuses and in 78% of SVT-fetuses. Nineteen of the 28 children in the SVT group were treated with medication directly after birth. SVT was self-limiting in 14/19, and treatment could be stopped within the first year of life.

Table 6. Cardiac anomalies found during short-term follow-up.

Cardiac defects	Supra Ventricular Tachycardia (N=28)	Atrial Flutter (N=7)	Atrio Ventricular Block (N=9)	Total (N=44)
Cardiac anomalies	2	1	5	8
Congenitally corrected transposition of the great arteries			2	2
Ventricular Septal Defect	1			1
Atrial Septal Defect				
Coarctation aortae		1		1
Left atrial isomerism			1	1
Ventricular Septal Defect, Left-Right-shunt, pulmonalisstenose, cardiomyopathy			1	1
Cardiomyopathy, polyvalvular disease, pulmonary stenosis	1			1
Endocardial fibroelastosis			1	1

In 5 of 28 SVT cases preexcitation (delta wave) was present on ECG after birth (Wolff Parkinson White (WPW) syndrome). In 2 cases, radiofrequency ablation of an accessory bundle was performed in the first months of life. AF was treated with antiarrhythmic therapy (n= 4) or cardioversion (n=2). After initial conversion to sinus rhythm, AF did not recur in all 6 cases. Interestingly, in two AF cases the presence of an accessory pathway was also demonstrated. One AF case showed preexcitation on ECG after cardioversion (WPW syndrome), another AF case developed recurrent atrioventricular reentrant tachycardia that required antiarrhythmic therapy. All 4 survivors with AVB received pacemaker therapy shortly after birth.

Long-term follow-up

Informed consent for neurodevelopmental follow-up was obtained from 28 infants of the 36 survivors. Eight of the 36 surving infants could not be followed due to declined consent or lack of contact address. At the time of neurodevelopmental and cardiological assessment the median age of the children was 76 months ranging from 6 months to 15 years of age. A summary of long-term follow-up is presented in **Table 7**.

Table 7. Long-term follow-up with cardiological, neurological, motor system and psychological characteristics of the study population (N=28) by type of arrhythmia.

Type of arrhythmia	Supra Ventricular Tachycardia (N=23)	Atrial Flutter (N=4)	Atrio Ventricular-block (N=1)
Median follow-up time in months (range)	91 (6-186)	62 (21-96)	25
Abnormal cardiological examination (incl ECG)	3	1	1
Abnormal neurological and/or motor system examination	0	1	1
Mean Intelligence Quotient score (Standard Deviation)	113 (16)	102 (7)	Not performed
Mean mental Developmental Index (Standard Deviation)	99 (11)	95	62
Mean Psychomotor Developmental Index (Standard Deviation)	120 (18)	134	55
Child Behaviour Check List indicative of need for extra attention	3	0	1

In the SVT-group, 23 children, median age 91 months (range 6-186) were examined. No cases still required drug therapy and, no cases were treated with catheter ablation after the first year of life. WPW syndrome was demonstrated on ECG in 3 of 23 children. Surprisingly, the ECG showed previously unknown preexcitation (deltawave) in 1 case. One case was a six year old child with short episodes of palpitations since one year. In the neonatal period, this child had self-limiting SVT. Preexcitation was present at birth, which initially had disappeared on ECG afterward. The new case was a 9 year old asymptomatic child with WPW syndrome that had self-limiting SVT after birth. Yearly check-ups were advised and instructions were given on how to act when symptoms occur. In the SVT group, 18 children were tested with the SON–R test and five with the BSID-II-NL test. Scores were within the normal range in 14 children (14/23, 61%) and above average in 9 children (9/23, 39%). These children all had a normal neurological examination.
The CBCL was indicative of behavioral problems in 3 children. These children were offered closer attention by the hospitals psychologist.

The median age in the AF group was 62, (range 21-96), 5 of the 6 cases remained free of arrhythmia symptoms. Four of 6 underwent neurological and cardiological examination. The ECG was normal in 3 of 4. One 2 year old AF case with postnatal WPW syndrome still showed preexcitation on ECG but had remained asymptomatic. One 9 year old AF case with AVRT after birth underwent catheter ablation at the

age of 4 years and has remained asymptomatic thereafter.

One 4 year old AF child had coarctation of the aorta and a self-limiting atrial flutter. It underwent coarctectomy and remained asymptomatic after the operation. A 5 year old child (AF-group) suffered from plexus brachialis lesion due to shoulder dystocia.

In the AF group, 3 children were tested with the SON-R test and one with the BSID-II-NL test. Scores were within the normal range. The CBCL was within normal range for all children.

The group of AVB showed a very high morbidity and mortality risk. Two children had congenitally corrected transposition of the great arteries (ccTGA). One of these cases was stillborn. The other case was lost to follow-up but from his record analysis we knew that the child received a pacemaker at the age of 6 years and was in good condition at the age of 9 years. A third child in this group, who could not be followed up, showed congenital cardiac anomalies (ventricular septal defect, left to right shunt and hypertrofic cardiomyopathy) and a pacemaker was implanted. This child had been suspected for mental retardation. A fourth case survived 1.5 years after birth. She had an AVB due to maternal antibodies. A pacemaker was placed but she suffered from cardiomyopathy and died during a period with fever and pneumonia. A fifth child received immediately after birth a pacemaker because of third grade AVB. The child died the second day after birth. Postmortem analysis showed endocardial fibroelastosis. In the AVB group there were two cases of a severe form of long QT syndrome, LQTS 8, or Timothy syndrome. In one case a pacemaker was placed, but unfortunately the infant died 29 days after birth because of persistent VF. The other case also received a pacemaker and an implantable cardioverter defibrillator (ICD) afterwards. We performed follow-up of this child at the age of 2 years and he suffered from severe mental and motor retardation (MDI 62 and PDI 55). The ECG showed extreme QT prolongation and T-wave alternans. He had recurrent ICD shocks for torsade des pointes and died at the age of 2 years of ventricular arrhythmia and cardiomyopathy after stellectomy of the left ganglion stellatum.

Discussion

We studied a complete cohort of fetuses with arrhythmia. Hydrops was seen in 42% and 50% of cases with SVT/AF and AVB respectively. Fetal antiarrhythmic medication was given in 76% of cases. Fetal and postnatal mortality in the SVT and AF group was low (6%) and limited to cases with cardiomyopathy and trisomy 21. There was a high percentage of neonatal arrhythmia in our series and 21% of cases were shown to have WPW syndrome. Although 72% of SVT/AF cases have remained

free of symptoms after the first year of life, 12% had underwent radiofrequency catheter ablation at a young age. Mental scores were normal in all survivors.

The group of AVB showed very high risk of mortality and morbidity. Today, of the seven cases of AVB included in the follow-up there is no survivor. The other two cases were lost for long-term follow-up, but their medical records noted pacemaker therapy in one and severe mental retardation in the other.

If the postnatal ECG in cases of fetal SVT or AF reveals preexcitation (WPW-syndrome) long term follow-up of the child is important, even in the absence of symptoms. Complaints can arise later in life and WPW-syndrome can be a cause sudden cardiac death in older children and adults. Follow-up is necessary because curative treatment by radiofrequency ablation of the accessory pathway is indicated in older symptomatic children to prevent sudden death.[13]

The observations of Schade *et al.* 1999 indicate that patients with fetal tachycardia may develop cerebral complications already in utero.[6] These authors believe that a fetus with tachyarrhythmia and subsequent hydrops is at increased risk for the development of cerebral complications, due to the circulatory disturbances and sudden changes in heart rate which may lead to fluctuations in cerebral perfusion. Therefore, it is from the utmost importance to aim at immediate and complete control of the heart rate in the treatment of fetal tachyarrhythmia. Transplacental or direct fetal therapy of the arrhythmia is probably preferable to premature delivery because of the neonatal complications especially in cases with hydrops.

We searched the literature for follow-up studies on children born after fetal arrhythmia. In 2003, Boldt *et al.* reported on long-term outcome of 35 fetuses with SVT and 36 with AVB.[1] They conclude that fetal tachy- or bradyarrhythmias were associated with a moderately high risk for fetal distress. In their study, the survival rates were 91% in SVT and 82% in AVB. After the neonatal period the overall prognosis was good; 93% of the infants with fetal arrhythmias were still alive at a median follow-up time of 5 years. Only 3% of these children had a neurologic disorder. In concordance with our results Jaeggi *et al.* described a poor outcome in a large series (n=59) of AVB cases.[14] They compared cases of isolated AVB with cases associated with major structural congenital heart disease (CHD). Live birth and 1-year survival rates of AVB with CHD were 56% and 19% respectively when compared to cases of isolated AVB with 88% and 75% respectively ($p<0.0001$). They conclude, like in earlier reports, that AVB associated with major structural heart disease other than cc-TGA has an extremely poor outcome. Patients with LQTS 8 or Timothy syndrome with or without 2nd degree AVB have a poor postnatal outcome due to lethal ventricular arrhythmias as was also demonstrated in our series.
In 2006, Cuneo *et al.* reviewed the literature in order to summarize the outcome of fetal cardiac defects.[15] They describe that in SVT conversion rates range from 23 to 62% with standard transplacental therapy and that mortality is very low. If second-line

agents were indicated, mortality rates of 18.5% with flecainide and 25-30% with sotalol were reported. The combined mortality rate for hydropic and non-hydropic fetuses with AF was 8%. In the period 1950-2003, survival rate of fetuses with isolated atrioventricular block before dexamethasone treatment varies between 44 and 88%. Survival rate of these fetuses after dexamethasone treatment is around 88% in the period 1997-2005. Fetuses with left atrial isomerism and atrioventricular block do very poorly, survival rates were between 0 and 22%. They concluded that in utero management of tachyarrhythmia and conduction system disease has improved in utero survival.

Conclusion

In conclusion, mortality in SVT and AF patients in our study was 6% but mental scores were normal in all survivors. Twenty-one per cent of survivors had WPW syndrome. Prognosis in AVB patients was poor.

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CHAPTER 9

General Discussion

In the past decades, outpatient clinics have been instituted for the follow-up of extremely preterm born babies. Standard tests for assessment of neurodevelopment according to age are used. Trained staff is performing these tests. This follow-up is important for the evaluation of the therapies that have been used, for the guidance of the parents to the necessary support services for the child, and for update of the information that is presently used in counselling.

It seems clear that, with the introduction of new diagnostic procedures and therapies in fetal medicine, a structured follow-up should be standard of care in this field. Ideally, follow-up of infants should be performed at the right time, it should consist of the most relevant tests, and, in order to avoid bias, it should include all patients.

In the following, both the problems in determining the right child age for follow-up and suggestions for the optimal time will briefly be discussed. In addition, proposals will be given about the best test to be performed and how to enhance participation in follow-up after fetal diagnosis and therapy. Finally, the literature on perceived problems associated with incomplete follow-up will be summarized.

What is the optimum age for performing the follow-up? It is known that conditions such as diabetes or hypertension later in life may be associated with intrauterine growth retardation. Therefore, it may be necessary to wait until well into adulthood before obtaining a complete picture of all the consequences of prenatal diseases and interventions. However, because of constant development of new therapies and diagnostic tools, timely evaluation of these therapies by follow-up of mothers and infants is warranted. In addition, the later in life follow-up is performed, the more variables are involved that may influence the test results. In my opinion, two years of age is an appropriate age to test children after fetal interventions. The Bayley Scales of Infant Development (Second Edition-Dutch version: BSID-II-NL) can be used to test neurodevelopment in children aged two years.[1,2] This test, for infants from one to 42 months of age, is often used in follow-up studies in the literature and consists of three separate scales (mental scale, motor scale, and behavioral rating). Mental and motor scale scores are converted to a mental developmental index (MDI) and a psychomotor developmental index (PDI). A second appropriate time to test is at the age of 5 to 6 years, because children are then attending school and can be tested for cognition, speech and language, behavior and social skills. At this age an almost complete picture can be obtained. An appropriate test at this age seems to be a questionnaire for the parents about school performance. Standardised and normalised instruments to detect neurological problems, developmental motor coordination disorders, learning and behavioral problems can also be used.

The aim is to obtain a 100% follow-up rate. This is more difficult when the time period that has elapsed since pregnancy is longer. Several factors may

contribute to a low follow-up rate. First, young families are at high risk to move and are therefore, easily lost to follow-up. Second, parents who have not come to terms with the disabilities of their child are likely to be lost to follow-up, because they are afraid for more medical interventions. In this thesis, we describe long-term outcome after several prenatal interventions trying to achieve as little loss to follow-up as possible. Strategies to achieve this included: counselling of parents during pregnancy that follow-up was planned, we were very persevering in trying to locate our patients, and very cautious in contacting them. In order to achieve this, the family physicians and referring physicians were contacted, to help us with the follow-up, telephone books were used, and city councils were contacted for addresses of the ones who moved. The strength of most of our studies is that there was only very few losses to follow-up. In general we observed that parents were very willing to contribute in the follow-up of their infants. Many couples were grateful for the care during the pregnancy and were happy to be able to do something in return for the medical team. To make follow-up easier in the future, we advise to inform parents during the pregnancy that standard follow-up will be done at a certain age of the child. It should be described in the patient information leaflet about the fetal intervention. When possible a home visit can be offered in case parents decline a hospital visit.

A problem in long-term follow-up is that the response rate decreases with the lapse of time between the original event and the follow-up assessment. It is not clear how the loss to follow-up influences the results of studies. McCormick *et al.* and Castro *et al.* suggest that those who are compliant with follow-up have more adverse outcome. Because children with a disability need continuing contact with health services and therefore are more easily contacted than healthy children.[3,4] In contrast, a number of other studies have shown that loss to follow-up probably decreases the proportion of infants with adverse outcome because children who are lost to follow-up are at higher risk for developmental problems associated with a lower socio-economic background and a higher rate of developmental problems at an early age.[5-9] Wolke *et al.* showed that non-response decreases the proportion of infants with adverse outcomes in assessed children because parents of disabled children are harder to persuade to cooperate in an assessment.[5] Tin *et al.* found that the inclusion of children who were hard to follow-up raised the severe handicap rate by one third.[10] In 1992, Jane Haliday reported on the importance of complete follow-up of spontaneous fetal loss after amniocentesis and chorionic villus sampling.[11] She found that women who are the most difficult to trace after amniocentesis or chorionic villus sampling are often those who have had an adverse pregnancy outcome. Both Wariyar *et al.* and Wolke *et al.* describe in their studies that parents who have not come to terms with their child's disability may tend to avoid situations where that disability is highlighted.[5,8] Wariyar *et al.* states that it is difficult and expensive

to achieve a 100% follow-up.[8] They suggest that trying to persuade those parents who seem to be reluctant for their children to be examined is a better way of reducing bias than tracking of families who are highly mobile. Hille *et al.* wrote that for many reasons 100% follow-up is not feasible.[12] This is not only true for perinatal studies but in all studies that evaluate late outcome. Follow-up reports should therefore include a drop-out analysis quantifying the extent by which those who did not participate at a later stage are more or less likely to have developmental problems and be more or less disadvantaged. In this way, comparison between different follow-up studies can be made more reliable.

In conclusion, outcome data, neonatal and long-term follow-up are extremely important in counselling families considering prenatal medicine. These families often have many questions concerning long-term outcome, because, as has been said in the introduction, the fetus is all future and no past. Centers involved in prenatal medicine have a responsibility toresponsibility to provide data on treated patients, including neonatal and long-term follow-up, and to publish the results of these follow-up studies in peer reviewed journals.

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CHAPTER 10

Summary

Summary

With the availability of prenatal diagnostics in the last century, the fetus became a patient. Obstetricians looked togheter with neonatologist and pediatric surgeons, who in the past needed to treat sick neonates, for an earlier moment of treatment. An example of such a shift towards an earlier moment of treatment is the treatment of fetal tachycardia. Allready in utero medication can be given to the fetus transplacentally or direct fetally. In order to convert the tachycardia into a sinus rhythm. Another example is the anemic fetus who can be given an intrauterine blood transfusion to treat the anemia. A further example is the monochorionic twin with twin to twin transfusion syndrome. It is possible to coagulate the pathologic bloodvessel connections which cause the syndrome. Fetal death can be prevented by performing this procedure.

A condition for the introduction of new techniques in medicine is that they are tested on efficacy and safety. That's why new diagnostic and therapeutic procedures demand proper follow-up. Unwanted side effects, such as clubfeet after early amniocentesis, can be detected through careful and thorough follow-up before new techniques are applied on larger scale. Because follow-up research is needed after introduction of new techniques and because prognosis of the future child is very important for the expectant parents, we conducted the following studies.

Chapter one comprehends the introduction of the thesis with a brief history of prenatal medicine. The introduction of new intrauterine treatment options increased possibilities. Not only can we timely diagnose abnormalities that cannot be treated (eg Down syndrome) but we can also diagnose diseases timely and treat abnormalities. Abnormalities that otherwise would lead to intrauterine fetal death (eg hydrops fetalis). Even performing intrauterine procedures that will increase a better start in life and therefore better starting point for postnatal treatment (eg prune belly syndrome). The importance of follow-up at infancy is on the one hand for the evaluation of new techniques, and on the other hand to inform parents adequately in case the fetus has an abnormality. Information on prognosis is important in making difficult decisions on either terminating the pregnancy, start intrauterine treatment or expectant management.

Chapter two describes the annual results from all centers for invasive prenatal diagnosis in the Netherlands over the period 1991-2000, with particular emphasis on indications, abnormal results, type of invasive procedures, and terminations of pregnancy. The percentage of invasive prenatal diagnosis increased from 5% of births in 1991 to 6% in 1996 and subsequently remained level. During the study

period, the number of pregnant women aged 36 and older increased by 70%, but the number of procedures because of maternal age remained stable. The percentage abnormal test results was 4.7 and increased from 3.6 in 1991 to 5.4 in 2000. The detection rate for abnormal results varied from 2% for maternal age to 28% for abnormalities detected by ultrasound examination. Important trends were the relative decrease of cordocentesis (-82%) and chorionic villi biopsy (-18%) in favour of amniocentesis. There was a significant decrease in the percentage of pregnant women aged 36 or older who underwent invasive prenatal diagnosis without previous screening.

Chapter three represents de results of a (semi) randomized controlled study that compared the effects of transabdominal chorionic villus sampling and early amniocentesis on fetal mortality and child morbidity. Women requesting early prenatal diagnosis for advanced maternal age were allocated to early amniocentesis or transabdominal chorionic villus sampling either by randomization or, if they declined randomization, by their own choice.
Of the 212 women who entered the study, 117 were randomized, 70 chose early amniocentesis and 25 chose transabdominal chorionic villus sampling. Overall, 130 women underwent early amniocentesis and 74 underwent transabdominal chorionic villus sampling at a median gestation of 12 weeks. Mosaic karyotypes were found in 5.4% of the early amniocenteses and in none of the chorionic villus samples. All unintended fetal losses occurred after early amniocentesis with a frequency of 6.2%. Talipes equinovarus was only observed after early amniocentesis with a frequency of 3.1%. The results of this study are in the Cochrane Database. In the nineties the early amniocentesis was abandonded because of the results of 3 controlled studies, including our study, that showed an increased risk of miscarriages and higher incidence of clubfeet. The conclusion of this chapter is that chorionic villus sampling remains the method of choice if prenatal diagnosis is needed in the first trimester of pregnancy.

In ***chapter four*** the outcome of pregnancies with prenatally diagnosed central nervous system (CNS) malformations are described. Maternal and neonatal records of prenatally diagnosed CNS malformations were retrospectively reviewed over a 6-year period (1993–1998). Information on current development of surviving children was obtained by contacting the care-giving pediatric neurologist. During the study period 124 fetuses were diagnosed with a CNS malformation. Data on pregnancy and delivery were available for 118 pregnancies. Additional malformations were present in 47% of fetuses. A total of 46% of pregnancies were terminated, and 15% ended in spontaneous intrauterine death. A total of 39% of pregnancies resulted in live birth, and 25% of the infants were still alive at the age of 3 months. One child was lost to follow-up, one infant died

at the age of 4 months, and two children died at the age of 3 years. Psychomotor development of the remaining 25 children was normal for 5, slightly disabled for 7, moderately disabled for 5 and severely disabled for 8.

The conclusion of this chapter is that due to the high rate of termination of pregnancy and to the frequent association with other anomalies, the survival rate of pregnancies in which a CNS defect had been diagnosed prenatally was only 25%. More than 50% of surviving children were moderately or severely disabled.

Chapter five decribes the neurodevelopmental assessment in children born with an umbilical artery pH < 7 in the period 1991-1992. During the study period, 1614 umbilical artery pH measurements were performed. Thirty (1.9%) were < 7. Of all infants born with an umbilical artery pH < 7 obstetric, neonatal, and pediatric records were reviewed. From this group 23 infants were admitted to the neonatal intensive care unit, and 8 of them required intubation. Twenty-eight children survived the neonatal period. At an age of 1 to 3 years, children were visited at home for semi-structured questioning of the mother and a Denver Developmental Screening Test of the child.Three children experienced an episode of mild hypertonia. One child had a mild motor developmental delay.

The conclusion of this study is that babies born with an umbilical artery pH < 7 are at great risk to experience considerable short-term morbidity. Those who leave the neonatal intensive care unit without major problems have good outcomes, and pessimism in counselling their parents is unwarranted.

Chapter six describes the long-term neurodevelopmental outcome in 33 children after twin-to-twin transfusion syndrome (TTTS). Maternal and neonatal medical records of all TTTS-cases admitted to our center between 1990 and 1998 were reviewed. Neurological and mental development at school age was assessed during a home visit in all TTTS-survivors. A total of 33 pregnancies with TTTS were identified. Four couples opted for termination of pregnancy. All other pregnancies were managed conservatively, 18 (62%) with serial amnioreductions and 11 (38%) without intrauterine interventions. Mean gestational age at delivery was 28 (range: 20-37) weeks. Perinatal mortality was 50% (29/58). Birth weight of donor twins was less than recipient twins. Systolic blood pressure at birth was lower in donors than in recipients and donors required more frequently inotropic support postnatally than recipients. The incidence of hypertension at birth was higher in recipients than in donors. Abnormal cranial ultrasonographic findings were reported in 41% (12/29) of the neonates. All long-term survivors (n = 29) were assessed during a home visit. Mean gestational age at birth of the surviving twins was 31 (range: 25-37) weeks. Mean age at follow-up was 6 (range: 4-11) years. The incidence of cerebral palsy was 21% (6/29). Five out of six children with cerebral palsy had an abnormal mental development. The incidence of

cerebral palsy in the group of survivors treated with serial amnioreduction was 26% (5/19). Four children were born after intrauterine fetal death of their co-twin: two of them had cerebral palsy. The conclusion therefore is: the incidence of adverse neurodevelopmental outcome in TTTS-survivors is high, especially after intrauterine fetal death of a co-twin.

In ***chapter seven*** the long-term neurodevelopmental status of children treated with intrauterine red blood cell and platelet transfusion (IUT) for fetal hydrops caused by parvovirus B19 infection is described. Maternal and neonatal records of all intrauterine transfusions for congenital parvovirus B19 infection in our center between 1997 - 2005 were reviewed. A total of 25 IUT sessions were performed in 24 hydropic fetuses. Sixteen survivors aged 6 months to 8 years were included in the follow-up study. All children underwent a general pediatric, a neurological examination and a neurodevelopment examination (developmental index by Bayley Scales of Infant Development or Snijders-Oomen test). Eleven children (68%) were normal and 5 children (32%) demonstrated a delayed psychomotor development with a suboptimal neurological examination (mild delay n=3, severe delay n=2). Neurodevelopmental status did not correlate with pre-IUT hemoglobin, platelet, or blood pH values. Growth and general health status were normal in all. Two children had minor congenital defects. Neurodevelopmental status was abnormal in 5 out of 16 survivors and was not related with the severity of fetal anemia and acidemia. We hypothesize that fetal parvovirus B19 infection may induce central nervous system damage.

Chapter eight describes the results of a retrospective cohort study of children with fetal arrhythmia. In the Leiden University Medical Center, 44 fetuses were diagnosed with fetal cardiac arrhythmia between January 1990 and December 2005. Twenty-eight with supravenricular tachycardia (SVT), 7 with atrial flutter (AF) and 9 with atrioventricular block (AVB). The incidence of cardiac anomalies was 18%. Hydrops was seen in 42-50%. Direct or transplacental fetal antiarrhythmic medication was given in 76% of cases. In the SVT group, 19 children needed medication postpartum. In 16/19 infants, the arrhythmia ceased within the first year of life. In the SVT and AF group mortality was 6%. In 21% of these cases Wolff Parkinson White (WPW) syndrome was diagnosed. Mental scores were normal in all survivors. Of the seven cases of AVB included in the follow-up there is no survivor. The other two cases were lost for long-term follow-up, but their medical records noted pacemaker therapy in one and severe mental retardation in the other. In conclusion, mortality in SVT and AF patients in our study was 6% but mental scores were normal in all survivors. Twenty-one per cent of survivors had WPW syndrome. Prognosis in AVB patients was poor.

Chapter nine comprehends the general discussion. We look into the demands of follow-up after prenatal diagnosis and therapy. How does loss to follow-up influence outcome? What is the best age to test for follow-up? Which test to use. After prenatal therapy, follow-up should always be performed as a standard procedure. Follow-up needs to comprehend the review of the medical records, specific testing and standard neurologic and developmental tests. An example of a good test, and age of testing is to perform a Bayley Scale of Infant Development test at the age of 2 with neurologic testing (e.g. Touwen). At the age of 5-6 years a further examination can be performed. Follow-up at a later age looks less sensible because postnatal factors influence outcome and prenatal techniques are developing continuously.

HOOFDSTUK 10

Samenvatting

Samenvatting

Met het beschikbaar komen van prenatale diagnostiek in de laatste decennia van de twintigste eeuw is de foetus patiënt geworden. Neonatologen en kinderchirurgen die voorheen pasgeborenen met afwijkingen moesten behandelen, hebben samen met obstetrici gezocht naar een eerder moment van behandeling. Een voorbeeld van een dergelijke verschuiving van het moment van behandelen is de behandeling van foetale tachycardie. Intrauterien kan transplacentair of direct foetaal medicatie worden toegediend en kan de tachycardie geconverteerd worden naar een sinusritme. Een ander voorbeeld is de anemische foetus die in utero behandeld kan worden met een bloedtransfusie. Nog een ander voorbeeld is de monochoriale tweeling met het tweeling transfusie syndroom. Hierbij is het mogelijk om de pathologische vaatverbindingen ongedaan te maken met behulp van lasercoagulatie. Door deze behandeling kan foetale sterfte voorkomen worden.

Een voorwaarde bij de introductie van nieuwe technieken in de geneeskunde is dat ze worden getoetst op effectiviteit en veiligheid. Daarom vereisen nieuwe diagnostische en therapeutische procedures goede follow-up. Door zorgvuldige en volledige follow-up kunnen eventuele ongunstige neveneffecten, bijvoorbeeld klompvoeten na vroege amniocentese, ontdekt worden voordat de techniek op grote schaal wordt toegepast. Omdat follow-up onderzoek nodig is na introductie van nieuwe technieken en omdat de prognose van het kind voor ouders zo belangrijk is hebben wij de volgende onderzoeken verricht.

Hoofdstuk één bevat de inleiding tot het proefschrift met hierin een beknopte beschrijving van de geschiedenis van de prenatale geneeskunde. Door het ontstaan van nieuwe intrauteriene behandeltechnieken is er een uitbreiding van mogelijkheden ontstaan. Behalve het vroegtijdig opsporen van onbehandelbare afwijkingen en afbreken van die zwangerschappen binnen de wettelijke termijn (bv Down syndroom), kunnen we nu ook aandoeningen vroegtijdig opsporen en behandelen. Aandoeningen die anders in utero tot sterfte zouden leiden (bv hydrops foetalis). Zelfs het verrichten van intra-uteriene ingrepen die erop gericht zijn een betere uitgangssituatie te creëren voor postnatale behandeling (bv prune belly syndroom) zijn mogelijk geworden.

Het belang van follow-up op kinderleeftijd ligt enerzijds in de noodzaak van evaluatie van nieuwe technieken en anderzijds in de wens ouders adequate informatie te geven die hen kan helpen bij de moeilijke keuze die zij moeten maken indien bij hun ongeboren kind een behandelbare afwijking is vastgesteld: afbreken van de zwangerschap, intrauteriene behandeling, of natuurlijk beloop.

Hoofdstuk twee beschrijft de kerncijfers van de Nederlandse centra voor invasieve

prenatale diagnostiek over de periode van 1991-2000 en bevat een analyse van trends. De cijfers uit de jaarverslagen 1991-2000 van de 13 centra werden samengevoegd en beschreven, met speciale aandacht voor aantallen en ingrepen, de indicaties en de gevonden afwijkingen. Het deel van zwangeren dat invasieve prenatale diagnostiek liet verrichten steeg van 5% in 1991 naar 6% in 1996 en bleef daarna stabiel. "Maternale leeftijd"was de voornaamste indicatie; het aandeel hiervan varieerde van 69,2% tot 73,3%. Het percentage afwijkende onderzoeksuitslagen bedroeg gemiddeld 4,7 en nam toe van 3,6 in 1991 tot 5,4 in 2000. Naar gelang de indicatie voor het onderzoek varieerde de kans op een afwijkende chromosoom uitslag van 2% voor de indicatie maternale leeftijd tot 28% voor de indicatie afwijkingen bij echoscopisch onderzoek. Bij 70,8% van de afwijkende uitslagen besloot de zwangere tot afbreking van de zwangerschap. De voornaamste trends waren de afname van het aantal navelstrengpuncties (-82%) en vlokkentests (-18%) ten gunste van de vruchtwaterpunctie (+48%). Verder was er een duidelijke afname van het aantal zwangeren van 36 jaar en ouder dat koos voor invasieve diagnostiek zonder vooraf prenatale screening te laten verrichten.

Hoofdstuk drie beschrijft de resultaten van een (semi) gerandomiseerde studie waarin de effecten op foetale mortaliteit en neonatale morbiditeit worden vergeleken tussen transabdominale vlokkentest en vroege vruchtwaterpunctie. Vrouwen die verzochten om vroege prenatale diagnostiek in verband met maternale leeftijd werden ingedeeld voor vroege vruchtwaterpunctie of transabdominale vlokkentest ofwel door randomisatie ofwel, indien zij randomisatie weigerden, door eigen keuze. Van de 212 vrouwen die tot de studie werden toegelaten, werden 117 gerandomiseerd, 70 kozen voor vroege vruchtwaterpunctie en 25 kozen een transabdominale vlokkentest. In totaal ondergingen 130 vrouwen een vroege vruchtwaterpunctie en 74 ondergingen een transabdominale vlokkentest bij een mediane amenorroeduur van 12 weken. Mozaïek karyotypes werden gevonden in 5,4% van de vroege vruchtwaterpuncties en in 0% van de vlokkentesten. Alle onbedoelde foetale dood trad op na vroege vruchtwaterpunctie met een frequentie van 6,2%. Talipes equinovares (klompvoeten) werd alleen vastgesteld na vroege vruchtwaterpunctie met een frequentie van 3,1%. De resultaten van dit onderzoek zijn opgenomen in de Cochrane Database. In de jaren negentig werd de vroege vruchtwaterpunctie verlaten aangezien er 3 gecontroleerde studies, waaronder die van ons, een verhoogde incidentie van miskramen liet zien en een hogere incidentie van klompvoeten.

De conclusie van dit hoofdstuk is dat de vlokkentest de methode van keus is wanneer invasieve prenatale diagnostiek is gewenst in het eerste trimester.

In ***hoofdstuk vier*** wordt de uitkomst beschreven van zwangerschappen met

prenataal gediagnosticeerde centraal zenuwstelsel afwijkingen. Van de periode van 1993-1998 werden de maternale en neonatale statussen van foetussen prenataal vastgestelde centraal zenuwstelsel afwijkingen ingezien. Informatie over de huidige ontwikkeling van de overlevende kinderen werd verkregen door informatie op te vragen bij de behandelende kinderneuroloog. Gedurende de studie periode werden 124 kinderen met een centraal zenuwstelsel afwijking gediagnosticeerd.
Van 118 zwangerschappen waren gegevens over de zwangerschap en bevalling beschikbaar. Extra afwijkingen waren aanwezig in 47% van de foetussen.
Een totaal van 46% van de zwangerschappen werd afgebroken, en 15% eindigde in een spontane intrauteriene vruchtdood. Een totaal van 39% van de zwangerschappen resulteerde in een levend geboren kind, en 25% van de kinderen waren nog in leven op de leeftijd van 3 maanden. Eén kind was lost to follow-up, één kind overleed op de leeftijd van 4 maanden, en twee kinderen overleden op de leeftijd van 3 jaar. Psychomotore ontwikkeling van de overgebleven 25 kinderen was normaal voor 5 kinderen, licht afwijkend voor 7 kinderen, matig afwijkend voor 5 en ernstig afwijkend voor 8 kinderen. De conclusie van dit hoofdstuk is dat ten gevolge van een hoog zwangerschapsafbreking percentage en de frequente associatie met andere afwijkingen, het overlevingspercentage van zwangerschappen met een prenataal gediagnosticeerde centraal zenuwstelsel afwijking slechts 25% is. Meer dan 50% van de overlevende kinderen waren matig tot ernstig geïnvalideerd.

Hoofdstuk vijf beschrijft de neurologische ontwikkeling van kinderen die geboren zijn met een arteriële navelstreng pH lager dan 7 in de periode 1991- 1992. Gedurende de studieperiode werden 1614 arteriële navelstrengbloedgasanalyses verricht. Dertig (1,9%) daarvan waren < 7. Van alle kinderen die geboren waren met een arteriële navelstreng pH lager dan 7 werden de obstetrische, neonatale en kindergeneeskundige statussen doorgenomen. Van deze groep werden 23 kinderen opgenomen op de neonatologie intensive care unit, en acht van hen hadden beademing nodig. In totaal overleefden 28 kinderen de neonatale periode. Op de leeftijd van 1 tot 3 jaar werden de overlevende kinderen thuis bezocht en getest met de Denver Ontwikkelings Screening-test. Drie kinderen hadden een episode doorgemaakt van milde hypertonie en één kind had een milde motorische achterstand. De conclusie van deze studie is dat baby's die geboren worden met een arteriële navelstreng pH van < 7 een groot risico hebben op ernstige korte termijn morbiditeit. Degene die de neonatologie intensive care unit verlaten zonder ernstige problemen hebben echter een goede prognose, en pessimisme in het counselen van hun ouders in dit aspect is dus niet aan de orde.

Hoofdstuk zes beschrijft de uitkomst van 33 zwangerschappen in de periode van 1990-1998 die gecompliceerd werden door twin-to-twin-transfusion syndrome

(TTTS). De studie werd gedaan om vast te stellen wat op lange termijn de neurologische ontwikkeling is van kinderen geboren na TTTS. Hiertoe werden alle statussen ingezien van de moeders en de neonaten. Van de overlevende kinderen werd de neurologische en mentale ontwikkeling vastgesteld tijdens een huisbezoek. Van de 33 zwangerschappen gecompliceerd door TTTS, werden 4 zwangerschappen afgebroken op verzoek van de aanstaande ouders. Alle andere zwangerschappen werden conservatief behandeld, 18 (62%) met seriële amnioreductie en 11 (38%) zonder intrauteriene interventies. De gemiddelde zwangerschapsduur bij de bevalling was 28 (range: 20-37) weken. Perinatale mortaliteit was 50% (29/58). Geboortegewicht van de donoren was lager dan van de recipiënten. Systolische bloeddruk bij geboorte was lager bij de donoren dan bij de recipiënten en de donoren hadden frequenter inotropica nodig postnataal dan recipiënten. De incidentie van hypertensie bij geboorte was hoger in recipiënten dan bij donoren. Abnormale craniale echo werd gerapporteerd in 41% (12/29) van de neonaten. Alle lange termijn overlevers (N=29) werden nagekeken tijdens een huisbezoek. Gemiddelde zwangerschapsduur van de overlevers bij geboorte was 31 (range: 25-37) weken. De gemiddelde leeftijd ten tijde van de follow-up was 6 (range: 4-11) jaar. De incidentie van cerebral palsy was 21% (6/29). Vijf van de 6 kinderen met cerebral palsy hadden een gestoorde mentale ontwikkeling. De incidentie van cerebral palsy in de groep van overlevers behandeld met seriële amnioreductie was zelfs 26% (5/19). Vier kinderen werden geboren na intrauteriene vruchtdood van hun co-twin: twee (50%) van hen hadden cerebral palsy. De conclusie is dan ook: de incidentie van abnormale neurologische ontwikkeling bij TTTS overlevers is hoog, in het bijzonder na het overlijden van een co-twin.

In ***hoofdstuk zeven*** wordt de lange termijn neuropsychologische uitkomst beschreven van de kinderen die geboren zijn na behandeling met intrauteriene transfusie bij foetale hydrops ten gevolge van parvovirus B19 infectie. Voor deze studie werden de maternale en neonatale statussen ingezien van alle intrauteriene transfusies vanwege parvovirus B 19. De studie periode was van 1997 tot 2005. In totaal werden 25 transfusies verricht bij 24 hydropische foetussen. Er waren 16 overlevende kinderen in de leeftijd van 0 tot 8 jaar. Deze overlevers werden allen geincludeerd in de follow-up studie. Alle kinderen ondergingen een algemeen lichamelijk onderzoek, een gedetailleerd neurologisch onderzoek en een neuropsychologische test, ofwel de Bayley Scale of Infant Development test (BSID-II-NL) ofwel de Snijders-Oomen test (SON-R test) afhankelijk van hun leeftijd. Neuropsychologische ontwikkeling was normaal in 11 kinderen. Vijf kinderen (32%) vertoonden een vertraagde psychomotore ontwikkeling en een afwijkend neurologisch onderzoek (milde neurologische achterstand bij 3 kinderen, en ernstige neurologische achterstand bij 2 kinderen). Lineaire regressie analyse

toonde geen correlatie tussen neuropsychologische uitkomst en hemoglobine gehalte, thrombocyten aantal of pH waarde vóór de intrauteriene transfusie. Groei en algemene gezondheid waren normaal bij alle kinderen. Twee kinderen hadden lichte aangeboren afwijkingen (mitraal klep insufficiëntie en hypospadie).

Hoofdstuk acht beschrijft de resultaten van een retrospectieve cohort studie van kinderen met foetale arrhythmia. In het LUMC werd in de periode januari 1990 tot en met december 2005 bij 44 foetussen foetale arrhythmia gediagnosticeerd. Er was sprake van 35 foetussen met tachycardie en 9 foetussen met bradycardie ten gevolge van een hartblock. In de groep van foetale bradycardie was bij 2 foetussen sprake van een lang-QT-syndroom. Tijdens de zwangerschap was het noodzakelijk om 19 foetussen al intrauterien te behandelen vanwege tachycardie (waarbij er in 9 casus sprake was van hydrops) en 3 casus werden intrauterien behandeld in verband met bradycardie. Er was 18% (8/44) sterfte. Van de overlevende kinderen na foetale tachycardie kon van 82% (27/33) follow-up worden verkregen.Mortaliteit in tachycardie groep was 6% maar de mentale scores waren normaal bij alle overlevenden. Wolff Parkinson White syndroom kwam in 21% voor in de tachycardia groep. De prognose voor foetussen met atrioventriculair block was slecht.

Hoofdstuk negen bevat de algemene discussie. Hier wordt ingegaan op eisen van follow-up na prenatale diagnostiek en therapie. Hoe vertekenend werkt loss to follow-up. Op welke leeftijd kan het beste follow-up gebeuren? Welke testen kunnen we gebruiken voor follow-up? Na foetale therapie zou steeds follow-up moeten worden verricht. De loss to follow-up rate daalt als ouders al tijdens de zwangerschap worden geïnformeerd over de wenselijkheid van deze follow-up. De follow-up dient te bestaan uit het opvragen van de medische gegevens, orgaanspecifieke testen en gestandaardiseerde neurologische en ontwikkelingstesten. De follow-up kan bijvoorbeeld plaatsvinden op de leeftijd van 2 jaar met een Bayley Scale of Infant Development test en een gestandaardiseerd kinderneurologisch onderzoek (bv van Touwen). Op de leeftijd van 5-6 jaar kan een volgend onderzoek volgen. Follow-up op latere leeftijd heeft minder zin omdat postnatale factoren steeds meer invloed uitoefenen en ook omdat de prenatale technieken nog steeds aan verandering onderhevig.

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Curriculum Vitae

The author of this thesis was born on 16 January 1968, in Rijswijk, The Netherlands. She attended the Sint Maartenscollege at Voorburg. From 1986 to 1994 she studied medicine at the University of Leiden. From 1990 to 1991 she studied Arabic, before she went to the Assiut University Hospital in Egypt for a traineeship in Obstetrics and Gynecology.

In 1990 she started the first follow-up study on "twin pregnancies and methylene blue dye" under supervision of Prof. Dr. J. Bennebroek Gravenhorst and Dr. I.L. van Kamp at the Leiden University Medical Center. From 1993 she worked with Dr. F.P.H.A. Vandenbussche (Leiden University Medical Center) in several follow-up projects.

Between 1994 and 1996 she worked as a resident in Obstetrics and Gynecology at the St Clara Hospital, Rotterdam and at the Bronovo Hospital, The Hague. Her official residency in Obstetrics and Gynecology was from 1996 to 2002 at the Bronovo Hospital, The Hague (director: Dr. R.A. Verwey) and at the Leiden University Medical Center (director: Prof. Dr. H.H.H. Kanhai). Since July 2002, she is a member of the Obstetrics and Gynaecology staff at the Bronovo Hospital.

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