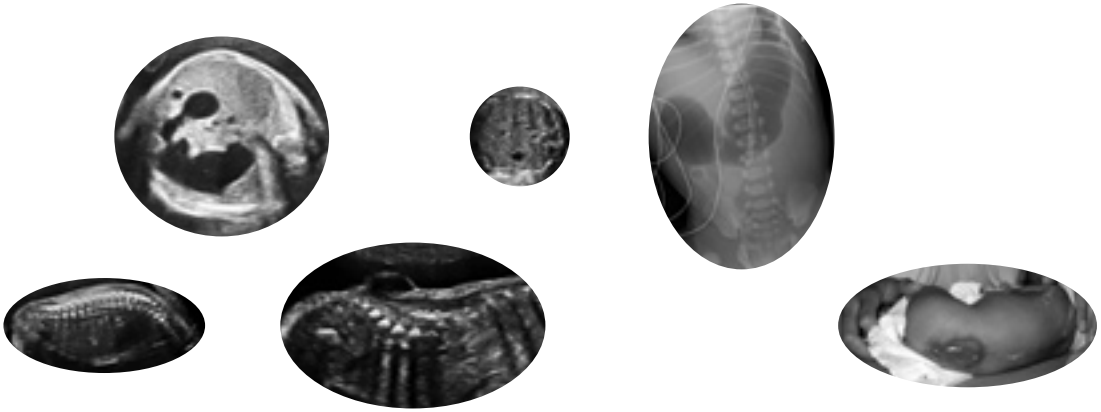
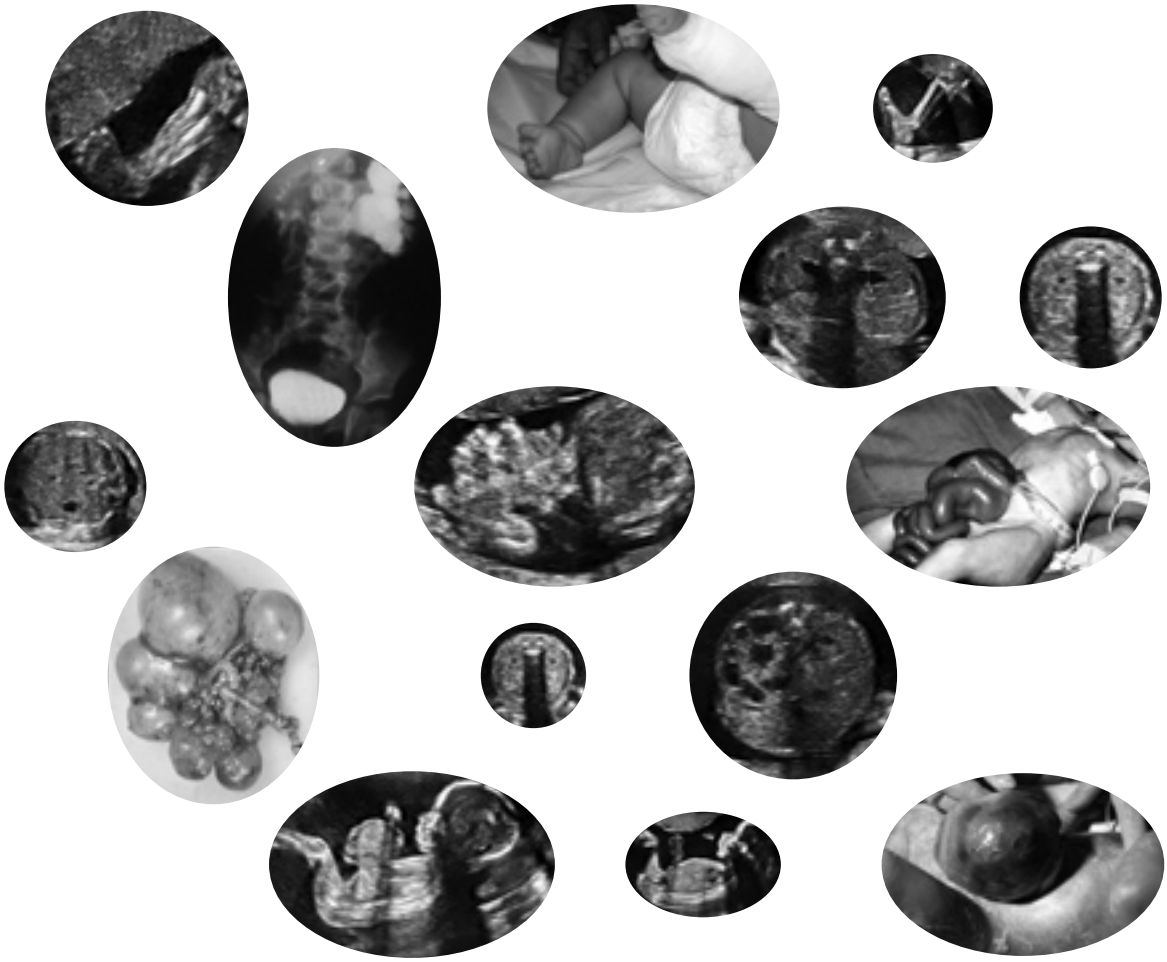


DETECTION OF CONGENITAL ANOMALIES BEFORE OR AFTER BIRTH; DOES IT MAKE A DIFFERENCE?



Dedicated to my father
Prof.dr. J.Th.G.Overbeek (1911-2007)
who encouraged me to be curious.

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DESIGN Caroline de Lint, Voorburg (caro@delint. nl)

Detection of congenital anomalies before or after birth; does it make a difference?

Diagnose van congenitale afwijkingen voor of na de geboorte; maakt het uit?

Proefschrift
ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. dr. S. W. J. Lamberts
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 29 oktober 2008 om 15.45 uur

door

Titia Edie Cohen-Overbeek
geboren te de Bilt

PROMOTIECOMMISSIE

Promotoren	Prof. jhr. dr. J.W. Wladimiroff Prof. dr. D. Tibboel
Overige leden	Prof. dr. N.M.A. Bax Prof. dr. G.J. Bonsel Prof. dr. J. Deprest

1 Introduction and research objectives

Introduction

Stuart Campbell produced the first ultrasound image of a congenital anomaly in the human fetus in 1972[1]. This revolutionised Obstetrics and Gynecology. Reliable determinations of gestational age[2] and cervical competence[3] can be made and information on fetal and utero-placental perfusion[4], fetal growth[5] and a vast number of fetal anomalies can now be obtained[6]. Major fetal anomalies are associated with preterm delivery[7], perinatal mortality and morbidity[8], unwarranted obstetric surgery and prolonged hospitalisation[9]. About 2 to 3% of newborns have detectable congenital anomalies[10,11], of which 20% will result in perinatal death[9,12]. When ultrasound techniques became sufficiently powerful, many countries introduced a second trimester ultrasound screening test to detect these anomalies[13,14].

Screening-universal or risk based?

When addressing screening one should distinguish between universal screening and targeted screening[15]. Targeted screening refers to the examination of women at known increased risk of having off-spring with congenital anomalies. Two risk situations can be distinguished for such an indication-based only ultrasound scan.

Firstly, there is the situation that risk factors are known prior to the pregnancy, i.e. a previously affected infant, a parent with a congenital anomaly, maternal type 1 Diabetes Mellitus, maternal use of antiepileptic drugs. In this subset of women, 18-22 weeks is the ideal time for a thorough fetal anomaly scan. We found an overall prevalence of major fetal anomalies in this increased risk subset of 4-5%[16].

In another group the ultrasound scan for suspected fetal anomalies is based on abnormal obstetric findings that appear during the current pregnancy. Whereas in early pregnancy it is fetal nuchal translucency which is closely associated with chromosomal abnormalities, notably trisomy 21 and cardiac anomalies[17], obstetric markers for fetal congenital anomalies later in pregnancy include poly- and oligohydramnios, severe fetal growth restriction and fetal cardiac arrhythmias[18]. In this subset of women the prevalence of fetal congenital anomalies approximates 40 to 60%[16]. Until recently (1st January 2006) in the Netherlands anomalies were often detected beyond the second half of the second trimester due to the lack of a population-based 18-22 week fetal screening program.

Population-based universal screening involves low-risk populations not known to have clinical risk factors. This examination includes determination of gestational age, number of fetuses, fetal viability, placental location and a search for fetal congenital anomalies. The rational for such a universal screening test is that approximately 75% of infants with congenital anomalies are born out of low risk pregnancies[19].

The 18-22 week screening ultrasound scan

The 18-22 week period is determined by the high quality sonographic images available at this time of pregnancy and the possibility to detect the majority of structrural anomalies. The legal upper limit of 24 weeks of gestation for termination of pregnancy in case of a major fetal congenital anomaly may also play a role but fortuitously the opportunities for detection by ultrasound are also diminished beyond this period. The acoustic window, provided by amniotic fluid, becomes relatively smaller due to fetal growth and increased mineralization of the fetal skeleton creates ever more shadows with advancing gestational age. The clear visualization of fetal structures is therefore limited in later gestation. It has been reported that in two-third of prenatally diagnosed fetal anomalies clinical symptoms may develop as late as 23-24 weeks of gestation[18]. Prenatal screening at 18-22 weeks has now become a routine part of antenatal care in most European countries[20]. In case of detection of a fetal anomaly compatible with life, there will be the option of adjusting obstetric management in terms of timing, mode and location of the delivery[21]. In some instances intrauterine treatment may be contemplated[22].

Requirements for screening tests

In general a screening test should meet a number of conditions. The prevalence of the anomaly should be high enough to ensure that the application of the test – providing it has an acceptable sensitivity and specificity – will result in a measurable and cost-effective improvement in health outcome. There has to be an appropriate hospital infrastructure allowing women with a positive screening result to be referred for further examination. Additionally there have to be adequate therapeutic options and the test itself has to be safe without any side effects.

The efficacy of screening

The pick up rate at routine ultrasonographic screening in the Eurofetus Study, in which 2262 malformed fetuses are registered, was 56.2%. Sensitivity was higher for major anomalies (73.7%) compared to minor anomalies (45.7%). Within the subset of major anomalies, detection was high for central nervous system anomalies (88.3%) and urinary tract anomalies (88.5%), and lower for heart and great vessel anomalies (38.8%)[23]. Various studies reported a specificity for the test between 99.5% and 99.9%[24,25]. No side effect has been demonstrated[26] and studies in Finland and England have shown the test to be cost effective[27,28]. In the Netherlands with 8 academic centers and 13 satellite centers the infrastructure for further examinations within a week following a positive screening test is present as well, although legal and political objections led to a relatively late introduction compared with other countries in Europe.

Therapeutic options following a positive screening result include termination of pregnancy in the presence of a major or lethal anomaly. In case of an ongoing pregnancy adjustment of obstetric management may contribute to a favorable outcome. In addition, parents are counseled so that they can prepare themselves for the birth of a child facing multiple problems. A 50% reduction in perinatal mortality has been demonstrated with routine 2nd trimester ultrasound. But this was the result of parents requesting a termination of pregnancy and should strictly speaking not be referred to as a reduction in mortality but rather a temporal shift[29]. Large screening studies failed to reveal an effect on morbidity, as measured by the proportion of babies with an Apgar score <7 at 1 minute[29]. Each anomaly carries it's own specific type of morbidity and end-points such as the Apgar score may not be able to demonstrate a difference in morbidity between prenatally and postnatally diagnosed anomalies. Only very few studies have been able to determine a reduction in morbidity for infants with a specific anomaly detected prenatally versus detection at birth, such as transposition of the great vessels, complete atrioventricular septal defect, tetralogy of Fallot and pulmonary atresia[30,31]. More premature births have been demonstrated for infants with a prenatally as opposed to a postnatally detected gastrointestinal malformation[32], without further information on morbidity and outcome, however.

Late introduction of screening as a research opportunity

There was no nationally implemented screening at 18-22 weeks in the Netherlands until the beginning of 2006[33]. Fetal anomalies were therefore often diagnosed late in pregnancy (beyond 24 weeks of gestation) or were only detected at birth. The previous non-screening situation in the Netherlands set the scene for the research presented in this thesis. In the absence of the 18-22 week fetal screening test one can expose the impact of the indication-based only scan approach on the prenatal detection rate and outcome of major fetal congenital anomalies compatible with life but associated with severe handicap. A non screening situation also allows an answer to the question as to whether prenatal detection of less severe fetal anomalies amenable to postnatal treatment would improve postnatal outcome when compared with detection only at birth. Prenatal detection of milder fetal congenital anomalies may assist in determining which newborn need to be referred for further postnatal investigation and treatment. It may further optimise postnatal management.

The following research objectives were defined.

1. To determine the impact of prenatal detection of fetal spina bifida on outcome in a non-screening setting (Chapter 2.1)
2. To study the outcome of prenatally versus postnatally detected anomalies, that are amenable to postnatal treatment: (i) fetal duodenal atresia (Chapter 3.1), (ii) fetal gastroschisis (Chapter 3.2), (iii) fetal omphalocele (Chapter 3.3), (iv) fetal talipes equinovarus (Chapter 4.1)
3. To establish prenatal cut-off levels for postnatal referral of mild renal pyelectasis (Chapter 5.1) and to determine the impact of prenatally diagnosed fetal unilateral multicystic dysplastic kidney on postnatal optimilisation of diagnosis and treatment (Chapter 5.2)

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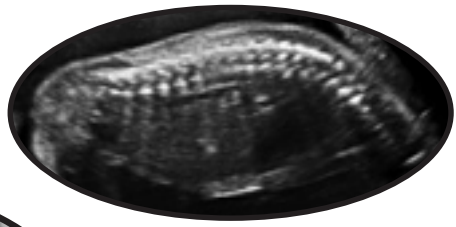
2 Diagnosis of a neural tube defect

This chapter deals with the poor detection rate of spina bifida in a non-routine ultrasound screening setting. Spina bifida is compatible with life, but for the vast majority of infants it has a devastating impact on quality of life. When diagnosed before 24 weeks of gestation most couples will opt for termination of pregnancy



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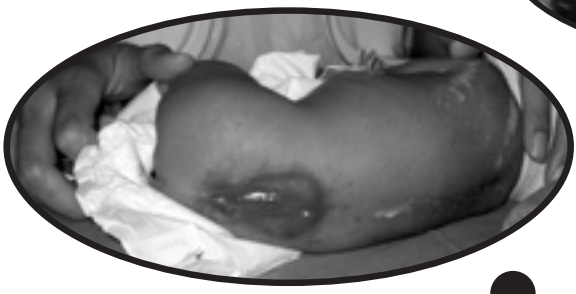

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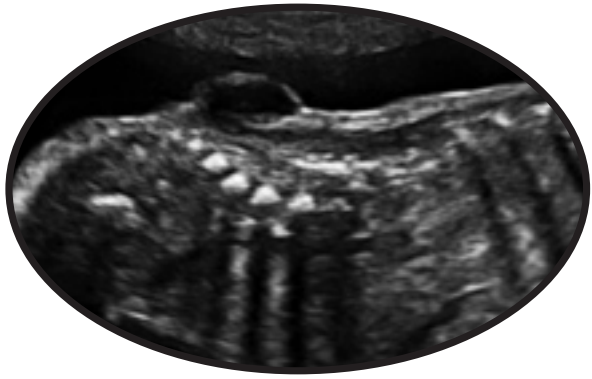

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1 Longitudinal image through the normal fetal spine at 20 weeks' gestation. The spine is bordered by the intact skin.
2 Longitudinal section through the fetal spine with the fluid-filled myelomeningocele.
3 Image of a newborn infant with a myelomeningocele at the lower end of the back.

2.1

Audit of prenatal and postnatal diagnosis of isolated open spina bifida in three university hospitals in the Netherlands

Ultrasound Obstet Gynecol 2003;21:48-52

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Abstract

Objective To audit the current Dutch policy of prenatal detection of isolated open spina bifida based on offering detailed ultrasound examination only on indication.

Methods A retrospective analysis of prenatally diagnosed isolated spina bifida cases and of newborns diagnosed with this condition was carried out in three university hospitals. The data were collected from databases and clinical records of the departments of prenatal diagnosis, obstetrics, neonatology, child neurology and neurosurgery of the three centers.

Results Between January 1996 and December 1999, 88 cases of isolated open spina bifida were diagnosed prenatally by ultrasound investigation. Thirty-eight cases (43%) were diagnosed before the 24th week of gestation. Of these, 35 (92%) ended in termination of the pregnancy at the parents' request. Of the remaining 50 cases (57%) diagnosed after the 24th week of gestation, eight (16%) pregnancies were terminated beyond the legal limit for termination due to the severity of the condition. Of the 88 cases of isolated spina bifida, 25 infants (28%) were still alive at the age of 4 years. In the same audit period 112 newborn infants with isolated open spina bifida were admitted to the neonatology, child neurology, or neurosurgery ward of the three centers. Of these cases, 47 (42%) had been diagnosed prenatally and 65 (58%) were an unexpected finding at birth. In 24 infants (21%) surgical treatment was withheld because of the severity of the condition and predicted poor outcome, whereas the remaining 88 (79%) infants underwent surgical repair.

Conclusion: The current practice in the Netherlands of offering ultrasound screening to high-risk patients only leads to early detection of a minority of cases of spina bifida. Most cases are diagnosed either after the 24th week of gestation or they remain undiagnosed until after birth. When spina bifida is diagnosed before the 24th week of gestation the vast majority of parents opts for termination. In order to reduce the birth prevalence of spina bifida in the Netherlands the introduction of a policy of routine ultrasound screening should be considered.

Introduction

Neural tube defects (anencephaly and spina bifida) are the most common severe congenital defects of the central nervous system. Their prevalence varies greatly, depending on ethnic, racial and socio-economic backgrounds[1]. The mortality and morbidity rates associated with spina bifida (rachischisis, myelocele and myelomeningocele) are high: 20% of affected infants die within the first year, 37% within the first decade, 44% within the second and only 50% survive beyond the third decade[2]. A total of 88% of the surviving infants suffer of variable degrees of life-long disabilities and are at risk for psychosocial maladjustment[3,4] although the intellectual performance may be normal in the vast majority of cases[5].

In the 1970s, measurement of maternal serum α-fetoprotein (AFP) at around 16 weeks' gestation was introduced as a screening method for open neural tube defects in countries with a high prevalence of this anomaly[6]. Definitive diagnosis was based on the AFP level in amniotic fluid. In the 1980s ultrasonography became the diagnostic method of choice, replacing amniocentesis almost entirely[7,8]. In the last decade, most European countries have adopted ultrasound examination as a routine part of antenatal care[9]. The combined effects of this screening strategy and use of periconceptional folic acid has led to a dramatic fall in the incidence of spina bifida at birth in many countries in and beyond Europe[1,10]. The practice is different in the Netherlands where both routine second-trimester ultrasonography and maternal serum AFP screening are not part of routine prenatal care. An ultrasound scan is either performed for specific obstetric indications or because of a suspected or known increased risk of fetal anomalies. The latter two categories are referred to tertiary centers for specialized ultrasonography. A baby born with spina bifida in the Netherlands is usually referred to a tertiary center for further investigations and is managed by a team of specialists.

At the request of the Ministry of Health, a working party of the Dutch Health Council has evaluated the necessity of screening for neural tube defects in the Netherlands. This working party initiated the present study, which aimed to audit the current Dutch policy and its consequences in three referral areas[11]. The frequency of open spina bifida based on the number of defects diagnosed prenatally and at birth, parents' choices, pregnancy outcome and post-natal outcome up to a maximum of 4 years of age were documented.

Patients and Methods

Prenatal diagnosis

Data were collected from the files of all patients scanned between January 1996 and December 1999 at the departments of prenatal diagnosis at the Academic Medical Center in Amsterdam, the Dijkzigt Academic Hospital in Rotterdam and the University Medical Center in Utrecht. There were 88

patients in whom the ultrasound diagnosis of isolated spina bifida (spina bifida with or without meningocele) was made prenatally. The following indications prompted a scan in these pregnancies: raised AFP in maternal serum or amniotic fluid (10 cases); increased anamnestic risk for congenital defects (four cases); Rhesus isoimmunization (two cases) and use of antiepileptic drugs (one case). The indication for referral of the remaining 71 patients was suspicion of an anomaly at a scan performed elsewhere or an obstetric condition such as oligohydramnios, polyhydramnios or fetal growth restriction entailing an increased risk of congenital structural defects. Information on subsequent management and outcome of pregnancy was obtained from obstetric records. Infant survival was documented from the medical records of the departments of neonatology, child neurology and neurosurgery from a minimum of 6 months up to a maximum of 4 years of age for the children born in 1996.

Postnatal diagnosis

The group in which the diagnosis of isolated open spina bifida (myelocele, myelomeningocele, rachischisis) was made or confirmed at birth consisted of 112 infants admitted to the neonatology, child neurology, or neurosurgery wards of the three university hospitals between January 1996 and December 1999. In 47 of these cases (42%) the condition was already known prenatally. This group included also the 25 fetuses of the above mentioned prenatal group who survived. The remaining 22 fetuses in which the diagnosis was made prenatally were referred to the above mentioned departments after birth for further treatment.
Information on the timing of diagnosis (whether prenatally or at birth), parents' choices with regard to subsequent management, pregnancy outcome, clinical management and outcome of the children up to a maximum of 4 years of age was recorded from the medical records.
In the Netherlands, spina bifida teams consisting of a neonatologist, a child neurologist, a neurosurgeon, a rehabilitation physician, an orthopedic surgeon, a child urologist and a social worker assess the affected newborns and counsel the parents on the prognosis and appropriateness of surgical treatment. The criteria for judging the prognosis may have differed slightly between the three centers, but consisted mainly of the criteria described by Lorber[12]. Poor prognostic factors are considered to be defects higher then L2-L3, presence of hydrocephalus at birth, or presence of a gross kyphosis or major associated defects. The latter have been excluded form the study group.

Results

Prenatal diagnosis

During the study period 88 cases of isolated open spina bifida were detected by prenatal ultrasound examination. In only 17 (19%) cases was the indication for the scan an increased *a priori* risk of neural tube defect or other structural anomalies. The findings in the other 71 cases (81%) were unexpected.

Of the 88 prenatally diagnosed cases of isolated open spina bifida, 38 (43%) were observed before the 24th week of gestation. Thirty-five of these cases (92%) were terminated at the parents' request. In the other three cases (8%) the parents chose to continue the pregnancy but requested no surgical intervention after birth. One of these children died soon after birth and two were still alive at the end of the study's follow-up period.

From the 88 prenatally diagnosed cases of isolated open spina bifida, 50 (57%) were diagnosed after the 24th week. In eight of these 50 cases (16%) the pregnancy was terminated. This was possible even beyond the usual Dutch legal term for termination (23 completed weeks), because the severity of the condition was judged by a panel of specialists as 'life threatening'. In 20 (40%) of these late diagnoses, the parents, based on the negative advice of the spina bifida team, requested no surgical intervention after birth. A total of 23 (46%) of these 50 neonates were still alive at the end of the observation period (Table 1). The overall survival rate was 28%.

Postnatal diagnosis

In the study period a total of 112 newborns with isolated open spina bifida were admitted to the neonatology, child neurology, or neurosurgery department of the three university hospitals. These included cases diagnosed elsewhere and referred after birth for postnatal assessment. Forty-seven (42%) of these 112 infants had been diagnosed prenatally. In 65 (58%) of these 112 infants, spina bifida was an unexpected finding at birth. Eight (12%) of these 65 cases had actually been overlooked at a third-trimester ultrasound scan performed for an obstetric indication. In 15 (32%) of the prenatally diagnosed cases and in nine (14%) of the postnatally diagnosed cases surgical repair after birth had been withheld due to the expected extremely poor prognosis (Table 2). Surgical repair was undertaken in 32 (68%) of the prenatally diagnosed cases and in 56 (86%) of the postnatally diagnosed cases. Of the 88 infants that underwent surgery, 75 (85%) had a myelomeningocele and 13 (15%) a meningocele. Hydrocephaly was present in 72 (82%) of these infants and in 69 (78%) a ventricle-peritoneal drain was inserted (Table 3). The overall survival rate in this group was 79%. Because of the still relatively young age of these 112 infants at the end of the study period, it is difficult to draw a definitive conclusion on the number and severity of handicaps and various disabilities. According to their condition

and development at the last visit a tentative prognosis could be made. The expectations was that approximately 33% would have a variable degree of mental retardation, 42% would be wheel-chair dependent, and 88% would suffer bladder dysfunction and 57% bowel dysfunction (Table 4).

Discussion

The present audit has revealed that in these three Dutch university centers the majority of spina bifida cases occurred in couples with no apparent *a priori* risk factors. In most cases the diagnosis was made at birth or at a prenatal stage beyond the legal limit for termination. Survival was strikingly different depending on the stage of diagnosis. In the case of an ultrasound diagnosis before 24 weeks of gestation, 92% of the parents opted for termination of pregnancy (TOP). The overall survival rate of the prenatally diagnosed group was 28%, whereas in the postnatally detected cases the survival rate was 79%. This latter category constitutes the major source of morbidity.

The potential role of ultrasound diagnosis

Of all congenital anomalies, neural tube defects are the most amenable to prenatal identification[9,13]. At present, ultrasound is the most accurate method of detecting neural tube defects in the second trimester of pregnancy, with a sensitivity of about 71% (95th CI, 60-80) and a specificity close to 100%[14]. Due to the continuous improvement of ultrasound techniques and the introduction of the ultrasonographic cranial signs associated with spina bifida ('banana-sign' and 'lemon-sign'), the diagnostic sensitivity of ultrasound has steadily increased even in units without the expertise of a tertiary center[14,15]. The importance of standardizing ultrasound scans at around 20 weeks' gestation-the most favorable moment for diagnostic purposes-is demonstrated by the fact that in the audit eight cases of spina bifida were overlooked on ultrasound examination carried out in the third trimester. This may have partly been attributable to lack of experience of the sonographer, or to the presence of unfavorable conditions such us maternal obesity, oligohydramnios or breech presentation masking a myelomeningocele. Hydrocephaly was not present in any of the mis-diagnosed cases.

Apart form the role in diagnosing major structural anomalies[9] the impact of this technique on perinatal outcomes is still subject of debate[16,17]. The only randomised study which thus far has proven an impact of routine ultrasound on perinatal mortality has only been able to show a shift from perinatal death to TOP in cases in which structural anomalies were diagnosed during pregnancy without any clear impact on neonatal morbidity[18]. This argument has thus far discouraged health planners in the Netherlands

from investing resources in a screening program. Although the general feeling of obstetricians and midwifes is that ultrasound is an invaluable diagnostic tool, given the widespread use of this technique and the fact that most women highly value it, it has become impossible to carry out a large randomised controlled trial to provide evidence that ultrasound screening may be justified.

Living with spina bifida

Despite the improvement in surgical management of spina bifida in recent decades resulting in prolonged life expectancy, no improvement in the degree of disabilities or quality of life of affected individuals has been demonstrated[2,3,5]. Spina bifida patients rarely reach independence, have a satisfactory job or manage to have a partner or start a family[4,19]. In the USA the lifelong cost of an individual born with spina bifida has been estimated to be about $300.000[20,21]. However, besides the medical and social costs it is impossible to quantify in monetary terms the psychological burden of the condition for the affected individual and his/her family. This is clearly reflected by the fact that parents, when faced with a diagnosis of spina bifida and with the option to decide on the future of the pregnancy, mostly opt for TOP. In a multicenter study conducted in several countries, Mansfield reported a termination rate associated with prenatally diagnosed spina bifida of between 20% and 100% with an average of 64%[22]. In the present study the termination rate for spina bifida was 92%, similar to that for Down syndrome reported in the study of Mansfield[22]. Also striking is the difference in survival rate among newborns in which the condition was known prenatally (28%) or only after birth (79%). The explanation for this is that those detected prenatally, even at late scans, included the most severe cases presenting with hydrocephaly, breech presentation or polyhydramnios, as clearly suggested by the higher incidence of hydrocephaly in this group.

Effects of prevention on the prevalence of spina bifida in the Netherlands

Given the regional character of the audit we cannot extrapolate the obtained data to a national prevalence figure for isolated spina bifida. According to an estimate based on data from the obstetrical and pediatric registry and from the EUROCAT registry of congenital malformation in two geographical areas, the yearly prevalence of isolated spina bifida in the Netherlands is supposed to be about 0.5‰[11]. However, underestimation of the true prevalence, due to incomplete registration of severe cases resulting in early neonatal deaths from home deliveries, cannot be ruled out. The introduction of periconceptional folic acid supplements has been successful in the Netherlands from 1995 onwards and the estimate is that about 36%

of pregnant women are currently using folic acid[23]. Yet national data have thus far failed to show a significant decrease in the incidence of neural tube defects[23]. This may be in keeping with the suggestion that folic acid may not be all that effective in preventing the occurrence of new cases of spina bifida in low-risk women, and only shows an effect in areas with poor socio-economic status and low dietary intake[24,25]

In Britain the incidence of live births, stillbirths and pregnancies terminated because of a fetal neural tube defect has fallen steadily from 1972 to 1992 from 215:100.000 to 38:100.000 and has stabilised ever since[10,26]. It is possible that the effect of an improved diet during pregnancy, together with a successful folic acid campaign, has reduced the prevalence of the condition to a minimum beyond which further reduction is not achievable. As a result of routine ultrasound screening 'spina bifida teams' in Britain have been made redundant as a liveborn infant with a severe form of spina bifida is now seldom seen.

The situation in the Netherlands is clearly different. A lower ethnic predisposition to spina bifida and a higher and more homogeneous socio-economic level have been associated with a lack of a significant decline in the incidence of the condition after the introduction of folic acid supplements.

New therapeutic initiatives

A promising new development in the therapy of spina bifida has been suggested by recently published experiences on *in utero* repair of isolated spina bifida[27]. The procedure is still in an early stage of development but when performed before 24 weeks of gestation it appears to improve neurologic outcome[28,29]. Early detection of the disease will provide parents with more choices than simply TOP

Conclusion

An ultrasound screening policy for congenital anomalies based on 'indications' only inevitably carries a poor pick-up rate for structural anomalies. This audit shows that the present Dutch screening policy enables early prenatal detection of only a minority of cases of isolated spina bifida. The success of prenatal screening programs in most European countries and recent promising attempts to intrauterine repair of the condition should encourage a reassessment of the Dutch policy.

TABLE 1 Indication for ultrasound scan and outcome of prenatally diagnosed isolated spina bifida

	<24 weeks (N=38) (N(%))	≥24 weeks (N=50) (N(%))	Total (N=88) (N(%))
Indication			
Specific indication	17	0	17 (19)
Incidental finding	21	50	71 (81)
Management			
Termination	35 (92)	8 (16)	43 (49)
Intervention*	0	22 (44)	22 (25)
Non-intervention	3 (8)	20 (40)	23 (26)
Outcome			
Stillbirth#	35 (92)	8 (16)	43 (49)
Neonatal death	1 (3)	17 (34)	18 (21)
Alive at the end of the study period	2 (5)	23 (46)	25 (28)
Lost to follow-up	0	2 (4)	2 (2)

* Surgical repair after birth; # Including pregnancy terminations.

TABLE 2 Number of infants with isolated open spina bifida admitted to three university centers, and management

	Prenatal diagnosis (N(%))	Postnatal diagnosis (N(%))	Total (N(%))
Infants	47 (42)	65 (58)	112 (100)
Non-intervention	15 (32)	9 (14)	24 (21)
Surgery	32 (68)	56 (86)	88 (79)

TABLE 3 Clinical features and need for ventricular-peritoneal drain, in relation to the time of diagnosis, in infants undergoing surgery for isolated spina bifida

Surgical repair	Prenatal (N=32) (68%) (N(%))	Postnatal (N=56) (86%) (N(%))	Total (N=88) (79%) (N(%))
Meningocele	5	8	13 (15)
Myelomeningocele	27	48	75 (85)
Hydrocephaly	29 (91)	43 (77)	72 (82)
Ventricular-peritoneal drain	26 (81)	43 (77)	69 (78)

TABLE 4 Expectations concerning mental development, ability to walk and bladder/bowel dysfunction in the 112 surviving infants with isolated spina bifida

Expectation	N	%
Mental development		
Normal development	50	57
Mental retardation	29	33
Unpredictable	7	8
Unknown	2	2
Ambulation		
Walk without support	16	18
Walk with instruments	25	28
Wheelchair	37	42
Unpredictable	9	10
Unknown	1	1
Bladder /bowel dysfunction		
Bladder dysfunction	77	88
Bowel dysfunction	50	57
Unpredictable	27	31
Continence	11	12
Unknown	2	2

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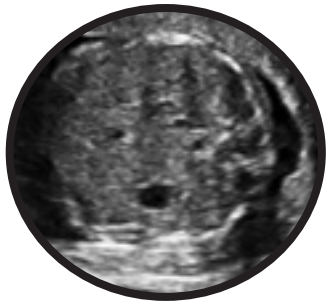
3 Diagnosis of gastro-intestinal anomalies and abdominal wall defects

In this chapter, perinatal outcome following prenatal diagnosis versus postnatal diagnosis is presented for three major fetal anomalies at abdominal level, notable duodenal obstruction (chapter 3. 1), gastroschisis (chapter 3. 2), and omphalocele (chapter 3. 3).
Whereas the latter two anomalies should be picked up at an 18-22 week ultrasound scan, this is not the case for duodenal obstruction, which is usually detected as late as the third trimester of pregnancy.
Gastroschisis and omphalocele are both abdominal wall defects. Gastroschisis is usually diagnosed as a simple anomaly for which perinatal outcome depends on the subsequent occurrence of intestinal complications. Omphalocele is clearly associated with other anomalies and numerical chromosomal abnormalities, such as trisomy 18 and 13.



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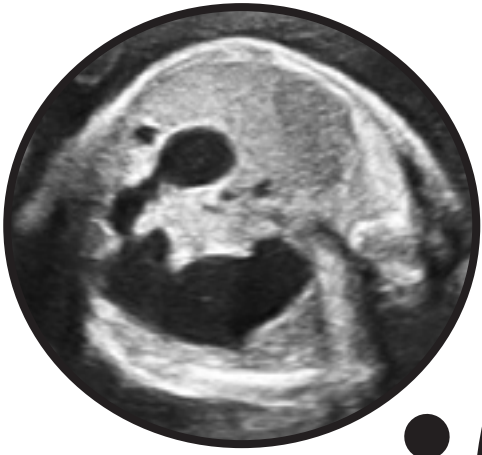

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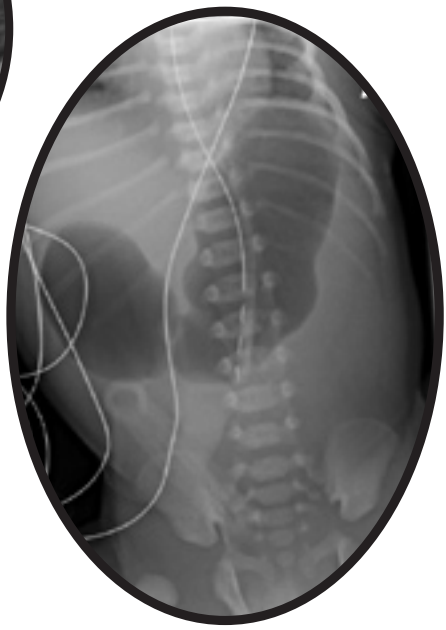

3

1 Transverse plane of section through the normal fetal abdomen with the spine at 3 o'clock and stomach at 6 o'clock.

2 Transverse plane of section through the fetal abdomen showing the dilated stomach and duodenum (double-bubble phenomenon). A connection between the two dilated structures is visible, indicating an obstruction of the duodenum.

3 X-ray of newborn infant with duodenal obstruction showing the air-filled stomach and duodenum

3.1

Isolated or non-isolated duodenal obstruction: perinatal outcome following a prenatal diagnosis or a diagnosis only after birth

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Abstract

Objectives To determine whether the pre- or postnatal diagnosis of either isolated or non-isolated duodenal obstruction (DO) is associated with different outcomes.

Methods A single center retrospective analysis was carried out of 91 cases diagnosed with a DO between January 1991 and June 2003. Data on the diagnosis, treatment and outcomes of the cases were gathered, and differences between the groups were analyzed.

Results 28 cases were diagnosed before and 63 after birth. Of 15 presumed isolated cases in the prenatal group four revealed associated or chromosomal anomalies after birth. The prenatally (N=11) and postnatally (N=27) detected subsets of isolated DO were significantly different for the type of obstruction. The prenatal subset displayed a lower median gestational age at delivery, lower median birth weight and a higher prematurity rate (8/11 versus 8/27). After delivery the detection of DO occurred significantly later in the postnatal subset. In the non-isolated cases with DO no difference existed for the type of chromosomal or associated anomaly or the type of obstruction between the prenatal (N=17) and postnatal subset (N=36). Trisomy 21 was present in 7/17 (41%) versus 22/36 (61%) cases. Two terminations and three intrauterine deaths occurred in the prenatal non-isolated subset. The liveborn infants from the prenatally (N=12) detected non-isolated subset showed a significantly higher prematurity rate (9/12 versus 14/36), lower median birth weight and earlier diagnosis after delivery. After surgery outcome was similar between both subsets of either isolated or non-isolated DO. All infants with an isolated DO survived. Neonatal death occurred in three prenatally and five postnatally diagnosed cases with non-isolated DO.

Conclusions Outcome of prenatally and postnatally diagnosed DO is not essentially different despite more prematurity and a lower birth weight. Of the prenatal cases of DO assumed isolated, 25% revealed additional chromosomal or associated anomalies after delivery, which influenced outcome.

Introduction

Duodenal obstruction (DO) is a congenital abnormality which occurs in 1.3 per 10,000 live births [1,2] and is the small-bowel obstruction most commonly detected during fetal life[3]. Approximately half of the cases is associated with other abnormalities[4] (non-isolated DO), particularly cardiac, vertebral, renal and gastrointestinal such as anal atresia and tracheoesophageal atresia[5]. DO is complicated in 30% with trisomy 21[5].
Intrinsic DO is presumed to result from failed canalisation of the lumen in the 9th-10th week of embryonic life leading to stenosis or atresia[6]. It is still not clear in what way disturbed intercellular contact or abnormal resolution forms an etiological basis for intrinsic duodenal obstruction, as appropriate animal models are lacking for this specific anomaly. Compression from a surrounding annular pancreas or peritoneal bands[5] may be the cause of extrinsic DO. The sonographic image of DO is characterized by a 'double-bubble' appearance as a result of dilatation of the stomach and duodenum. A connection between the two dilated structures can always be demonstrated. Often polyhydramnios develops during the late second or third trimester of pregnancy[7]. A timely prenatal diagnosis of DO would allow proper counselling of the couple[2] regarding additional karyotyping and adjustment of obstetric management. In case of severe associated anomalies and/or aneuploidy, there may be the option of pregnancy termination if detected early in pregnancy. However, only just over half of the cases of DO are diagnosed prenatally[3] and often beyond 24 weeks of gestation. This may be due to the fact that only small amounts of amniotic fluid are swallowed by the fetus during the first half of pregnancy[8]. The reduced reabsorbtion capacity in duodenal atresia and the increase in swallowing of amniotic fluid as pregnancy progresses leads to the 'double-bubble' appearance and polyhydramnios. At delivery bile stained amniotic fluid may be present due to intrauterine vomiting, sometimes mistaken as meconium containing amniotic fluid. Few studies have compared the outcome of a DO detected before birth and a diagnosis first made after birth. Neonatal morbidity was reduced in the prenatally diagnosed subset of DO in one study[9]. In two other studies, the age of the newborn at diagnosis and at surgery was significantly earlier resulting in less metabolic complications[10] and significantly earlier start of intestinal feeding[11] in cases diagnosed prenatally. However, no impact on overall outcome could be demonstrated by others which was mainly attributed to the high incidence of associated major anomalies[4,12].
In these and other studies [13-15] the outcome of fetuses and infants with or without associated anomalies has not been assessed separately. For parental counselling and obstetric management this information is of paramount importance as there is a suggestion that outcome in the absence of associated anomalies (isolated DO) may be excellent[4].
In our study the following questions were addressed: (i) what is

the impact of prenatal diagnosis on outcome of isolated and non-isolated DO; (ii) is there a difference in outcome between prenatally diagnosed and postnatally diagnosed isolated or non-isolated DO in liveborn infants; (iii) is there a difference in the type of obstruction between the prenatally and postnatally established subsets.

Methods

The Erasmus University Medical Center serves as the single referral center for both fetal anomaly scanning and pediatric surgery in the South West of the Netherlands, a referral area with 35.000 newborns/year. A retrospective data analysis was carried out of all fetuses and infants from singleton pregnancies diagnosed with a congenital DO either pre- or postnatally during the period January 1991-June 2003. Cases were collected from the ultrasound database of the Division of Prenatal Medicine and the patient database of the Department of Pediatric Surgery. Inclusion criteria were prenatal diagnosis and postnatal treatment in our center or postnatal treatment in our center without a prenatal diagnosis elsewhere.

Additional investigations included fetal karyotyping and serial sonographic follow-up of fetal growth and amniotic fluid volume. DO was considered non-isolated if other anomalies were also present. This included, but was not limited to, aneuploidy. In all other cases DO was classified as isolated. Fetal growth restriction (FGR) was defined as a fetal upper abdominal circumference below the 10th centile for gestational age. Polyhydramnios was defined as an amniotic fluid volume above the 95th centile[16] for gestational age. Amniotic fluid drainage was performed in case of massive polyhydramnios and extreme maternal discomfort. Prematurity was defined as a delivery before 37 weeks of gestation. Infants with a birth weight below the 10th centile adjusted for gender[17] were considered small-for-gestational age (SGA). Counselling by a pediatric surgeon was offered to all couples during the prenatal period. All women with a prenatal diagnosis of duodenal obstruction were delivered vaginally unless obstetric reasons dictated otherwise.

In the majority of cases whether presented before or after birth the diagnosis was confirmed by plain abdominal X-ray. Occasionally, a contrast swallow examination, an ultrasound examination of the abdomen or a combination of the above methods was needed. When a termination of pregnancy (<24 weeks) or intrauterine death had occurred the obstruction was determined at post mortem examination if permission was granted.

Surgery was planned as an elective procedure as soon as the metabolic status had stabilized and presence or absence of associated anomalies was assessed. All newborns were evaluated by a consultant clinical geneticist and karyotyping was performed in case of suspicion of syndromal (Down syndrome in most cases) or other dysmorphic features. At surgery the nature

of the duodenal obstruction, i.e. atresia, stenosis or membrane as well as the presence or absence of an annular pancreas and malrotation was established. Atresia was defined as complete obstruction of the duodenum. A limited passage of the duodenum was considered a stenosis. Depending on the type and level of obstruction a duodenoduodenostomy, a duodenojejunostomy, a duodenogastrostomy or a membrane resection was performed. The necessity of more than one day artificial ventilation was recorded. Due to motility disorders of the bowel, infants were primarily given parenteral nutrition (TPN) and enteral feeding was instituted as soon as stomach retentions diminished. Adverse neonatal outcome was defined as neonatal death or complications resulting from the abnormality itself or the subsequent surgical procedure.
Notes were reviewed for fetal sonographic data, neonatal and surgical outcome with a minimal follow up of 12 months. Statistical analysis of comparing groups was performed using the Mann-Whitney test or Fisher's exact test of continuous or categorical data, respectively. P=0.05 (two-sided) was considered the limit of statistical significance.

Results

The total study group consisted of 109 cases, of which 30 were prenatally and 79 postnatally diagnosed. Of the prenatal group, two were delivered and treated elsewhere and were therefore excluded. Sixteen out of 79 cases in the postnatal group were excluded because of a prenatal diagnosis elsewhere. Of the remaining 28 cases in the prenatal group, 15 were initially considered isolated. However, after delivery additional anomalies were recorded in three cases involving a membranous ventricular septal defect and coarctation of the aorta, a case of hemivertebra at C2-C3, combined with only 10 right sided ribs and a case of esophageal atresia without tracheoesophageal fistula. One patient presented at 36 weeks with polyhydramnios and a 'double-bubble' phenomenon. Amniocentesis was performed but trisomy 21 without associated anomalies was revealed only after delivery at 38 weeks of gestation.

Prenatally diagnosed isolated versus non-isolated DO (N=28)

Details of the prenatal group comparing the isolated (N=11) and the non-islolated subset (N=17) of DO are given in Table 1. The median gestational age at detection of the DO for the isolated subset (33.3 wks) was significantly ($p<0.05$) higher than for the non-isolated subset (31.0 wks). Polyhydramnios was present in 9/11 (82%) isolated cases and in 13/17 (76%) non-isolated cases, and mostly established after 24 weeks of gestation. Amniotic fluid drainage was required in four cases of the isolated subset and in one case of the non-isolated subset.

The nature of the associated anomalies in the non-isolated subset was mainly cardiac, gastro-intestinal and skeletal (vertebral). In five cases of the non-isolated subset additional anomalies in the gastrointestinal tract were only diagnosed after delivery. These included one case of anal atresia and sacral vertebral anomalies, one case of apple peel atresia of the proximal jejunum and intestinal malrotation and three cases of esophageal atresia, twice associated with a tracheoesophageal fistula. Karyotyping was carried out in 10/11 isolated cases with normal results. However, the karyotype was abnormal in 7/17 (41%) non-isolated cases, each representing trisomy 21. Only two patients presented with a 'double-bubble' before 24 weeks of gestation and in both cases a termination of pregnancy was requested and performed. Trisomy 21 was established in one case without associated structural anomalies. The second case revealed an additional esophageal atresia without a tracheoesophageal fistula at the post mortem examination. Three cases of intrauterine death occurred at 33.4, 33.6 and 38 weeks of gestation, respectively. In the first case an additional esophageal atresia with fistula was diagnosed at autopsy. The latter two were associated with trisomy 21. One showed a grossly dilated duodenum with stenosis and growth below the 10th centile at autopsy, while in the other case autopsy was refused.

No significant difference existed between the prenatally diagnosed isolated versus prenatally diagnosed non-isolated subsets for median gestational age at delivery, prematurity rate, spontaneous delivery rate, median birth weight and fetal gender. Three neonatal deaths occurred in the non-isolated subset. In all cases delivery was premature at 29, 30 and 34 weeks of gestation. The first case was associated with a transposition of the great arteries and the second case revealed ventriculomegaly, Tetralogy of Fallot and a multicystic kidney. In the latter the anomalies were confirmed and additionally anal atresia and sacral vertebral anomalies were diagnosed, consistent with a VACTERL association. A duodenoduodenostomy was performed but neonatal death occurred at the age of 10 days. In the third case the fetus was known with a mulitcystic kidney and an apple peel jejunal atresia was diagnosed at surgery. The post operative period was complicated by encephalitis and meningitis and the infant died on day 19. The combined mortality (IUD and neonatal death) between the isolated (0/11) and non-isolated (6/17) subset did not reach statistical significance.

Prenatally versus postnatally diagnosed isolated DO (N=38)

When comparing the prenatally (N=11; 29%) and postnatally detected subset of isolated DO (N=27; 71%) (Table 2), an overall significant difference for the type of obstruction (intrinsic versus extrinsic) was established. Intrinsic obstruction was significantly more common in the group with a postnatal diagnosis (p=0.017). Due to the small numbers it was impossible to determine which subtype of obstruction led to this significant difference.

Data comparing delivery and outcome of infants between prenatally (N=11) and postnatally (N=27) diagnosed isolated DO are shown in Table 3. Whereas median gestational age at delivery and median birth weight were significantly lower, prematurity rate was significantly higher in the prenatal subset compared with the postnatal subset. The overall mode of delivery was similar in both subsets. The mode of delivery could not be retrieved in 3/27 cases in the postnatal subset. After delivery the detection of duodenal obstruction occurred significantly later ($p<0.001$) in the postnatal subset with only 10/27 infants diagnosed before day 4. The method of diagnosis in the prenatal subset only required an abdominal x-ray, whereas in the postnatal subset several different and sometimes multiple methods were necessary to establish the diagnosis.
The nature of the surgical correction was significantly different ($p=0.028$) between the prenatally diagnosed isolated versus postnatally diagnosed isolated subset. This could be contributed to the duodenoduodenostomy which was performed in all 11 prenatally detected cases as opposed to only 15/27 (55%) posnatally detected cases of DO. In the period after surgery no significant differences were seen between the pre- and postnatal subset for the time on parenteral nutrition, infants requiring more than one day artificial ventilation, the number of complications occurring and the length of hospital stay. Gastrointestinal complications required a total of 12 readmissions for eight infants in the postnatal subset as opposed to only one in the prenatal subset. All infants with an isolated DO survived.

Prenatally versus postnatally diagnosed non-isolated do (N=53)

In the presence of non-isolated DO, 17 (32%) cases were detected prenatally and 36 (68%) cases postnatally. No significant difference was found for the type of chromosomal anomaly or congenital organ defect (Table 4) and no overall difference could be established for the type of obstruction between the two subsets (Table 5).
Data comparing delivery and outcome of liveborn infants between prenatally (N=12) and postnatally (N=36) detected non-isolated DO are given in Table 6. The prematurity rate was significantly higher and median birth weight significantly lower in the prenatal subset compared with the postnatal subset. Gestational age at delivery and overall mode of delivery did not reach a significant difference. For ten cases in the postnatal subset the delivery mode could not be retrieved. Both the prenatal and postnatal subset of non-isolated DO contained a high proportion of SGA infants (6/12 (50%) versus 14/36 (39%)). One case from the prenatal subset and one case from the postnatal subset was excluded from the analysis referring to treatment. This was due to demise within one week of delivery and no surgical intervention as a result of the associated anomalies. A significant difference ($P<0.001$) was revealed for the age at diagnosis between the prenatal and postnatal subset of non-isolated DO. All cases of the prenatal subset were confirmed

before day 2. In the postnatal subset only 11/36 infants were diagnosed before day 4. Twelve infants were diagnosed between day 8 and day 814 (median day 116); 10 cases with a duodenal membraneous obstruction and two cases with an annular pancreas. The methods required to reach a diagnosis and the nature of the surgical procedure were not significantly different between the prenatal and postnatal subset of non-isolated DO. In the period after surgery no difference was established between the two subsets for days on parenteral nutrition, complication rate, readmissions for gastrointestinal complications, and length of hospital stay. Significantly (p=0.03) more infants required artificial ventilation for more than one day in the prenatal (5/12) versus the postnatal subset (3/36) of non-isolated DO. Neonatal death occurred in three prenatally and five postnatally diagnosed infants with DO. There were 29 cases of Down syndrome, seven of which were diagnosed in the prenatal subset of non-isolated DO and 22 cases in the postnatal subset of non-isolated DO. In one case the cause of obstruction was not established as autopsy was refused after intrauterine death had occurred. No overall difference could be established for the type of obstruction between the prenatal and postnatal subset with trisomy 21 and DO (Table 7).

Discussion

This is a first report on the perinatal outcome of DO in which isolated or non-isolated cases diagnosed prenatally or after birth are analyzed separately. Both in the isolated and non-isolated form birth weight was significantly lower and prematurity rate significantly higher in the prenatal subsets. Additionally the gestational age at delivery was significantly lower in the prenatal isolated subset. Whereas the age at postnatal confirmation of the DO was significantly lower in both prenatal isolated and non-isolated subsets, perinatal outcome after surgery was similar between both pre- and postnatal isolated and non-isolated subsets. Intrauterine and neonatal death only occurred in the presence of non-isolated DO. Of the prenatal cases of DO presumed isolated, 25% revealed additional chromosomal or associated anomalies after delivery.

A recent analysis of 1047 liveborn infants with gastrointestinal malformations such as esophageal atresia, duodenal obstruction, omphalocele, diaphragmatic hernia or a combination of these anomalies from 14 population based registries of congenital malformations (EUROCAT)[18] pointed at the significantly shorter gestational age at delivery in the prenatally detected cases compared to those detected after birth. Although in this study the delivery mode was not registered, it was suggested that the shorter gestational age at birth in prenatally detected cases was due to clinicians planning the delivery under strictly controlled conditions. This is supported by a study on the effect of prenatal diagnosis on outcome of D-Transposition of the great arteries[19], in which a reduced spontaneous

delivery rate and a lower birth weight was noted in the group with a prenatal diagnosis compared to the group with a diagnosis only at birth. In our study the mode of delivery was recorded in all prenatal cases, but data on delivery mode were missing in 3/27 postnatal isolated and 10/36 postnatal non-isolated cases. Even when the missing data on delivery mode were all replaced by a spontaneous vaginal delivery, the overall delivery mode would not show any significant difference between both the prenatal and postnatal subsets. The shorter gestational age at birth, the higher prematurity rate and lower birth weight in the prenatal isolated subset are more likely due to the difference in type of obstruction between these two isolated subsets, as demonstrated in Table 2. The postnatal isolated subset required no intervention during pregnancy. However, in the prenatal isolated subset, polyhydramnios gave rise to amniotic fluid drainage in 4/11 cases, presenting a risk factor for premature labor. No difference in type of associated anomaly or type of obstruction was recorded between the prenatal and postnatal non-isolated subset and only 1/17 prenatal non-isolated cases required amniotic fluid drainage. This does not explain the higher prematurity rate and lower birth weight in the prenatal non-isolated subset compared to the postnatal non-isolated subset. Other factors may have contributed to the high prematurity rate. Women who are informed that their offspring suffers a severe congenital anomaly experience increased psychological instability[20]. It has been well documented that stress and pregnancy related anxiety are associated with spontaneous preterm birth[21,22].

Increased morbidity and mortality are described following preterm and near-term delivery[23,24]. The major morbidity from late prematurity may be respiratory. The prenatal non-isolated subset with DO showed an increased need for ventilatory support of more than one day. This subset contained significantly more premature infants although there was no difference in gestational age at birth compared to the postnatal non-isolated subset with DO. According to unit practice neonates will receive artificial ventilation for one day following upper abdominal surgery. Older infants, beyond the immediate postnatal age, do not need this support. At least 8 infants from the postnatal non-isolated subset underwent surgery beyond 3 months of age which explains this different requirement for artificial ventilation. Other post surgery parameters assessing outcome did not reveal a difference between the non-isolated prenatal and postnatal subsets. Despite increased prematurity and a lower gestational age at delivery in the prenatal isolated subset with DO the outcome following surgery was similar compared to the postnatally detected isolated subset. Earlier confirmation of the diagnosis and earlier surgery may have contributed to this favorable result. Similar to our findings, previous studies comparing pre- and postnatally established DO, describe earlier confirmation of the diagnosis and earlier surgery in prenatally detected DO with less metabolic complications before surgery[9,10] or earlier feeding transition[11] but no difference in length of hospital stay[11] and overall outcome[4]. Contrary to our investigation, gestational age at birth

was not taken into account in these studies. The need for artificial ventilation has not been assessed previously in this context.
In a study of prenatally and postnatally diagnosed small bowel atresia[25], it was demonstrated that a prenatal diagnosis was associated with a lower birth weight and a longer period of parenteral feeding and hospital stay. It was presumed that small bowel atresia diagnosed before birth was associated with a more pronounced in utero distension of the bowel and hence a relative longer period of postnatal gut dysfunction, even after earlier repair. Alternatively, a more severe form of obstruction may have been the reason for the prenatal detection of DO when compared to cases detected after birth. In our series, polyhydramnios was present in 81% of the prenatal isolated and in 76% of the prenatal non-isolated subset. In two studies the incidence of polyhydramnions has been reported as high as 75% and 80% in the prenatal group, as opposed to 14% and 32% in the postnatal group[4,10]. Postnatal series have reported maternal polyhydramnios as a complication of DO in only 32-48%[13,15,26].
Clinical symptoms that lead to the postnatal diagnosis of DO are bilious vomiting, distended abdomen and failure to pass meconium[5]. However, in the presence of complete obstruction non-bile stained vomit and normal passage of meconium have been documented in 39% and 30% of cases, respectively[15]. Membraneous DO, in a number of cases containing a hole resulting in intermittent or less severe intestinal obstruction, has been reported to be associated with other anomalies in 75% of cases, mostly presenting trisomy 21[27]. Here, the obstruction is often associated with non-bilious vomiting and failure to thrive. A diagnosis of obstruction may be delayed as symptoms are frequently attributed to the other anomalies present[9]. In our study, 10/25 cases of membraneous DO were of the isolated form, of which nine were diagnosed postnatally. The latter attributed to the majority of DO cases diagnosed between day 5 and day 39. In the postnatal non-isolated subset the delay in diagnosis was even more striking. Ten out of twelve cases of DO diagnosed between day 8 and day 814 represented the membraneous form of DO, of which nine were associated with trisomy 21. A delayed diagnosis of DO is frequently reported[11,15] with in some cases a delay of up to 3, 4 or even 14 years[14,27,28]. Membraneous obstruction can result in major diagnostic challenges as it results in intermittent feeding problems delaying an ultrasound examination or a contrast swallow examination. Especially the alternating periods of normal enteral feeding and vomiting is troublesome in many cases. Moreover in Down syndrome numerous reasons are present for recurrent refusal of enteral intake. The possibility of DO in these infants should be acknowledged.
Until January 2006 maternal age related detection of fetal chromosomal anomalies was only provided for women of 36 years and older. Screening tests such as the triple test or nuchal translucency measurement were not available for the general pregnant population. This may explain the high incidence of Downs's syndrome cases (22/63, 35%) in the postnatal subset.

At the time of the study routine ultrasound to detect fetal anomalies was not a policy in the Netherlands. All pregnant women underwent an ultrasound scan in the first trimester to determine the gestational age but no further scans were performed unless an abnormal clinical finding would indicate this. This policy may explain why only 28 (30%) out of 91 cases were detected prenatally. Although this detection rate is double that of a study that had started in the seventies[26], it is far from the 58% prenatal detection rate reported by Singh et al.[14] during the same period as the present investigation. Theoretically one may assume that in countries where 3rd trimester ultrasound scan is common practice more cases with DO will be detected prenatally. No such studies have been published sofar.

In the entire prenatal group the non-isolated cases are diagnosed significantly earlier then the isolated cases, confirming data from the EUROSCAN study group[3]. Polyhydramnios was present in more than 75% in both isolated and non-isolated cases but only two non-isolated cases were detected before 24 weeks of gestation. One case was complicated by polyhydramnios and trisomy 21 and in the other esophageal atresia without a fistula was established after termination of pregnancy. In an earlier study[2], four out of five cases of DO detected before 24 weeks of gestation were non-isolated with two presenting a chromosomal anomaly. The mechanism responsible for the early appearance of the 'double-bubble' sign in case of a chromosomal anomaly is not clear. Early diagnosis of DO has been reported in combination with esophageal atresia[29,30]. It has been suggested that accumulations of secretions in the closed loop of stomach and duodenum in case of DO with esophageal atresia without fistula[31] seem responsible for the early dilatation of stomach and duodenum.

Perinatal outcome between the prenatal isolated and non-isolated subset did not reveal any significant difference except for the high incidence of intrauterine and neonatal death in the non-isolated subset. This is in agreement with previous studies[32,33] in which intrauterine death is reported in non-isolated DO. Brantberg et al.[7], however, described two cases of intrauterine death occurring in isolated DO.

Mortality in our study only involved the non-isolated cases with an incidence in the pre- and postnatal subset of 40% and 14%, respectively. The percentage in the prenatal non-isolated subset seems high compared to percentages between 17 and 24% reported in the literature[2,7]. These series, however, did not differentiate between isolated and non-isolated cases of DO.

For counselling purposes one must realize that not all associated or chromosomal anomalies are known at the time of the ultrasound detection of DO. Of the cases in our prenatal subset presumed isolated, 25% proved to be non-isolated after delivery with serious consequences for the outcome. This phenomenon is known in cases of prenatally suspected isolated talipes equinovarus[34], but not yet described in the presence of DO. The nature of some of the anomalies, typically associated with DO such as esophageal

atresia with fistula, anal atresia, vertebral and rib anomalies are difficult to detect by antenatal ultrasound[35,36] and may therefore explain the relatively high percentage of missed anomalies.

It can be concluded that the overall outcome of liveborn infants after a pre- or postnatal diagnosis of isolated or non-isolated DO is similar despite more prematurity and a lower birth weight in the subsets with a prenatal diagnosis. The age at postnatal confirmation of the DO is significantly lower in both prenatal subsets and this may have contributed to the favorable outcome. Intrauterine and neonatal death only occurred in the presence of associated or chromosomal anomalies. Of the prenatal cases of DO assumed isolated, 25% revealed additional chromosomal or associated anomalies after delivery which influenced outcome.

TABLE 1 Prenatal, delivery and outcome data from the prenatally detected isolated and non-isolated cases with duodenal obstruction.

	Isolated N=11	Non-isolated N=17	P
GA at detection (weeks)	33.3 (27.8-37.3)	31.0 (20.3-36)	<0.05
Polyhydramnios <24 weeks	-	1	-
Polyhydramnios >24 weeks	9	12	1.00
Amniotic fluid drainage	4	1	0.15
Fetal growth retardation	1	2	1.00
Associated anomalies			
Cardiac	-	5	NT
Gastro-intestinal tract	-	5	NT
Renal tract	-	2	NT
Central nervous system	-	1	NT
Vertebral	-	4	NT
Other	-	3	NT
Karyotyping performed	10	17	0.39
Abnormal karyotype	-	7	NT
Intrauterine death (IUD)	0	3	0.26
Termination of pregnancy (TOP)	0	2	0.51
Delivery* <37w	8	9	1.00
Delivery mode overall			0.85
Spontaneous delivery *	6	8	0.68
Induced delivery*	2	1	0.57
Cesarean section*	3	3	1.00
GA at delivery (weeks) *	35.4 (30.1-39.3)	35.7 (29.3-39.1)	0.56
Birth weight (g) *	2320 (1455-3480)	1917 (1155-3390)	0.14
Birth weight <10th centile *	3	6	0.40
Male/Female	7/4	9/8	0.70
Neonatal death * (NND)	0	3	0.22
Combined mortality (IUD + NND)	0	6	0.055

Data presented as median and range. GA, gestational age; g, gram; NT, not tested.

* excluding cases of IUD or TOP.

TABLE 2 Type of obstruction in the prenatal and postnatal subset with isolated duodenal obstruction.

	Prenatal subset N=11	Postnatal subset N=27	P
Type of obstruction overall (intrinsic/extrinsic)	4/7	22/5	0. 017
Intrinsic obstruction			
Duodenal membraneous obstruction	1	9	0. 23
Duodenal stenosis	0	2	1. 00
Duodenal atresia	3	11	0. 49
Extrinsic obstruction			
Annular pancreas	5	5	0. 12
Annular pancreas with intestinal malrotation (Ladd's bands)	2	0	0. 08

TABLE 3 Delivery and outcome data of the prenatal and postnatal subset with isolated duodenal obstruction

	Prenatal subset N=11	Postnatal subset N=27	P
GA at delivery (weeks)	35.4 (30.1-39.3)	40.0 (31.1-41.6)	0.011
Delivery <37 weeks	8	8	0.04
Mode of delivery overall‡			0.24
Spontaneous delivery	6	19	0.23
Induced delivery	2	1	0.23
Cesarean section	3	4	0.65
Birth weight (g)	2320 (1455-3480)	2945 (1670-4350)	0.04
Birth weight <10th centile	3	2	0.3
Age at diagnosis (days)	0 (0-2)	4 (0-39)	<0.001
Method of diagnosis			
X-ray of abdomen	11	19	0.08
Contrast swallow examination	0	7	0.08
Ultrasound of abdomen	0	4	0.6
>1 method required for a diagnosis	0	4	0.3
Surgery overall			0.028
Duodenoduodenostomy	11	15	0.008
Duodenojejunostomy	0	4	0.3
Membrane resection	0	8	0.08
>1 day artificial ventilation	2	6	1.00
Days to first oral feeds	5 (4-10)	6 (3-23)	0.56
Days on parenteral nutrition	11 (4-16)	11 (5-33)	0.85
Infants with complications after surgery	2	5	1.00
Number of complications after surgery	2	6	1.00
Infants requiring readmission	1	8	0.24
Number of readmissions	1	12	0.23
Length of hospital stay (days)	23 (15-48)	22 (11-48)	0.67

Data presented as median and range. GA, gestational age; g, gram

‡ The mode of delivery could not be retrieved for 3/27 cases in the postnatal subset

TABLE 4 Associated anomalies in the prenatal and postnatal subset with non-isolated duodenal obstruction and separated in cases with and without trisomy 21.

	Prenatal subset N=17	Postnatal subset N=36	P
Cases associated with trisomy 21	7	22	0.24
Cardiac	1	8	0.63
Gastro-intestinal tract	0	5	0.55
Esophageal atresia	0	1	1.00
Renal tract	0	0	-
Central nervous system	0	1	1.00
Vertebral	0	1	1.00
Other	0	0	-
Total number of anomalies	1	16	0.25
Cases not associated with trisomy 21	10	14	0.24
Other abnormal karyotype	0	1	1.00
Cardiac	4	8	0.68
Gastro-intestinal tract	2	5	0.65
Esophageal atresia	3	1	0.27
Renal tract	2	2	1.00
Central nervous system	1	1	1.00
Vertebral	4	3	0.39
Other	3	5	1.00
Total number of anomalies	19	25	0.56

TABLE 5 Type of obstruction in the prenatal and postnatal subset with non-isolated duodenal obstruction.

	Prenatal subset N=17*	Postnatal subset N=36	P
Type of obstruction overall (intrinsic/extrinsic)	13/3	25/11	0.43
Intrinsic obstruction			
Duodenal membraneous obstruction	3	12	0.34
Duodenal stenosis	1	2	1.00
Duodenal atresia	9	11	0.12
Extrinsic obstruction			
Annular pancreas	3	8	1.00
Annular pancreas with intestinal malrotation (Ladd's bands)	0	3	0.54

* In one case of intrauterine death associated with trisomy 21 post mortem investigation was not permitted which prevented a final diagnosis of duodenal obstruction

TABLE 6 Delivery and outcome of the liveborn infants in the prenatal and postnatal subset with non-isolated duodenal obstruction.

	Prenatal subset N=12	Postnatal subset N=36	P
GA at delivery (weeks)	35.7 (29.3-39.1)	38 (30.1-42)	0.10
Delivery <37 weeks gestation	9	14	0.046
Mode of delivery overall ‡			1.00
Spontaneous delivery	8	16	1.00
Induced delivery	1	3	1.00
Cesarean section	3	7	1.00
Birth weight (g)	1918 (1155-3390)	2770 (1130-3780)	0.04
Birth weight <10th centile	6	14	0.74
Age at diagnosis (days)*	0 (0-2)	5 (1-814)	<0.001
Method of diagnosis*			
X-ray of abdomen	10	21	0.13
Contrast swallow examination	2	13	0.45
Ultrasound of abdomen	0	5	0.56
>1 method required for a diagnosis	1	4	1.00
Surgery overall*			0.31
Duodenoduodenostomy	7	18	0.73
Duodenojejunostomy	3	4	0.34
Duodenogastrostomy	0	1	1.00
Membrane resection	1	12	0.14
>1 day artificial ventilation*	5	3	0.03
Days to first oral feeds*	5 (4-12)	5 (2-22)	0.53
Days on parenteral nutrition*	12.5 (5-18)	9 (3-31)	0.20
Infants with complications after surgery*	7	13	0.17
Number of complications after surgery*	15	24	0.16
Infants requiring readmission*	1	4	0.71
Number of readmissions*	1	5	0.55
Length of hospital stay (days)*	26 (12-46)	24 (9-332)	0.47
Neonatal/infant death	3	5	0.39

Data presented as median and range. GA, gestational age; g, gram

‡ The mode of delivery could not be retrieved for 10/36 cases in the postnatal subset.

* Prenatal subset: one case of neonatal death after 6 days, no surgery, excluded from analysis. Postnatal subset: one case of neonatal death two days after delivery, not included in analysis

TABLE 7 Causes of duodenal obstruction associated with trisomy 21

	Prenatal subset N=7 *	Postnatal subset N=22	P
Type of obstruction overall (intrinsic/extrinsic)	5/1	16/6	0.83
Intrinsic obstruction			
Duodenal membraneous obstruction	2	9	1.00
Duodenal stenosis	1	1	0.39
Duodenal atresia	2	6	1.00
Extrinsic obstruction			
Annular pancreas	1	6	1.00

* In one case of intrauterine death associated with trisomy 21 post mortem investigation was not permitted, precluding a final diagnosis of duodenal obstruction

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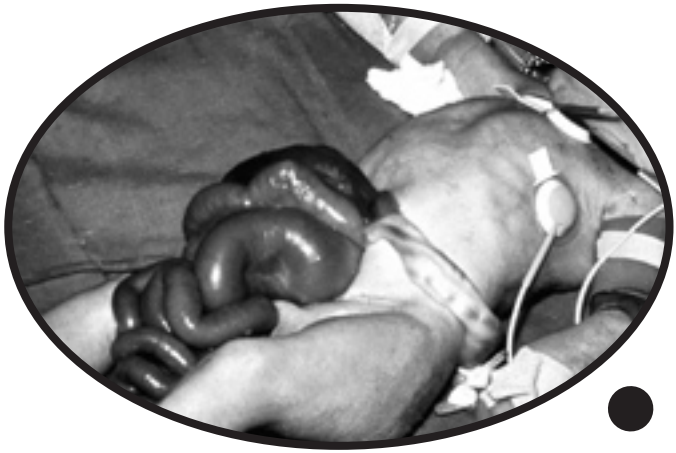

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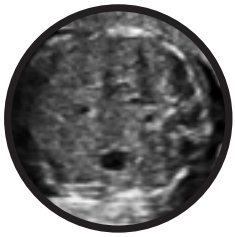

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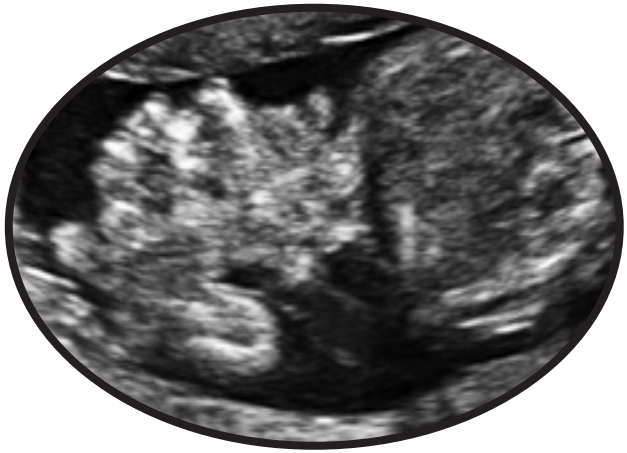

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1 Transverse plane of section through the normal fetal abdomen with the spine at 3 o'clock and stomach at 6 o'clock.
2 Cross sectional plane of the fetal abdomen showing free floating intestines in the amniotic fluid.
3 Newborn infant with gastroschisis; the intestines are herniated through an abdominal wall defect at the right of the umbilical cord insertion.

3.2

The outcome of gastroschisis after a prenatal diagnosis or a diagnosis only at birth. Recommendations for prenatal surveillance.

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Abstract

Objectives To establish in infants with gastroschisis whether outcome is different when comparing a prenatal diagnosis with a diagnosis only at birth with the intention to develop a prenatal surveillance protocol. Intestinal atresia established after birth and preterm versus term delivery were studied as risk factors.

Study design All 24 fetuses and 9 infants diagnosed with gastroschisis and referred to our tertiary center between January 1991 and June 2003 were studied retrospectively.

Results The infants of the prenatal subset delivered at our tertiary center and 18 survived. There were two pregnancy terminations, three intrauterine deaths at 19,33 and 36 weeks respectively and one neonatal death. All nine infants in the postnatal subset survived. Eight were out born and one was delivered at our tertiary center. Prenatal bowel dilatation did not correlate with outcome. Between the prenatal and postnatal subset no significant difference in outcome of liveborn infants was established. For four infants with intestinal atresia a significant difference was demonstrated for induction of preterm labor ($P<0.05$), duration of parenteral nutrition ($P<0.01$), number of additional surgical procedures ($P<0.001$) and length of hospital stay ($P<0.01$) . The fifteen infants born prior to 37 weeks of gestation spent a significantly longer period in hospital compared to those delivered at term. When the cases with bowel atresia were excluded this difference was no longer present. Five of the 33 cases were diagnosed with associated anomalies which mainly involved the urinary tract.

Conclusion Neonatal outcome of liveborn infants following a prenatal diagnosis of gastroschisis is not different from a diagnosis at birth. The presence of intestinal atresia is the most important prognostic factor for morbidity. The supplemental value of prenatal diagnosis to the outcome of infants with gastroschisis may be in the prevention of unnecessary intrauterine death and detection of intestinal complications. A proposed surveillance protocol for fetuses with gastroschisis focused on intrauterine signs of pending distress such as a dilated stomach, intra abdominal bowel dilatation with peristalsis, notches in the umbilical artery Doppler signal, development of polyhydramnios and an abnormal CTG registration may improve outcome.

Introduction

Gastroschisis is a congenital defect of the abdominal wall characterized by the evisceration of abdominal organs without a covering membranous sac. The anomaly can easily be detected by prenatal ultrasound. The detection rate has been reported to be as high as 83%, with the majority being diagnosed before the third trimester[1].
Infants with gastroschisis have a high overall survival rate, however, the rate of intrauterine fetal death and morbidity due to gastrointestinal complications is considerable[2]. Bowel dilatation[3] and polyhydramnios[4] have been suggested as prenatal predictors of adverse postnatal outcome, although for the size of the dilated bowel[5] this may be questioned.
Preterm delivery and particularly pre-labor cesarean section may result in a reduction in the formation of a fibrous coating on the bowel as well as reduce complications such as atresia, stenosis, necrosis and perforations of the bowel[6]. However there is still controversy regarding the use of cesarean section and preterm instead of term delivery[7]. Several studies have come to the conclusion that term vaginal delivery will improve outcome[8,9]. The positive effect of prenatal diagnosis on the outcome of gastroschisis has not been established, although these studies were conducted a decade ago[10-12].
Routine ultrasound to detect congenital anomalies was not part of recent policy in the Netherlands therefore some cases of gastroschisis remained undiagnosed in the antenatal period. This provided us with the opportunity to assess the value of prenatal diagnosis for fetuses with gastroschisis and to propose a surveillance protocol according to outcome parameters and data from the literature. We studied (i) the influence of prenatal diagnosis on the outcome of fetuses with gastroschisis compared with a group of infants where this diagnosis was only established at birth and (ii) the influence of bowel atresia on outcome of infants with gastroschisis and (iii) the outcome of infants with gastroschisis born before or after 37 weeks of gestation.

Material and Methods

The University Medical Center Rotterdam serves as the referral center for both fetal anomaly scanning and pediatric surgery in the South West of the Netherlands. We performed a retrospective analysis of all infants from singleton pregnancies diagnosed with a gastroschisis either pre- or postnatally between January 1991 and June 2003. Cases were identified from our ultrasound database and from the patient database of the Department of Pediatric Surgery.
Following prenatal detection of a gastroschisis, regular ultrasound scans were performed during pregnancy to evaluate fetal growth, the presence of bowel dilatation and amniotic fluid volume. During the study period no structured protocol was applied to monitor the fetal condition. Fetal growth

restriction (FGR) was defined as a fetal upper abdominal circumference <10th centile. Bowel dilatation was determined by the inner to inner bowel wall distance. Maximum bowel dilatation prior to delivery was stratified employing a cut-off level of 10 and 17 mm and correlated with outcome. Amniotic fluid volume was considered abnormal for measurements below the 5th and above 95th percentile[13]. Counselling by a pediatric surgeon was offered to all couples during the prenatal period. According to the hospital protocol all women with a prenatal diagnosis of gastroschisis were delivered in our center by vaginal delivery unless obstetric reasons required otherwise. Prematurity was defined as a delivery prior to 37 weeks of gestation. Infants with a birth weight below 10th percentile, adjusted for sex[14], were defined as small for gestational age (SGA).

After delivery the presence or absence of a fibrous coat on the bowel (bowel peel) was documented. Management of the gastroschisis consisted of closure of the defect within hours following birth, by means of primary closure or Siliastic Silo depending on the size of the defect and ventilatory pressures during the procedure. Due to motility disorders of the bowel infants were given primarily parenteral nutrition (TPN) and enteral feeding was instituted as soon as stomach retentions diminished.

Adverse neonatal outcome was defined as neonatal death or complications resulting from the abnormality itself (intestinal atresia, necrotising enterocolitis), the subsequent surgical procedure (anatomic or functional short bowel syndrome, TPN associated cholestasis jaundice, venous line sepsis), or other significant morbidity not directly related to the gastroschisis. Distinction was made between: (i) a diagnosis prenatally and a diagnosis only postnatally, (ii) presence and absence of intestinal atresia and (iii) delivery before and after 37 weeks of gestation. Charts were reviewed for maternal demographic data, fetal ultrasound surveillance data, fetal outcome, neonatal surgical and subsequent outcome data.

Statistical analysis of comparing groups was performed using the Mann-Whitney test or Fisher's exact test in case of continuous or categorical data, respectively. P=0.05 (two-sided) was considered as the limit of statistical significance.

Results

We reviewed the data of 24 prenatally diagnosed and 9 postnatally diagnosed cases of gastroschisis. Three prenatal cases have been described previously[15]. In the prenatal subset, mean maternal age (± SD) at diagnosis was 25.9 ± 6 years. Mean gestational age at diagnosis was 23.3 ± 6.6 weeks. In six out of 24 women (25%) the gastroschisis was detected after 24 weeks gestation. Two pregnancies were terminated before 24 weeks gestation. Three women were diagnosed with FGR. Five pregnancies were complicated by oligohydramnios and two by polyhydramnios. Associated fetal anomalies were detected in

4/22 (17%) pregnancies, unilateral hydronephrosis in three cases and bilateral talipes equinovarus in one. Three fetuses (12,5%) died in utero at 19, 33 and 36 weeks of gestation, respectively. One intrauterine death represented a combination of gastroschisis, bilateral talipes equinovarus and early FGR. The two intrauterine deaths in the third trimester revealed normal amniotic fluid volume, no altered aspect of the stomach and intestines and no evidence of FGR or abnormal Doppler measurements within two weeks of fetal demise. Apart from the gastroschisis neither intestinal atresia nor other anomalies were revealed in both cases at post mortem investigation.

Delivery data and outcome variables of the liveborn prenatal subset (N=19) and postnatal subset (N=9) are provided in Tables 1 and 2. The postnatal subset consisted of one infant born at home, seven infants delivered in a regional general hospital and one infant delivered in our tertiary care facility at a gestational age of 36 week. No statistically significant difference was found between the two groups. In the liveborn prenatal subset labor was induced before 37 weeks in 3/7 cases: at 32 week due to ruptured membranes and developing fever; at 36 weeks because of FGR and dilated bowel loops; and at 36 weeks due to FGR, oligohydramnios and dilated bowel loops. In the latter two infants, atresia of the bowel was suspected prenatally, but only confirmed in one. One cesarian section was performed because of fetal distress noticed during spontaneous labor at 36 weeks of gestation.

Postnatal evaluation of the prenatal subset revealed seven infants presenting solely with bowel in the evisceration, eight infants with evisceration of the bowel and stomach, one with evisceration of the bowel and ovaries and three with evisceration of bowel, stomach and ovaries (50% of females). In the subset in which gastroschisis was first diagnosed after delivery (postnatal subset), two infants presented with bowel evisceration, six with bowel and stomach evisceration, and in one infant the evisceration included the urinary bladder.

All infants were transferred to the pediatric surgical ICU on the day of delivery. In the prenatal subset all three cases of suspected unilateral hydronephrosis were confirmed. They were the result of a pelvic ureteric junction obstruction, a primary mega ureter and a vesicoureteric reflux, respectively. In addition, one other case of vesico-urethral reflux was diagnosed. Complications developing in the postnatal period included a frontal temporal hypoxia causing a convulsion and a venous infarct in the corticospinal tract resulting in mild hemiplegia in one patient. In the postnatal subset no other anomalies or complications other than those related to the gastroschisis were diagnosed.

Intestinal atresia was suspected prenatally in 3/19 liveborn infants, twice due to a herniated stomach together with dilated bowel loops of 11 and 33 mm, respectively. The latter case was also complicated by polyhydramnios and intra abdominal dilated bowel loops with active peristalsis; the third case revealed dilated echogenic bowel loops with a diameter of 23 mm. Bowel atresia was confirmed at birth in the first two cases. The first infant

was delivered at 36 weeks and it's bowel was covered by peel. Closure of the defect required a Siliastic Silo. Definitive closure of the defect was undertaken on day 14. At this time the presence of bowel peel was not documented. Additional surgery necessary for persistent stomach retentions was performed at the age of 3 months and a jejunal atresia was corrected.
The second infant required almost total bowel resection due to complete bowel necroses established at birth, resulting in withdrawal of treatment and neonatal death one day after delivery. This fetus presented at 35 weeks gestation with a polyhydramnios, dilated intra-abdominal bowel loops. He was born at 37 weeks gestation with a birth weight of 2745 grams. One infant was delivered after premature rupture of membranes and onset of labor at 31 weeks. There was no ultrasound evidence of polyhydramnios or dilated bowel loops at 29 weeks of gestation, however atresia was established.
In none of the nine infants diagnosed with gastroschisis only at birth, an atresia was noted at initial surgery. In one infant re-evaluation due to persistent stomach retention showed a jejunal atresia at the age of 8 weeks, leading to two additional surgical procedures.
Extra-abdominal bowel dilatation was seen in 14/21 fetuses (67%) of the prenatal subset which reached the third trimester. The mean bowel dilatation measured was 18.3 ± 6 mm with a minimum of 11 and a maximum of 33 mm. Based on reported cut-off levels of 10 and 17 mm the number of fetuses with a bowel diameter of <10 mm was seven, between 10 and 17 mm six and ≥17 mm eight. One case of atresia was diagnosed postnatally in each of these subgroups.
To evaluate the effect of atresia on outcome, the 4 infants with atresia were compared with the 24 infants without this complication. A significant difference was established for induction of labor prior to 37 weeks, 2/4 compared to 1/24 ($P<0.05$). Excluding the neonatal death, the median total duration of parenteral nutrition (range) 148 days (148-149) versus 32 days (19-96) ($P<0.01$), the number of additional surgical procedures 3 versus 0 ($P<0.001$) and the median length of hospital stay (range) 145 days (68-149) versus 33 days (12-100) ($P<0.01$) demonstrated a significant difference.
Liveborn delivery occurred in 15 of 28 infants prior to 37 weeks. Bowel peel was documented in 7/15 cases of the premature infants and 3/13 infants of the subset born after 37 weeks of gestation and did not show a significant difference between these two subsets. Intestinal atresia in combination with bowel peel was present in only one of the premature infants. There was a significant difference for mean birth weight (± SD) 2350 grams (± 310) versus 2717 grams (± 305) ($P<0.01$) and median length of hospital stay (range) 58 days (28-149) versus 31 days (12-74) ($P<0.05$) in infants born prior to 37 weeks of gestation compared to infants born after this period. The prolonged duration of artificial ventilation for premature infants just did not reach statistical significance ($P=0.053$). When the cases with bowel atresia were excluded the significant difference for length of hospital stay (range) 44 days (28-100) versus 31 days (12-74) was no longer present.

Comment

The majority of infants born with gastroschisis are detected before birth. This provides an opportunity to influence management with the aim to improve outcome. In order to diminish insults to the exposed intestines, elective preterm delivery[6] or pre-labor cesarean section has been recommended[16]. In a meta-analysis of studies investigating delivery modes in fetuses with gastroschisis, no advantage of cesarean section over vaginal delivery could be established[17]. Furthermore, no advantage could be demonstrated for preterm delivery in a first randomized controlled trial studying elective preterm delivery versus spontaneous delivery[18]. In this study the median duration of hospital stay in the elective preterm delivery group versus the spontaneous group was not significantly different (47.5 versus 53 days). These findings remained unaltered if data from infants with intestinal atresia were excluded.

Our study confirms previous data[10-12] where a significant difference in outcome could not be demonstrated between liveborn infants following a prenatal diagnosis or only a diagnosis at birth. The Netherlands is a small country with easily available tertiary level resources and out born infants with severe anomalies can be transported within 15-30 minutes to one of these facilities. This may have biased our results compared to remote areas where infants are born distant from tertiary care resources. A recent study from Australia[19], however, analyzing data from 181 liveborn infants with gastroschisis revealed that place and mode of delivery, distance from tertiary centers, time to surgery and type of closure did not influence neonatal outcome.

In our preterm delivery group a significantly longer length of hospital stay was demonstrated compared with infants born at term. When cases with bowel atresia were excluded, this difference was no longer present but tended towards significance (P=0.10). Calculation of the 95% confidence interval for the difference (subset 1 minus subset 2) of mean values resulted in a wide interval ranging from-0.6 up to 32.6 days. The power to demonstrate a difference was apparently too low with the studied number of patients and a larger study would be valuable to address this question. However, similar findings were reported by Huang et al.[20] who studied 57 infants with gastroschisis. In their study all cases of atresia were delivered before 37 weeks. Prematurity together with atresia may contribute to the unfavorable outcome.

Infants with gastroschisis can be divided in two categories; those with a simple defect comprising approximately 80% of cases and those where the gastroschisis is complicated by bowel pathology such as atresia, stenosis, perforation or volvulus[21]. Morbidity in the latter group is considerable and expressed by a significantly prolonged hospital stay and longer periods of mechanical ventilation and enteral feeding[22]. Although our study consists of small numbers the unfavorable outcome for infants with atresia could

be demonstrated. Prenatal selection of these cases proved difficult and measurement of extra abdominal bowel dilatation was not useful. One of the two cases of polyhydramnios was diagnosed with atresia, in agreement with data from Japaraj et al.[4] who found a clear correlation between polyhydramnios and severe bowel complications. Intra abdominal bowel dilatation together with active peristalsis was in our study associated with bowel atresia and necrosis. This combination has only been previously described in 19 cases[16,23-26] all with confirmed atresia.

Amniotic fluid of fetuses with gastroschis contains an inflammatory exudate and this may have a deleterious effect on the exposed bowel[27]. It has been suggested that amnioexchange using warm saline[28] or amnioinfusion in case of oligohydramnios[29] may prevent or diminish intestinal compromise. On the other hand a higher incidence of premature delivery has been reported as a result of this intervention[30]. In the present study 7/15 premature infants presented with bowel peel compared to 3/13 infants delivered after 37 weeks of gestation. Only one of the 7 premature infants revealed bowel peel together with intestinal atresia. This is in agreement with a recent large neonatal study[8] containing 75 liveborn infants with gastroschisis where infants born before or after 37 weeks showed evidence of bowel peel in 50% and 57%, respectively. Only 5 cases in this study suffered from an intestinal atresia, whether or not associated with bowel peel was not documented. Until a prospective randomized trial with sufficient numbers can demonstrate an improved outcome after prenatal intervention, this treatment should not generally be instituted in the management of fetuses with gastroschisis.

Intrauterine death in our study occurred in 3/22 (13.6%) prenatal cases. This is comparable to previous investigations[1,2], before the commencement of intense fetal monitoring, where figures of 10.6% and 12%, respectively, are quoted. The two cases with intrauterine death in our study did not reveal an explanation for fetal demise at post mortem investigation which was also previously described in the literature[2]. The contribution of prenatal diagnosis to the management of gastroschisis may be in the prevention of intrauterine deaths and adverse neurological outcome[2]. Intrauterine deaths usually occur in the third trimester as was the case in the present study despite normal Doppler studies of the umbilical artery and no evidence of FGR within 2 weeks of fetal demise. Regular fetal cardiotocography (CTG) in third trimester management has been proposed in order to avert these intrauterine deaths. In one study intense third trimester CTG monitoring was not commenced unless there was evidence of FGR or abnormal umbilical artery Doppler studies and no intrauterine death occured in 45 fetuses[4]. Others suggest weekly CTG from 34 weeks[31] onwards or daily or every second day CTG starting at 34 weeks[16]. Salomon et al.[29] performed daily CTG examinations from 27 until 35 weeks, but despite intensive monitoring both latter studies[16,29] could not prevent the occurrence of an intrauterine death. In the first study the intrauterine death occurred at 35 weeks but

only a CTG 2 weeks prior to this event was registered. Pathologic CTG's are documented in a high percentage of fetuses with gastroschisis who after delivery do not demonstrate evidence of hypoxia[16]. It is suggested that fetal heart rate variability may be affected by alterations in vagal output caused by stomach dilatation[32] or by the mechanical effect of gut herniation[31]. Other signs of fetal compromise such as a notch in the umbilical artery Doppler waveform[23], possible caused by compression of the cord due to dilated bowel, and the development of polyhydramnios[4] may be equally important to detect those fetuses at risk of fetal demise or a complicated neonatal road to recovery. A new surveillance protocol summarizing the most recent information from the literature integrated with our own data is presented in Box 1. We speculate that this protocol may improve the detection of fetusus at risk and in the future an analysis of outcome data after the commencement of this regimen should be performed.

In the present study one intrauterine death occurred at a gestational age of nineteen weeks and besides gastroschisis, bilateral talipes equinovarus had been diagnosed. In five out of our 33 cases (15%), associated extra gastrointestinal anomalies were diagnosed, the majority of which concerned the urinary tract. Two previous studies[33,34] demonstrated similar numbers of associated urinary tract anomalies. Some cases of urinary tract obstruction may be the result of evisceration of the bladder[35,36] which over time returns to normal after correction of the abdominal wall defect. In our study only one case of bladder evisceration was documented and this was not associated with urinary tract obstruction. Surgical correction of the urinary tract anomalies was not required but antibiotic prophylaxis was commenced to prevent infection. The relative high frequency with which urinary tract obstructions are encountered would suggest that in all infants with gastroschisis ultrasound investigation of the urinary tract should be recommended after the first week of life.

It can be concluded, that for liveborn infants there is no difference in perinatal outcome between a prenatal diagnosis of gastroschisis and a diagnosis only at birth. Preterm delivery results in prolonged hospital stay which is mainly associated with bowel atresia. In the presence of gastroschisis, infants with bowel atresia have a prolonged total duration of parenteral nutrition and hospital stay, and require more additional surgical procedures, compared with infants without additional gastrointestinal complications. The added value of prenatal diagnosis to the outcome of infants with gastroschisis may be in the prevention of unnecessary intrauterine death and detection of intestinal complications. Protocols to monitor fetuses with gastroschisis focused on intrauterine signs of pending distress such as a dilated stomach, intra abdominal bowel dilatation with peristalsis, notches in the umbilical artery Doppler signal, development of polyhydramnios and an abnormal CTG registration may improve outcome.

TABLE 1 Delivery data of the prenatal liveborn subset and postnatal subset with gastroschisis

	Prenatal subset N=19	Postnatal subset N=9	P
Male/female ratio	11/8	4/5	NS
GA at delivery (weeks)*	36.2 ± 1.7	37 ± 1.3	NS
Delivery<37 weeks (%)	11 (58%)	4 (44%)	NS
Induced delivery<37 weeks (%)	3 (16%)	0 (0%)	NS
Vaginal delivery (%)	17 (90%)	9 (100%)	NS
Mean birth weight (g)*	2461 ± 408	2582 ± 302	NS
Birth weight<P10 (%)	4 (21%)	4 (44%)	NS
Apgar score at 1 min#	8 (1-10)	7 (6-9)	NS
Apgar score at 5 min#	9 (3-10)	9 (8-10)	NS

* Data presented as mean ± SD. # Data presented as median (range). GA, gestational age; g, gram; NS, not significant.

TABLE 2 Outcome data of the prenatal liveborn subset and postnatal subset with gastroschisis

	Prenatal subset N=19	Postnatal subset N=9	P
Bowel peel	8 (42%)	2 (22%)	NS
Primary closure (%)	13 (68%)	9 (100%)	NS
Silo closure	6 (32%)	0 (0%)	NS
Atresia	3 (16%)	1 (11%)	NS
Days to first oral feeds# §	13.5 (6-126)	18 (7-68)	NS
Days on parenteral nutrition# §	32 (21-149)	45 (19-148)	NS
Days on antibiotics# §	6 (1-34)	8 (2-15)	NS
Days on ventilation# §	5 (1-36)	4 (1-17)	NS
Additional surgery §	2 (11%)	1 (11%)	NS
Short bowel syndrome §	1 (5%)	0 (0%)	NS
Sepsis §	8 (44%)	2 (22%)	NS
Cholestatic jaundice §	1 (5%)	1 (11%)	NS
Necrotizing enterocolitis §	0	1 (11%)	NS
Length of hospital stay (d)# §	33 (12-149)	40 (22-145)	NS
Neonatal death	1 (5%)	0 (0%)	NS
Other complications*§	2 (11%)	0 (0%)	NS
Associated anomalies	4 (21%)	0 (0%)	NS

Data presented as median (range). § excluded data of infant with neonatal death at day 1.
** Includes a frontal temporal hypoxia and a venous infarct in the corticospinal tract. d, days; ns, not significant.

BOX 1 Prenatal diagnosis and surveillance of a fetus with gastroschisis.

1	**2nd trimester diagnosis of gastroschisis**
	Ultrasound assessment of
	a. Biometry
	b. Presence of associated anomalies
	c. Intra-abdominal bowel dilatation and peristalsis
	d. Amniotic fluid volume
	Arrange counselling by a pediatric surgeon
2	**From 30 weeks gestational age**
	Once a week ultrasound assessment of
	a. Biometry
	b. Position and size of stomach
	c. Intra abdominal bowel dilatation and peristalsis
	d. Extra abdominal bowel dilatation
	e. Position and size of bladder
	f. Amniotic fluid volume
	g. Doppler of the umbilical artery at the abdominal insertion
	CTG monitoring twice weekly
3	**Arrange for vaginal delivery from 37 weeks onwards**
	In case of detection of alterations or signs of fetal distress during surveillance consult with fetal maternal medicine specialist, neonatologist and pediatric surgeon for possible adaptation of management

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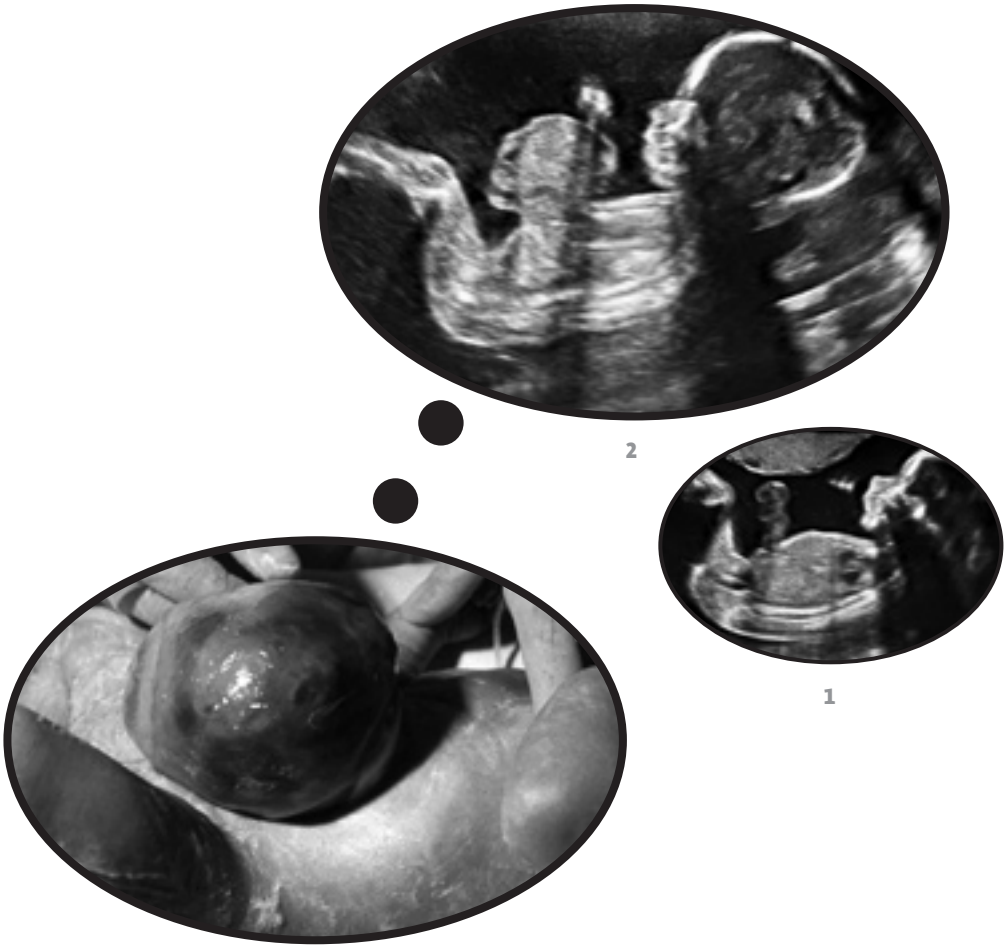

1 Longitudinal plane of section of a normal fetus at 20 weeks' gestation with intact abdominal wall and normal insertion of the cord.
2 Longitudinal plane of section of a fetus at 20 weeks' gestation with an omphalocele. The organs outside of the abdominal wall are covered by a membrane.
3 Newborn infant with an omphalocele. The organs outside of the abdominal wall are covered by a membrane.

3.3

Omphalocele; comparison of the perinatal outcome following a prenatal diagnosis or a diagnosis at birth.

Submitted

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Abstract

Objectives To compare the outcome of prenatally and postnatally diagnosed isolated and non-isolated omphaloceles.

Methods A retrospective analysis of 101 prenatally and 45 postnatally diagnosed cases.

Results Following confirmation at delivery or autopsy, prenatal omphaloceles included 21 isolated cases, 44 non-isolated cases with a normal karyotype and 36 non-isolated cases with an abnormal karyotype. Of the prenatally diagnosed isolated cases, 39% revealed associated anomalies after delivery. More infants survived with an isolated omphalocele (13/21) compared to those with a non-isolated omphalocele and normal karyotype (10/44; p=0.005) or abnormal karyotype (1/36; p<0.001). Liveborn infants with an isolated omphalocele had a significantly worse outcome following prenatal diagnosis (N=14) compared to a diagnosis at birth (N=29) i.e. a shorter gestational age at delivery, lower birth weight, lower Apgar scores, longer duration of ventilation and parenteral nutrition, more readmissions and a longer hospital stay. The prenatal subset contained more infants with a large omphalocele (9/14 versus 3/29, p=0.001). Outcome of liveborn infants with a non-isolated omphalocele diagnosed prenatally (N=17) was not different from a diagnosis at birth (N=16), except for an increased need of ventilation and parenteral nutrition in the prenatal subset.

Conclusion Of the prenatal isolated subset, 39% of omphaloceles was non-isolated. Liveborn infants with an isolated omphalocele detected prenatally had a worse outcome than similar cases detected at birth. For non-isolated omphaloceles, the prenatal subset displayed an increased need for ventilation and parenteral nutrition compared to detection at birth.

Introduction

Omphalocele is the most common abdominal wall defect with a reported frequency of 1:5,000 during pregnancy decreasing to 0.8:10,000 for live births[1]. This reduction is due to the high frequency of associated anomalies and abnormal karyotypes (non-isolated omphalocele) which present approximately 40% and 50%, respectively[2,3].
Additionally, genetic syndromes such as the Beckwith-Wiedemann syndrome, Pentalogy of Cantrell, the *o*mphalocele-*e*xtrophy of the bladder-*i*mperforate anus-*s*pinal abnormalities complex (OEIS) and amniotic band syndrome form 4.2% of cases of omphalocele[4]. Of all major congenital anomalies diagnosed prenatally by ultrasound, abdominal wall defects present the highest detection rate, after anencephaly[5] with a sensitivity of 75%[1]. Following ultrasound diagnosis of an omphalocele, associated anomalies should be looked for and karyotyping offered[6]. Early detection allows proper counselling of the couple and adjustment of obstetric management. Between 37% and 83% of couples request a termination of pregnancy (TOP)[1,3,7], usually for non-isolated cases. TOP is reported in 17%-27% of cases in the presence of an isolated omphalocele[1,4]. When the diagnosis is established before 15 weeks' gestational age this figure rises to 30%[8] . Spontaneous abortions and intrauterine death (IUD) occur in 5.5%-10% and include both isolated as well as non-isolated cases of omphalocele[7,9]. The survival rate of isolated omphaloceles is as high as 96%[9]. In the presence of associated anomalies or an abnormal karyotype this percentage drops significantly[10]. Prenatal diagnosis provides the opportunity to select those cases with a good prognosis and a high survival rate[3], although first and foremost the wishes of the parents should be considered. In continuing pregnancies antenatal management is transferred to a tertiary center with a pediatric surgery service in order to provide optimal conditions for delivery with multi-disciplinary care immediately after delivery[10].
Although abdominal wall defects are most often detected prior to delivery, some of these anomalies may still be missed[1,7]. Comparison of outcome between prenatally and postnatally diagnosed omphaloceles has produced controversial results. In one study a significantly lower birth weight and longer hospital stay was established in 4/16 cases following a prenatal diagnosis compared to the 12/16 following a postnatal diagnosis[11]. Dickens-st Vil et al.[12] found a significantly higher mortality in the prenatal group. Both studies suggest the poor outcome to be the result of more infants presenting with a large defect or liver herniation in the prenatal group. On the other hand a study from northern England did not detect a different outcome in cases delivered away from the regional pediatric surgical center and without a prenatal diagnosis despite a significant delay in time between delivery and surgery[13]. These studies were performed more than a decade ago and no distinction between isolated and non-isolated cases was made in comparing the perinatal outcome.

Routine ultrasound to detect congenital anomalies was not a policy in the Netherlands until recently. Therefore some cases of omphaloceles remained undiagnosed in the antenatal period. This provided us with the opportunity to determine the impact of prenatal diagnosis compared with a diagnosis only after birth in liveborn infants with an omphalocele.

In our study the following questions were addressed:
(i) What is the impact of prenatal diagnosis on the outcome of isolated and non-isolated omphaloceles; (ii) is there a difference in outcome between prenatally diagnosed and postnatally diagnosed isolated or non-isolated omphalocele in liveborn infants.

Methods

The University Medical Center Rotterdam serves as the referral center for both fetal anomaly scanning and pediatric surgery in the South West of the Netherlands. We performed a retrospective analysis of all infants from singleton pregnancies diagnosed with an omphalocele either pre- or postnatally between January 1991 and December 2004. Cases were collected from the ultrasound database of the Division of Obstetrics and Prenatal Medicine and the patient database of the Department of Pediatric Surgery. Omphaloceles were considered isolated if no other associated anomalies, genetic syndromes or abnormal karyotypes could be established. In all other cases the omphalocele was considered non-isolated. Inclusion criteria were prenatal diagnosis and postnatal treatment in our center or postnatal treatment in our center following postnatal referral from elsewhere, without a prenatal diagnosis. Cases with rare abdominal wall defects such as a bodystalk anomaly, bladder extrophy, pentalogy of Cantrell or amniotic band syndrome were excluded.
Following prenatal detection of an omphalocele, a search for associated anomalies was performed and karyotyping was offered. All couples were offered counselling by a pediatric surgeon. Requests for a TOP were granted. Following a TOP or intrauterine death, autopsy was advised in order to assess the presence of associated anomalies. In the Netherlands the upper limit for TOP is 24 weeks of gestation. However, in the presence of a fetal karyotype incompatible with life, a request for TOP beyond this gestational age would be granted. If in such a case it was decided to continue the affected pregnancy, postnatal care was focused on the prevention of pain and distress according to the guidelines of the Dutch Pediatric Association. Both non-pharmacological and pharmacological support were provided till neonatal death occurred, preferably in the arms of the parents. In those cases in which the pregnancy was continued with the intention to treat, antenatal care was provided in our tertiary center and regular ultrasound scans were

performed to evaluate fetal growth and amniotic fluid volume. Fetal growth restriction (FGR) was defined as a fetal upper abdominal circumference <10th centile. Amniotic fluid volume was considered abnormal for measurements below the 5th and above 95th percentile[14]. According to the hospital protocol all women with a prenatal diagnosis of omphalocele were delivered by vaginal delivery unless obstetric reasons required otherwise. Prematurity was defined as a delivery prior to 37 weeks of gestation. Infants with a birth weight below 10th percentile, adjusted for sex[15], were defined as small for gestational age (SGA).

After delivery assessment of associated anomalies and if appropriate karyotyping was performed. Management of the omphalocele consisted of primary closure of the defect depending on its size and peak inspiratory pressures during the surgical procedure. Large omphaloceles with a viscero-abdominal disproportion not eligible to primary closure were treated conservatively, allowing the sac to dissicate, contract and epithilialize with closure of the created ventral hernia at a later stage[16]. Artificial ventilation was weaned as soon as the infant could manage without this support.

As gastro-esophageal reflux was present in many patients due to the grossly abnormal position of the stomach, infants were primarily given parenteral nutrition (TPN) and enteral feeding was instituted as soon as stomach retentions diminished. In case persistent stomach retentions occurred a naso-jejunal tube was inserted under X-ray guidance.

Adverse neonatal outcome was defined as neonatal death or complications resulting from the abnormality itself (malrotation with or without volvulus, rupture of the omphalocele), the subsequent surgical procedure (dehiscence of the wound, TPN associated cholestasis jaundice, venous line sepsis), or other significant morbidity not directly related to the omphalocele. Distinction was made between: (i) pre- and postnatal diagnosis, (ii) isolated ompalocele and non-isolated omphalocele. Charts were reviewed for maternal demographic data, fetal ultrasound surveillance data, fetal outcome, neonatal surgical and subsequent outcome data.

Statistical analysis

Two or three groups comparisons for continuous data were performed by Mann-Whitney or Kruskal-Wallis test, respectively. Fisher's exact test was used for the comparison of categorical data. P=0.05 (two-sided) was considered as the limit of statistical significance.

Results

We reviewed the data of 106 prenatally and 45 postnatally diagnosed cases of omphalocele. Seven prenatal cases have been described previously[17].

Prenatally diagnosed omphaloceles (N=106)

The prenatally detected omphaloceles are divided in four subsets depending on associated anomalies and karyotype (Table 1); (i) isolated omphaloceles and normal karyotype (N=34); (ii) non-isolated omphaloceles and normal karyotype (N=29); (iii) isolated/non-isolated omphaloceles with an abnormal karyotype (N=36); and (iv) isolated/non-isolated omphaloceles and karyotype not available (N=7). The presence of liver herniation, FGR, ascites, hydrops, oligo- or polyhydramnion are documented for each subset as well as the outcome and additional information available following delivery.

ISOLATED OMPHALOCELES AND NORMAL KARYOTYPE. (N=34) TOP was carried out in eight cases (24%). Isolated omphalocele was confirmed in four, autopsy was refused in three and a cleft palate was established in one case at post mortem investigation. IUD occurred in three cases at 19,20 and 27 weeks, respectively. At autopsy two cases were confirmed and one case revealed an additional ventricular septal defect. Four infants suffered a neonatal death. One infant with a confirmed isolated giant omphalocele died after 6 months following complications of prolonged artificial ventilation in the presence of severe bronchopulmonary dysplasia due to a bleeding placenta previa and premature delivery at 30 weeks. The three remaining neonatal deaths occurred at the age of 3 to 10 months. Associated anomalies as well as prematurity, growth retardation and pulmonary hypertension contributed to this outcome (Table 6, cases 2, 3 and 12). An isolated omphalocele was confirmed after delivery in 12/19 liveborn infants. Associated anomalies or a genetic syndrome were detected in the remaining 7 liveborn infants (Table 6, cases 1, 4, 7, 10, 14, 15 and 17): Beckwith-Wiedemann syndrome (N=3), small bowel atresia (N=1) and cardiovascular anomalies (N=3; a ventricular septal defect, atrial septal defect requiring surgery and aortic valve stenosis). Altogether it was impossible to determine whether the omphalocele was isolated or non-isolated in 3 /34 (9%) cases where autopsy was declined. In the remaining 31 cases an isolated omphalocele was confirmed postnatally in 19 (61%) cases (95% confidence interval (CI) 42%-78%) and additional anomalies were detected postnatally in 12 (39%) cases (95% CI 22%-58%).

NON-ISOLATED OMPHALOCELES AND NORMAL KARYOTYPE (N-29) TOP was performed before 24 weeks of gestation in 17/18 cases. One case was diagnosed at 31 weeks with an associated large encephalocele and the pregnancy was terminated within a week following detection. There were six intrauterine deaths (IUD) between 18 and 35 weeks. Associated anomalies were confirmed in all TOP cases. Autopsy was declined in one case of IUD. Despite an intention to treat, two cases suffered early neonatal death due to associated anomalies or prematurity (Table 6, cases 5 and 11). Three infants survived. (Table 6, cases 6, 8 and 16). The associated anomalies were correctly diagnosed prior to delivery

in two cases but in one case with a large omphalocele only an associated small thorax was detected whereas postnatally vesicourethral reflux became evident.

ISOLATED /NON-ISOLATED OMPHALOCELES AND ABNORMAL KARYOTYPE (N=36)

Abnormal karyotypes were mainly trisomy 18 (N=28), mosaic trisomy 18 (N=1), trisomy 13 (N=3), Turner syndrome (N=1) and unbalanced karyotypes (N=3), notably 46,XX, der(7)t(7;10)(q36;q11.2), idic(10)(q11.2), 46,XX, add(8)p and 46,XY, add(3)(p24), of which only the last one survived (Table 6 case 13). 24/26 TOP's were conducted before 24 weeks of gestational age. TOP was performed in two cases of trisomy 18 at 29 and 31 weeks of gestation, respectively. IUD occurred in four cases of trisomy 18 at 21, 22, 36 and 37 weeks and in one case of 46,XX, add(8)p at 19 weeks. Two cases of trisomy 18, one of trisomy 13 and one of 46,XXder(7)t(7;10)(q36;q11.2), idic(10)(q11.2) died soon after delivery.

ISOLATED/NON-ISOLATED OMPHALOCELES AND KARYOTYPES NOT AVAILABLE (N=7)

A TOP was performed once for a non-isolated case with associated skeletal dysplasia, and twice for an isolated omphalocele. The diagnosis was confirmed in one case but in the other no autopsy was performed, which precluded differentiation between isolated and non-isolated omphalocele. IUD occurred twice at 25 and 28 weeks, respectively. After delivery, next to the omphalocele, a cardiac defect and abnormal position of the hands were confirmed in the former and hydrops in the latter. One neonatal death in this subset occurred two weeks after delivery due to unsuccessful ventilation of the infant as a result of so-called alveolar capillary dysplasia[18] (Table 6 case 9). One confirmed isolated omphalocele survived and is doing well. Altogether the presence of an isolated or non-isolated omphalocele could not be confirmed in three different subsets, isolated omphaloceles and normal karyotype (3/34), non-isolated omphaloceles and normal karyotype (1/29), isolated/non-isolated omphaloceles and karyotypes not available (1/7). We subsequently analyzed the prenatal ultrasound, delivery and outcome data in the confirmed isolated versus non-isolated cases.

Prenatally diagnosed and confirmed isolated versus non-isolated omphaloceles (N=101)

The prenatal ultrasound and outcome data of the confirmed isolated and non-isolated omphaloceles, the latter subdivided according to karyotype, are displayed in Table 2. The incidence of liver herniation was significantly lower in the presence of an abnormal karyotype compared to both isolated ($p=0.02$) and non-isolated ($p<0.001$) cases with a normal karyotype. A significant difference ($p=0.02$) was established for the presence of ascites between the isolated subset (1/21) and the non-isolated subset with an abnormal karyotype (12/36). The development of FGR, or abnormal amniotic fluid

volume was not different between the three subsets. The type of associated anomalies was not significantly different between the non-isolated subset with a normal karyotype and an abnormal karyotype except for cheiloschisis (0/44 versus 4/36; p=0.04) and the presence of more than 1 anomaly (18/44 versus 23/36; p=0.047). Significant male predominance was seen in the non-isolated subset with an abnormal karyotype (23/13) versus the isolated subset (7/13, p=0.05) and versus the non-isolated subset with a normal karyotype (17/22, p=0.02). A TOP was significantly more often performed in the non-isolated subset with an abnormal karyotype (26/36) compared to the isolated subset (5/21, p=0.001) and the non-isolated subset with a normal karyotype (20/44, p=0.02). The difference was not significant between the two subsets with a normal karyotype. IUD did not reveal a significant difference between the three subsets. Significantly more infants survived in the subset with an isolated omphalocele (13/22; 62%) compared to both the subset with a non-isolated omphalocele and normal karyotype (10/44; 23%) (p=0.005) and an abnormal karyotype (1/36;3%), (p<0.001). Also between the latter two subsets, the difference was significant (p=0.02).
For liveborn infants with intention to treat the delivery and outcome data of the confirmed isolated and non-isolated omphaloceles are displayed in Table 3. No difference existed for gestational age at delivery, premature delivery, delivery mode, birth weight and birth weight <10th centile. Spontaneous vaginal delivery took place in 8/14 (57%) cases of isolated omphalocele and in 11/17 (65%) cases of non-isolated omphalocele. Labor was induced at 37 weeks in the non-isolated subset in one instance due to progressive hydronephrosis (Table 6, case 9). Elective cesarean section was performed in the isolated subset for abnormal fetal position (breech position and transverse lie (N=2), and a history of maternal arachnoid bleeding (N=1) and in the non-isolated subset for progressive maternal hypertension (N=1) and the size of the omphalocele (N=1) (Table 6 cases 14 & 16). Emergency cesarean section took place for fetal distress (N=2) and placenta previa (N=1) in the isolated subset and for fetal distress (N=2) (Table 6 cases 15 & 17) and prolonged premature rupture of membranes (PROM) associated with maternal fever (N=1) in the non-isolated subset (Table 6, case 2). Neonatal and infant death within the first year did not reveal a difference between both subsets.

Prenatally versus postnatally diagnosed isolated omphalocele in liveborn infants (N=43)

When comparing the prenatal (N=14; 33%) and postnatal subset of liveborn infants with an isolated omphalocele (N=29; 67%) (Table 4), a significant difference for gestational age at delivery (p=0.004), premature delivery (p=0.01), birth weight (p=0.04), 1 and 5 minute Apgar score (p=0.007; p=0.02) was established. The location of delivery was significantly different (p<0.001) in that all infants in the prenatal subset were delivered in our tertiary center

whereas the majority of the postnatal subset was delivered in a regional district hospital (25/29) or at home (4/29). The delivery mode could not be retrieved for 1/29 infants in the postnatal subset. Labor was induced three times in the postnatal subset, once for a breech position at 40 weeks, the indication in the two other cases could not be retrieved. An elective cesarean section was performed twice for a transverse lie and once for a breech position. One patient required a repeat cesarean section. Fetal distress was the indication for the two emergency cesarean sections in the postnatal isolated subset. A spontaneous delivery took place in the remaining 19/28 infants. Liver herniation and giant omphalocele were significantly ($p=0.02$ and $p=0.001$) more often present in the prenatal subset (8/9) compared to the postnatal subset (6/3). Rupture of the omphalocele occurred in 2/14 infants of the prenatal subset versus 3/29 infants of the postnatal subset. Primary closure of the defect was significantly ($p=0.03$) more often performed in the postnatal subset, (27/29 versus 9/14). A significant difference between both subsets was demonstrated for days on ventilation ($p=0.02$), days to first oral feeds ($p=0.02$), total days on parenteral nutrition ($p=0.001$), number of infants with infection ($p=0.03$), number of readmissions ($p=0.04$) and length of hospital stay ($p=0.005$). In both subsets the main reasons for readmissions and additional surgery were inguinal hernia repair, orchidopexy, corrections of abdominal wall defects, feeding problems and infections. One infant death occurred in the prenatal subset compared to none in the postnatal subset.

Prenatally versus postnatally diagnosed non-isolated omphalocele in liveborn infants (N=33)

Delivery and outcome data comparing the prenatal (N=17) and postnatal non-isolated subset (N=16) are presented in Table 5. Individual data for each of the subsets are presented in Tables 6 and 7.
Gestational age at delivery, birth weight, and Apgar scores were similar in both subsets. The proportion of male/female infants was significantly ($p=0.01$) different between the pre- and the postnatal subset. The place and mode of delivery could not be retrieved in 1/16 infants in the postnatal subset. Delivery took place in our tertiary center for all prenatally diagnosed infants versus 12/16 of the postnatal subset which delivered in a district general hospital and 3/16 which delivered at home. In the postnatal subset spontaneous vaginal delivery took place in all but three cases which included a cesarean section for transverse lie (N=1) (Table 7, case 7) and fetal distress (N=2) (Table 7 cases 12 & 15). No significant difference was established for the mode of delivery between the two subsets. The same applies for the position of the liver, size of the omphalocele, rupture of the omphalocele, type of treatment and median days to surgery. In both subsets primary surgery was performed within the first few days following delivery. Surgery

was postponed until day 33 in one infant who delivered prematurely after PROM and subsequent maternal fever. Duodenal obstruction was present as well. In one case the omphalocele was temporarily covered by a Siliastic Silo with final closure of the defect at day 12 (Table 6, case 8). The number of days on artificial ventilation and total days on parenteral nutrition was significant ($p<0.05$) higher in the prenatal subset. Additional readmissions and type of additional surgery were similar in both subsets and indications similar to those described for the isolated subsets apart from the indications for the associated anomalies. There were three neonatal deaths in the prenatal subset characterized by; (i) premature labor due to polyhydramnios and associated diaphragmatic hernia (Table 6, case 11); (ii) associated anal atresia (Tabl 6 case 5); and (iii) associated VSD, urethral valve and alveolar capillary dysplasia (Table 6, case 9). Moreover, there were three deaths during the first year of life characterized by; (i) associated Tetralogy of Fallot and bronchopulmonary dysplasia (Table 6, case 3); (ii) associated VSD, corpus callosum agenesis and therapy resistant pulmonary hypertension (Table 6, case 12); and (iii) associated duodenal obstruction and non-communicating hydrocephaly (Table 6, case 2). Three neonatal death occurred in the postnatal subset, twice in association with trisomy 13 (Table 7, cases 4 and 16) due to withdrawal of treatment according to the guidelines of the Dutch pediatric association and once as a result of the complexity of the associated anomalies (Table 7, case 2).

Discussion

As far as we know, this is the first report on the perinatal outcome of omphaloceles treated in one hospital in which isolated or non-isolated cases diagnosed prenatally or after birth are analyzed separately.
Of all cases with a prenatally diagnosed omphalocele significantly less infants survived in the non-isolated subset compared to the isolated subset. This is particularly due to the high TOP rates in the non-isolated subsets regardless the karyotype. High TOP rates in the presence of non-isolated omphaloceles are common practice[2,3,8] as the combination of anomalies or abnormal karyotypes are often associated with severe morbidity or mortality. In the literature between 17 and 21 percent of parents will opt for a TOP in isolated cases[1,19] which is similar to the 23% in our study. Of the prenatally diagnosed isolated cases 39% turned out to be non-isolated. The anomalies not detected prenatally included three cases of Beckwith-Wiedemann syndrome, two cases of intestinal atresia and various cardiovascular anomalies such as atrial or ventricular septal defects, aortic-valve stenosis and a case of Tetralogy of Fallot. The latter occurred in the early days of this study and would most likely not be missed today. The position of the fetal heart in the presence of an omphalocele may be slightly altered in some cases due to traction of the abdominal organs, causing difficulties in

assessing the different cardiac structures. Duodenal obstruction and small bowel atresia often present only in the third trimester[20] and are likely to be missed at the time of the anomaly scan in the second trimester as was the case in our study. The prevalence of Beckwith-Wiedemann syndrome in association with omphalocele is reported to be between 8-10%[10,12,19] with the majority of infants only suspected of an isolated omphalocele prenatally[3,9,10]. Beckwith-Wiedemann syndrome is known to be associated with the deregulation of genes located at 11p15.5 [21]. DNA investigations to confirm the diagnosis are not yet applicable to prenatally detected isolated omphalocele cases. Most of the missed diagnoses in the prenatal isolated subset had consequences for both morbidity and mortality and parents and counselors should be aware of this limitation in prenatal diagnosis.

Our data confirms previous research[22] that non-isolated omphaloceles without liver herniation are highly associated with an abnormal karyotype. However except for cheiloschisis and the presence of more than one anomaly, the type of associated anomalies between omphaloceles with a normal and abnormal karyotype was not essentially different. Cheiloschisis was not associated with one particular abnormal karyotype as this anomaly was present in trisomy 13, 18 and an unbalanced karyotype similar to an earlier report[23].

Ascites was significantly more often seen in non-isolated omphaloceles with an abnormal karyotype than in isolated omphaloceles. Ascites in association with giant omphaloceles is thought to be caused by an abnormal position of the liver resulting in partial obstruction of hepatic veins. It should not be considered as a poor prognostic sign[24]. The prenatally detected isolated case of omphalocele with ascites was the only one of nine cases with a large omphalocele. This infant eventually died as a result of prematurity and the development of severe bronchopulmonay dysplasia. Three out of ten cases of the non-isolated subset with a normal karyotype and ascites were liveborn and stayed alive. In our study the majority of prenatal cases with ascites (20/23) did not survive and the diagnosis of it's presence could assist in the distinction between isolated and non-isolated omphaloceles and between those with a good and poor prognosis.

In the present study 70% of the omphaloceles were detected prenatally. This percentage is comparable to previous epidemiological studies[1,19], but lower then the 80% prenatal detection rate recently reported from Eurocat data where all omphaloceles with an abnormal karyotype were excluded[7]. A single center study from Norway reported a 95% detection rate[2] which shows that routine sonographic screening of all pregnancies does improve the pick-up rate of major fetal anomalies.

Following the prenatal diagnosis of an omphalocele, the presence of associated anomalies and karyotype anomalies are determined. Parents are subsequently counselled concerning the prognosis and management options. The survival rate for infants with an isolated omphalocele is as high as 95%[19]. The majority of omphaloceles are non-isolated and prenatal

selection of cases with a good prognosis, which in one study comprised only 10% of the prenatally detected omphaloceles[3], will ensure a high postoperative survival.
It is generally assumed that the prenatal selection and intrauterine transfer of omphalocele cases to tertiary units with pediatric surgical facilities is favorable to outcome[10]. In our study, 30% of omphalocele cases was diagnosed postnatally. This provided the opportunity to assess the impact on outcome of prenatal diagnosis for liveborn infants with either an isolated or non-isolated omphalocele.
Surprisingly, prenatally detected isolated omphaloceles had a significantly worse outcome than those only detected postnatally. A lower gestational age at delivery, a higher prematurity rate and therefore a significantly lower birth weight was established in the prenatal isolated subset. Despite all infants being delivered in our tertiary center the Apgar scores at 1 and 5 minutes were significantly lower in the prenatal isolated subset than in the postnatal subset. Postnatal herniation of the liver and large omphaloceles were more often present in the prenatal subset resulting in a significantly higher number of newborns to undergo conservative management in order to obtain closure of the defect. This again resulted in a less favorable outcome for the prenatal isolated subset as regards to days on ventilation, days to first oral feeds, days on parenteral nutrition, development of infections and readmissions and prolonged length of hospital stay. Recent epidemiological data revealed that the prenatal diagnosis of gastrointestinal malformations resulted in a shorter gestational age at birth compared to a postnatal diagnosis[7]. Although the mode of delivery was not registered in this study it was assumed that in prenatally detected cases, the cause of earlier delivery may be determined by clinicians aiming for controlled conditions at birth. This is supported by a study on the effect of prenatal diagnosis on outcome of D-transposition of the great arteries[25] in which a reduced spontaneous delivery rate and lower birth weight were noted in the group with a prenatal diagnosis compared to the group with a diagnosis at birth. Except for one case in the postnatal isolated subset, the mode of delivery was recorded for all liveborn infants in the two isolated subsets and was not significantly different. Previous studies comparing the perinatal outcome in infants with an omphalocele following a prenatal or postnatal diagnosis also reported lower birth weights and longer hospitalizations[11] or a higher mortality rate[12] when diagnosed prenatally. In neither of these studies isolated and non-isolated omphaloceles were analyzed separately. Similar to our results, liver herniation was associated with a poorer outcome in the largest of these studies, which analyzed 59 live births, with 33 infants diagnosed at birth[12]. The increased morbidity in our prenatal isolated subset is therefore more likely due to the higher pick up rate of the larger defects and subsequent poorer outcome compared to cases diagnosed only at birth. This difference in outcome for liveborn infants was far less obvious in the non-isolated pre- and postnatal diagnosed subsets. A high male

predominance was seen in the postnatal subset similar to the prenatal non-isolated subset with an abnormal karyotype. All four infants in the postnatal subset diagnosed with an abnormal karyotype were male. Male predominance in omphaloceles with an abnormal karyotype has been documented previously[23] and the relative high number of infants with an abnormal karyotype could in part have contributed to the marked male predominance in the postnatal non-isolated subset.
The increased need for ventilation and total days on parenteral nutrition in the prenatal non-isolated subset may be determined by the severity of anomalies being detected prenatally as has also been seen in other studies[11,12]. However, this is not reflected in the number of infants with a large defect or the type of treatment required for closure of the omphalocele. As has been demonstrated previously[13], delivery outside the tertiary center for all postnatal non-isolated cases had no adverse effect on outcome.
In the literature the mode of delivery for fetuses with an omphalocele is still a matter of debate. A meta-analysis concerning this subject did not provide evidence to support a cesarean section above a vaginal delivery, with the annotation that the results of the analysis might not be applicable to special cases such as extremely large defects[26]. Lurie et al.[27] proposed vaginal delivery with the exception of giant omphaloceles of >5cm, which should be delivered by cesarean section. This method has been employed by several authors[2,3] with the intention to minimize damage to the exposed organs and avoid rupture of the defect during delivery. No comparison with regard to outcome and delivery mode has been made in these studies, however. Heider et al.[9] compared neonatal outcome in omphalocele cases with (N=27) and without liver herniation (N=9). All cases with known liver herniation were routinely offered a cesarean section, thus 19/27 (70%) of these cases were delivered this way compared to 2/9 (22%) of cases with an intracorporeal liver. No association with outcome could be demonstrated for delivery mode in this study and ruptures of the defect were encountered both in association with a vaginal delivery and a cesarean section. In our study the presence of a ruptured omphalocele was not different in both the pre- and postnatal isolated subsets and occurred both following cesarean sections and vaginal deliveries. In one case of the prenatal non-isolated subset a cesarean section was indicated for a giant omphalocele, but rupture of the defect could not be avoided. In the presence of an omphalocele we advocate a vaginal delivery unless obstetric reasons require otherwise.
It can be concluded that of all cases with a prenatally diagnosed omphalocele significantly less infants survived in the non-isolated subset. Of the prenatal isolated subset, 39% were non-isolated with consequences for both morbidity and mortality. Liveborn infants with a prenatally detected isolated omphalocele displayed a significantly worse outcome compared to infants with a postnatally detected isolated omphalocele. This is due to both larger sized and more liver containing omphaloceles in the prenatal subset. One should be aware of the fact that prenatal diagnosis of isolated omphaloceles

may select those cases with a more complicated route to recovery. Infants with a non-isolated omphalocele did not demonstrate a difference in outcome following a prenatal diagnosis or a diagnosis at birth except for an increased need for ventilation and parenteral nutrition in the prenatal subset. Delivery outside the tertiary center did not adversely influence outcome in postnatally detected isolated and non-isolated omphaloceles.

TABLE 1 Outcome of the prenatal diagnosed subset with omphaloceles categorized according to prenatal information.

Prenatal diagnosis	N	Liver herniation	FGR	Ascites	Hydrops	Oligo	Ph	Outcome	Details of prenatal abnormal karyotypes, associated anomalies and additional information on postnatal outcome
Isolated and normal karyotype	34	22	14	2	0	4	6	TOP 8	4 cases confirmed, 1 case with a cleft palate, 3 cases with no autopsy
								IUD 3	Twice confirmed at autopsy, 1 case with a VSD,
								NND 4	1 isolated case (due to prematurity), for MCA see Table 6 cases 2, 3 and 12
								Alive 19	12 isolated cases, for MCA see Table 6 cases 1, 4, 7, 10,14, 15, 17
Non-isolated and normal karyotype	29	21	12	7	9	6	4	TOP 18	18 cases confirmed
								IUD 6	5 cases confirmed, 1 case with bilateral hydronephrosis declined autopsy
								NND 2	See Table 6 cases 5 and 11
								Alive 3	See Table 6 cases 6, 8 and 16
Isolated/non-isolated and abnormal karyotype	36	8	22	12	14	1	8	TOP 26	22 trisomy 18, 1 partial trisomy 18, 2 trisomy 13, 1 45, X.
								IUD 5	4 trisomy 18, at 21, 23, 36 and 37 weeks ga, 1 46, XX, add(8)p at 19 weeks ga
								NND 4	2 trisomy 18, 1 trisomy 13, 1 46, XX, der(7)t(7;10)(q36;q11. 2), idic(10)(q11. 2)
								Alive 1	See Table 6, case 13
Isolated/non-isolated and karyotype not available	7	1	3	2	1	0	0	TOP 3	1 skeletal dysplasia, 1 isolated case, 1 isolated case with no autopsy
								IUD 2	2 cardiac defects, once associated with hydrops, both confirmed
								NND1	See Table 6 case 9
								Alive 1	Isolated omphalocele
Total	106	52	51	23	25	11	18	TOP 56	
								IUD 15	
								NND 11	
								Alive 24	

FGR, fetal growth retriction; Oligo, oligohydramnios; Ph, polyhydramnios; TOP, termination of pregnancy; IUD, intrauterine death; NND, neonatal death; MCA, multiple congenital anomalies; ga, gestational age.

TABLE 2 Prenatal ultrasound and outcome data of omphalocele cases with a confirmed postnatal diagnosis subdivided in isolated cases, non-isolated cases with a normal karyotype and cases with an abnormal karyotype.

	Isolated N=21	Non-isolated with normal karyotype N=44	Abnormal karyotype N=36	P
GA at detection	19.4 (12.4-36.4)	21.4 (12.0-34.7)	19 (12.0-31.6)	NS
Prenatal liver herniation	13	28	8	**0.02 ***<0.001
Ascites	1	10	12	**0.02
Fetal growth restriction	8	15	22	NS
Polyhydramnios	3	7	8	NS
Oligohydramnios	3	7	1	NS
Associated anomalies				NS
Central nervous system	-	12	11	NS
Cardiovascular system	-	14	19	NS
Vertebral /skeletal	-	16	16	NS
Hydrops/ascites	-	12	9	NS
Gastrointestinal system	-	3	1	NS
Urogenital system	-	4	3	NS
Cheiloschisis	-	0	4	***0.04
Beckwith-Wiedemann syndrome	-	3	0	NS
Other	-	3	5	NS
>1 anomaly		18	23	***0.047
Male/Female $	7/13	17/22	23/13	**0.05 ***0.02
Intrauterine death	2	8	5	NS
Termination of pregnancy	5	20	26	**0.001 ***0.02
NND	0	2	4	NS
Infant death	1	4	0	NS
Alive	13	10	1	*0.005 **<0.001 ***0.02

Data presented as median and range, GA, gestational age; NND, neonatal death within 7 days;
Infant death, death >7 days <1 year; ns, not significant

$ Gender unknown in 1/21 isolated cases and in 5/44 non isolated cases with normal karyotype

*p p value for significant difference between isolated cases and non-isolated cases with a normal karyotype

**p p value for significant difference between isolated cases and cases with an abnormal karyotype

***p p value for significant difference between non-isolated cases with a normal karyotype and cases with an abnormal karyotype

TABLE 3 Delivery and outcome data of the prenatal isolated and non-isolated cases with an omphalocele, confirmed diagnosis and an intention to treat.

	Isolated N=14	Non-Isolated N=17	P
GA at delivery (weeks)	38.1 (30.0-41.0)	37.6 (29.6-41.7)	0.59
Delivery <37 weeks	4	7	1.00
Delivery mode			
Spontaneous delivery	8	11	0.95
Induced vaginal delivery	0	1	1.00
Elective cesarean section	3	2	0.63
Cesarean section	3	3	1.00
Birth weight (g)	2820 (1500-3960)	2500 (1130-3650)	0.34
Birth weight <10th centile	5	8	0.26
NND	0	2	0.48
Infant death	1	4	0.34
Combined NND and infant death	1	6	0.09

Data presented as median and range, GA, gestational age; g, gram; NND, neonatal death within 7 days; Infant death, death >7 days <1 year

TABLE 4 Delivery and outcome data of the liveborn pre- and postnatal subset with isolated omphalocele

	Prenatal subset (N=14)	Postnatal subset (N=29)	P
GA at delivery (weeks)	38.1 (30.0-41.0)	40.0 (36.3-41.5)	0.004
Delivery <37 weeks	5	1	0.01
Birth weight (g)	2820 (1500-3960)	3265 (1550-4800)	0.04
Birth weight <10th centile	3	5	1.0
Male/Female	4/10	13/16	0.3
Apgar score 1 minute &	7.5 (3-9)	9 (4-10)	0.007
Apgar score 5 minutes &	9 (6-10)	10 (8-10)	0.02
Delivery mode overall#			0.3
Spontaneous delivery	8	19	
Induced delivery	0	3	
Elective cesarean section	3	4	
Cesarean section	3	2	
Place of delivery overall;			<0.001
delivery at home	0	4	0.3
delivery at other hospital	0	25	<0.001
delivery at tertiary center	14	0	<0.001
Postnatal liver herniation	8	6	0.02
Omphalocele size$			
smal	5	25	0.001
giant	9	3	
Rupture of the omphalocele	2	3	1.0
Treatment			
primary surgery	9	27	0.03
conservative management	5	2	
Days to surgery	0 (0-3)	1 (0-5)	0.7
Days on ventilation	2 (0-45)	0 (0-3)	0.02
Days to first oral feeds	5 (1-36)	2 (0-9)	0.02
Total days on parenteral nutrition	12 (3-59)	4 (0-16)	0.001
Number of infants with infections (sepsis)	3	0	0.03
Length of hospital stay (d)	22 (6-192)	9 (3-36)	0.005
Number of readmissions**	1 (0-4)	0 (0-2)	0.04
Number of other surgeries	1(0-3)	0 (0-2)	0.09
Infant death	1	0	0.3

Data presented as median and range, GA, gestational age; g, gram; d, days, Infant death, death >7 days <1 year.

& Apgar scores were not available for 4/29 cases in the postnatal group

The mode of delivery could not be retrieved in 1/29 cases of the postnatal subset

$ The omphalocele size could not be determined in 1/29 cases of the postnatal subset

** Excluding the infant who was not discharged in the prenatal subset

TABLE 5 Delivery and outcome data of liveborn infants of the pre- and postnatal subset with non-isolated omphalocele

	Prenatal subset (N=17)	Postnatal subset (N=16)	P
Gestational age (GA) at delivery (weeks)	37.6 (29.6-41.7)	38.0 (35.3-40.1)	0.4
< 37 weeks	7	5	0.7
Birth weight (g)	2500 (1130-3650)	2790 (1700-3780)	0.3
Birth weight <10th centile	8	5	0.5
Male/Female	7/10	14/2	0.01
Apgar score 1 minute &	8 (1-9)	7 (3-10)	0.4
Apgar score 5 minutes &	9 (0-10)	8 (5-10)	0.4
Delivery mode overall#			0.7
Spontaneous	11	12	
Induced	1	0	
Elective section	2	1	
Cesarean section	3	2	
Place of delivery overall#			<0.001
delivery at home	0	3	0.1
delivery at elsewhere	0	12	<0.001
delivery at tertiary center	17	0	<0.001
Karyotype anomaly	1	4	0.3
Postnatal liver herniation	12	6	0.2
Omphalocele size			
smal	5	8	0.3
giant	12	8	
Rupture of the omphalocele*	4	0	0.1
Treatment*			
primary surgery	9	9	0.7
conservative management	6	4	
Days to surgery*	0(0-33)	0(0-4)	0.9
Days on ventilation*	7(0-321)	4(0-100)	0.04
Days to first oral feeds*	5 (0-76)	3 (0-10)	0.053
Total days on parenteral nutrition*	14 (0-150)	7 (0-20)	0.02
Number of infants with infections (sepsis)*	6	2	0.2
Length of hospital stay (d)*	35 (13-321)	31 (4-93)	0.2
Number of readmissions**	1(0-5)	2(0-6)	0.7
Number of other surgeries*	1(0-3)	1(0-2)	0·2
NND	2	3	0.7
Infant death	4	0	0.1
Combined NND and infant death	6	3	0.4

Data presented as median and range, GA, gestational age; g, gram; d, days; NND, neonatal death within 7 days; Infant death, death >7 days <1 year

& Apgar scores were not available for 4/16 cases in the postnatal group

The place and mode of delivery could not be retrieved in 1/16 cases of the postnatal subset

* Excluded data of 2 infants from the prenatal subset & 3 infants from the postnatal subset who died within the first week of live.

** excluding infants who had not been discharged

TABLE 6 Liveborn non-isolated cases with omphalocele; prenatal subset

Case year	GA at detection	Prenatal associated anomalies	Karyotype	FGR	PH	Liver herniation	Ascites	GA at delivery	Birthweigt <10th centile	Delivery method	Additional postnatal anomalies	Outcome
1 1991	24 w	none	46, XY	no	yes	yes	no	38 w + 3d	no	SVD	BWS	Alive
2 1992	23 w	none	46, XX	yes	yes	yes	no	31 w	yes	CS	Duodenal atresia, non communicating hydrocephalus	Deceased after 285 days
3 1993	13 w	none	46, XX	yes	no	yes	no	34 w + 2d	no	SVD	Tetralogy of Fallot	Deceased after 321 days
4 1994	21 w + 5d	none	46, XX	yes	no	yes	yes	36 w + 5d	no	SVD	ASD requiring surgery	Alive
5 1996	34 w + 5d	Unilateral abnormal position leg and foot	46, XX	no	yes	yes	yes	36 w + 5d	no	SVD	Abnormal postion leg, anal atresia, no autopsy	Deceased on day 1
6 1997	31 w	Tetralogy of Fallot	46, XX	no	no	yes	no	37 w + 6d	no	SVD	Tetralogy of Fallot	Alive
7 1997	20 w + 3d	none	46, XX	no	no	no	no	41 w + 5d	no	SVD	Small bowel atresia	Alive
8 1998	25 w	Unilateral hydronephrosis, ASD, ascites	46, XY	yes	no	yes	yes	36 w + 3d	yes	SVD	Hydronephrosis	Alive
9 1999	21 w + 1d	Bilateral hydronephrosis	not available	no	no	no	no	37 w + 4d	no	ID	Urethral valve, VSD, alveolar capillary dysplasia	Deceased after 14 days
10 2000	33 w + 1d	Ascites	46, XX	no	no	yes	yes	37 w + 4d	yes	SVD	VSD, lunghypoplasia	Alive
11 2001	21 w	Diaphragmatic hernia	46, XY	no	no	yes	no	29 w + 4d	no	SVD	Diaphragmatic hernia	Deceased on day 1

12 2002	14 w	none	46, XY	yes	yes	yes	no	38 w + 6d	yes	SV	Agenesis of the corpus callosum, VSD	Deceased on day 90
13 2002	28 w + 1d	Ascites, hypertelorism, polydactyly, micrognathia	46, XY, add (3)(p21)	no	yes	yes	yes	35 w + 5d	no	SVD	Cranio-synostosis, chochlear hearing loss	Alive
14 2003	20 w	none	46, XX	yes	yes	no	no	38 w + 1d	yes	CS	BWS Spastic diplegia	Alive
15 2003	22 w + 2d	none	46, XX, inv(14) (p12q13) mat	yes	no	yes	no	39 w	yes	CS	Aortic valve stenosis	Alive
16 2003	22 w + 6d	Small thorax	46, XX	yes	no	yes	yes	38 w + 6d	yes	CS	Vesicoureteric reflux	Alive
17 2004	34 w	none	46, XY	yes	yes	yes	no	37 w	no	CS	BWS	Alive

GA, gestational age; FGR, fetal growth restriction; PH polyhydramnios; w, weeks; d, days; SVD, spontaneous vaginal delivery; CS cesarean section; ID, induced delivery; BWS, Beckwith-Wiedemann syndrome; ASD, atrial septal defect; VSD ventricular septal defect

TABLE 7 Liveborn non-isolated cases with omphalocele; postnatal subset

Case year	Additional associated anomalies	Karyotype	Liver herniation	GA at delivery	Birth weight <10th centile	Delivery method	Outcome
1 1991	AVSD	47, XY, +21	no	38 w	no	Not available	Alive
2 1991	Microcephaly, cleft palate, micrognathia, cataract, agenesis of the corpus callosum, transposition of the great arteries, pulmonary atresia, arthrogryposis congenita	46, XY	no	38 w	yes	SVD	Deceased on day 4
3 1992	VSD, ASD	46, XX	yes	38 w	no	SVD	Alive
4 1992	Unilateral cleft lip and palate, hypoplasia of the corpus callosum, microcephaly, microphthalmia, low set dysplastisc ears, funnel chest, clenched hands, postaxial polydactyly of fingers and toes	47, XY, +13	Unknown	36w+2d	no	SVD	Deceased on day 3
5 1992	Unilateral renal agenesis	46, XY	yes	40w+1d	no	SVD	Alive
6 1993	Metopic ridge, craniosynostosis	46, XY	no	36 w	no	SVD	Alive
7 1993	Cardiac situs inversus	46, XY	yes	39 w	no	CS	Alive
8 1994	Hydrocephaly, capillary haemangioma, micrognathia, hypoparathyreoidism, hypotonia, ataxia	46, XY	Unknown	37 w	yes	SVD	Alive
9 1994	Cardiac situs inversus	47, XY, +13 [20] /46, XY [6]	no	37w+5d	no	SVD	Alive
10 1996	VSD	46, XY	no	40w+1d	no	SVD	Alive
11 1996	Total situs inversus, single cardiac ventricle, transposition of the great artetries	46, XY	no	38 w	yes	SVD	Alive
12 1999	Coarctation of the aorta	46, XY	yes	36w+6d	no	CS	Alive

13 1999	Funnel chest, scoliosis	46, XX	yes	39w+2d	yes	SVD	Alive
14 2000	Urachal fistel, neuroblastoma	46, XY	no	40	no	SVD	Alive
15 2000	Microcephaly, hypoplasia of the corpus callosum, focal cortical dysplasia	46, XY	yes	35w+3d	yes	CS	Alive
16 2003	Bilateral cleft lip/palate, clenched fists	47, XY+13	no	36w+2d	no	SVD	Deceased on day 1

AVSD, atrioventricular septal defect; VSD, ventricular septal defect; ASD, atrial septal defect; GA, gestational age; w, weeks; d, days; SVD spontaneous vaginal delivery; CS, cesarean section.

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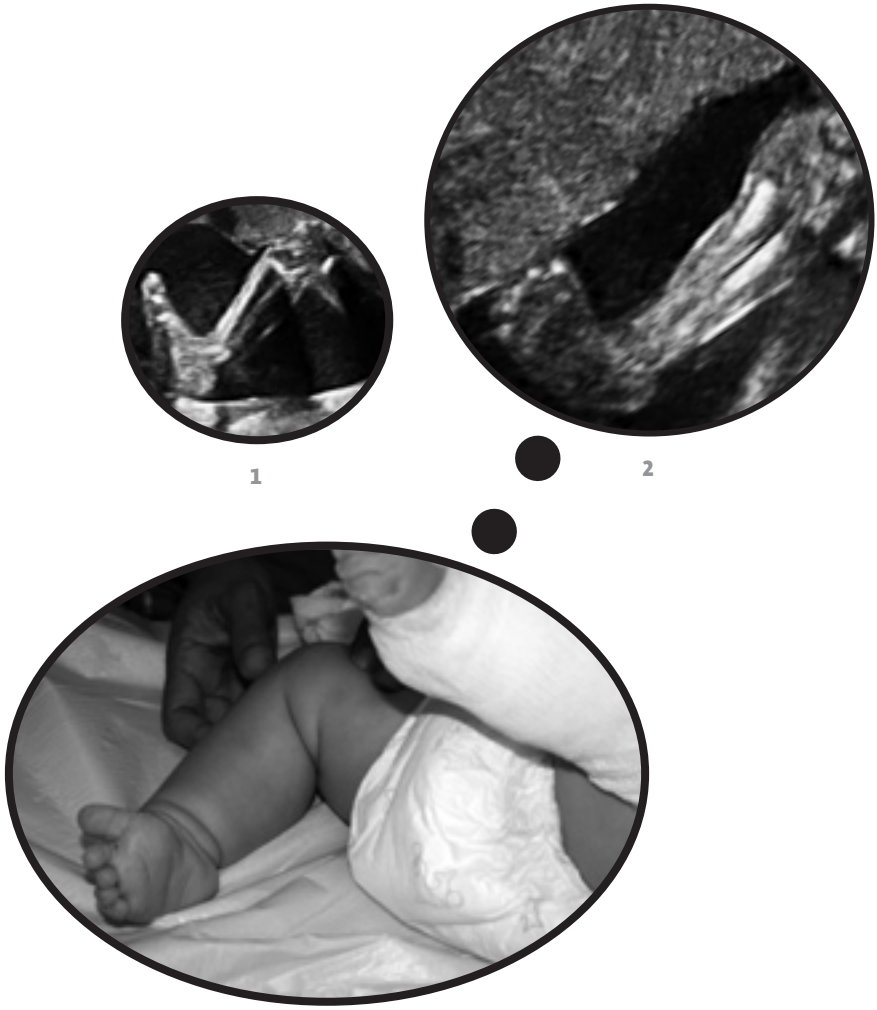
4 Diagnosis of Talipes equinovarus

The diagnosis of fetal talipes equinovarus is based on the tibia, fibula and sole of the foot being presented in the same plane on an ultrasound scan. Approximately half the prenatally detected cases, are associated with other anomalies or an abnormal karyotype, contrary to postnatal detected cases where only a minority is associated with these abnormalities. The prenatal diagnosis of talipes equinovarus appears to be associated with easier and less complicated postnatal surgical treatment providing the anomaly is isolated and the treatment is arranged at a Pediatric Orthopedic Center



1 Normal position of fetal knee, lower leg and foot.
2 Lower leg of a 20 week fetus with talipes equinovarus. The tibia and the fibula are visible in the same plane as the sole of the foot.
3 3-months old infant with bilateral talipes equinovarus. The right foot shows the abnormal position whereas the left foot is in a plaster cast.

4.1

Congenital talipes equinovarus; comparison of outcome between a prenatal diagnosis and a diagnosis after delivery

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Abstract

Objectives To establish the impact on outcome of prenatally versus postnatally detected talipes equinovarus (TEV).

Methods The prenatal group was represented by pregnancies with sonographically detected TEV of which 18 were isolated and 39 were complex. The postnatal group contained 64 infants with an isolated and 10 infants with a complex TEV detected at birth. Treatment consisted of redressement followed by surgical postero-lateral or postero-medial release in the University Pediatric Orthopedic Center. The postnatal isolated TEV group underwent redressement treatment in the University Center (subset A, N=39) or in a regional general hospital (subset B, N=25).

Results For isolated TEV statistically significant difference existed for the surgical procedure ($p<0.001$), age at surgery ($p<0.01$) and admission time ($p<0.001$) between the prenatal and postnatal subset B and between the postnatal subsets A and B. For the complex TEV no significant difference was found for these variables between the six surviving infants of the prenatal group and the postnatal group.

Conclusion Prenatal detection of isolated TEV results in earlier and less complicated postnatal surgery and a shorter admission time providing treatment is arranged in a Pediatric Orthopedic Center. After prenatal detection of a complex TEV survival is low and determined by associated anomalies.

Introduction

In the last 2 decennia, reports have appeared on the prenatal detection of talipes equinovarus (TEV). The first publications concentrated on the occurrence of TEV with other anomalies (complex cases) and the relative high frequency of an associated abnormal karyotype[1-3]. The prenatal detection rate demonstrated an increase from 11% in 1991 to 64% in 1999[4]. Apart from complex cases, a substantial number of isolated cases were revealed. During pregnancy or after delivery it may become evident, however, that a proportion of the isolated cases was in fact complex[5-7]. Furthermore, the false positive rate for isolated TEV varies between 6.4 and 35.3%[8,9]. In the presence of associated anomalies the prognosis is poor with only 10% normal outcome in contrast to a 94% normal outcome for isolated cases[5]. The need for surgical treatment in isolated cases varies between 18 and 72%[8-10]. This may be the result of different treatment modalities and the fact that prenatal ultrasound cannot distinguish between positional and structural TEV[9]. Particularly for the group of isolated TEV, counselling by an orthopedic surgeon will help future parents to understand the condition and the availability of treatment[11].

It may be assumed that the prognostic advantage of prenatal diagnosis of TEV is the detection of associated anomalies[5,9]. Depending on the severity of the associated anomalies, future parents have the opportunity to choose between different management options such as termination of pregnancy or continuation of pregnancy with non-intervention or standard management. In case of an isolated TEV they can prepare for the birth of an affected child that will require intensive treatment, particularly in the first year.

In the Netherlands, consensus was reached for the treatment of congenital TEV in 1992. Treatment should start early and initially consist of repeated redressements followed by plaster cast immobilisation. In the more severe cases surgical treatment is subsequently needed. This should preferably be performed between the age of 4 and 9 months and be completed before the child starts walking in order to facilitate normal motor development[12] without the need of wearing modified shoes. The aim of the present study was to retrospectively determine whether, for congenital TEV requiring surgical treatment, prenatal detection makes a difference in infant outcome compared to detection only at birth.

Patients and Methods

A diagnosis of TEV was made when both the tibia and the fibula were seen in the same plane as the sole of the foot. TEV was considered complex if other anomalies whether or not combined with an abnormal karyotype were also present.

Two groups of women were included in the study: a prenatal group in which the diagnosis of TEV was made by ultrasound in our own tertiary center and a postnatal group in which the diagnosis of TEV was only made at birth. In this latter group a prenatal ultrasound examination, if any, had always been carried out elsewhere. Inclusion criteria for both groups were as follows: a singleton pregnancy between 2000 and 2005 and redressement followed by surgical treatment; the latter always performed in the department of Pediatric Orthopedics of the Erasmus Medical Center (EMC). Adopted children were excluded from the study, since they always had started treatment much later.

In the postnatal group two subsets of infants could be distinguished. In the first subset (subset A) redressement treatment was commenced soon after birth followed by surgery in the department of Pediatric Orthopedics of the EMC. The second subset (subset B) received redressement treatment primarily in another hospital in the region followed by surgery at the department of Pediatric Orthopedics of the EMC.

In case of a complex TEV, treatment was only provided in the department of pediatric orthopedics of the EMC.

Redressement treatment consisted of application of a snugly fitted plaster cast well padded above the knee bent at 90 degrees to prevent the cast from sliding totally. Surgery was not considered necessary if at the end of the redressement treatment period radiographic examination demonstrated a completely corrected position of the foot. If the foot only showed a residual equinus deformity surgery primarily involved a simple postero-lateral release. In case the foot on clinical examination could not be put in valgus and abduction and on radiographic examination showed an abnormal relation between talus and os calcis, a more extensive postero-medial release was indicated.

On the basis of the retrospective nature of the study, the couples of the postnatal group were sent a questionnaire only following completion of the surgical treatment of the TEV. The purpose of this questionnaire was to obtain data concerning family and obstetric history by telephone.

Notes were reviewed for maternal demographic data, fetal sonographic data and neonatal and surgical outcome with a minimal follow up of 12 months. A family history was considered positive if a family member up to the third degree or less of relation was known with a TEV. Age at surgery, type of surgery, number of surgical procedures, duration of hospital admission and recurrence rate of TEV were compared between the pre- and postnatal cohorts.

The Pearson chi-square test or Fisher's exact test was used to analyse categorical variables and the unpaired t-test or the Mann-Whitney test was applied to analyse continuous variables. All calculations were performed using the SPSS software package (release 10.1,SPSS Inc, Chicago, Il, USA). A p-value of <0.05 was considered statistically significant.

Results

The total study group consisted of 151 cases from singleton pregnancies. The prenatal group was represented by 65 cases, of which 2 with an isolated TEV only underwent redressement therapy and a further 4 were treated elsewhere resulting in 59 cases for further analysis.
The postnatal group consisted of 86 infants, of which 3 were adopted and 5 for which there was no response to the questionnaire resulting in 74 infants for further analysis. TEV was isolated in 84 cases and complex in 49 cases.

Isolated TEV (N=84)

Isolated TEV was diagnosed in 20/59 (34%) fetuses in the prenatal group at a mean gestational age of 23 (19-36) weeks. Referral for a prenatal ultrasound examination was 14 (70%) times for a suspected abnormality and 6 (30%) times for an *a priori* risk of a fetal anomaly amongst those who had a positive family history of TEV (N=3). Unilateral TEV was established in 6 cases. There were 2 false positive cases associated with oligohydramnios due to premature rupture of the membranes or fetal growth restriction, yielding a 5.8% false-positive rate. One pregnancy ended in intrauterine death as a result of placental abruption at 31 weeks. In this case, a bilateral instead of the suspected unilateral TEV was diagnosed after delivery. Bilateral TEV was diagnosed prenatally and confirmed after delivery in 14 (70%) cases. Altogether 17 newborn from the prenatal group were eligible for treatment, representing 13 males and 4 females.
The postnatal group consisted of 64 infants with an isolated TEV, of which 43 were males and 21 females. A positive family history was present in 15/64 cases (23%). Bilateral TEV was established in 28/64 cases (44%). A total of 39 infants was referred directly after delivery for redressement treatment followed by surgery at a later stage (subset A) while in the remaining 25 infants redressement therapy was started at a regional hospital followed by surgery in the University Center (subset B). Delivery and postnatal treatment data for both the prenatal and total postnatal group are presented in Table 1. No significant difference was found for gestational age at delivery, birth weight and gender ratio between the prenatal and total postnatal group. The ratio of unilateral/bilateral TEV in the prenatal group (3/14) was significantly different ($p<0.01$) from the total postnatal group (36/28). No significant difference existed for age at surgery, type of surgery (postero-lateral or postero-medial release) and duration of admission between the prenatal group and postnatal subset A. However, a significant difference was found for all three variables ($p<0.01$; $p<0.001$; $p<0.001$) when comparing (1) the prenatal group and postnatal subset B and (2) postnatal subsets A and B. In postnatal subset A, three infants suffered a recurrence following surgery: one following a postero-lateral release at 9 months and two following a postero-medial release at 16 and 18 months, respectively.

Complex TEV (N=49)

Complex TEV was diagnosed prenatally in 39/59 (66%) fetuses at a mean gestational age of 24 (14-36) weeks. Reason for referral for a prenatal ultrasound examination was a suspected fetal anomaly in every instance; in one case, there was also a family history of TEV. There were 19 males and 20 females. Twelve pregnancies were complicated by oligo/anhydramnios (N=5) or polyhydramnios (N=7). Fetal chromosome analysis was carried out in 34/39 (87%) cases, resulting in six abnormal karyotypes: triploidy (N=2), trisomy 18 (N=2), trisomy 21, marker chromosome. Termination of pregnancy was opted by the patient in 19 cases and intrauterine death occurred in 5 cases resulting in 15 liveborn infants with a normal karyotype in which 2 demonstrated bilateral instead of unilateral complex TEV and 1 turned out to be a pes equines resulting in a 2.5% false positive rate. A further nine infants died during the neonatal period. The remaining six survivors underwent postero-medial surgical release.

The postnatal group consisted of 10 infants, of which nine were male and one was female. None had a positive family history. Bilateral TEV was diagnosed in eight cases.

All infants underwent both redressement and surgical treatment in the University Center, nine of which a postero-medial release and one a postero-lateral release.

A detailed list of the associated anomalies and outcome in complex TEV is given in Table 2. Delivery and treatment data are presented in Table 3. No significant difference was found for gestational age at delivery, birth weight, and distribution of unilateral and bilateral TEV between the prenatal and postnatal group. The same applied to the age at surgery, type of surgery and duration of admission. In the prenatal group, one infant with spina bifida suffered a recurrence of the TEV six months after a postero-medial release. When considering the confirmed isolated and complex cases of TEV together, a significant difference ($p<0.001$) in the proportion of isolated and complex TEV cases was established between the prenatal group (18 isolated and 39 complex TEV cases) and postnatal group (64 isolated and 10 complex cases)

Discussion

To our knowledge this is the first study that analyses the outcome of treatment between a group of neonates with a diagnosis of TEV before birth and a group in which this anomaly was diagnosed only after delivery. In the presence of isolated TEV, there is no difference in outcome after a prenatal or postnatal diagnosis if redressement treatment followed by surgery is performed at a specialised Pediatric Orthopedic Center. However, if after a postnatal diagnosis of isolated TEV redressement treatment was commenced outside such a specialised center, surgery took place later, was of a more

complicated nature (postero-medial in stead of postero-lateral release) and required a longer admission period. Counselling of women by a pediatric orthopedic surgeon during the prenatal period will, in most cases, result in postnatal treatment in the corresponding department. The majority of infants with isolated TEV that require surgical treatment are referred to the pediatric orthopedic department. Our study may be slightly biased as a small proportion of infants will remain for treatment in a regional general hospital. This mainly concerns the positional TEV where surgery is often not indicated. There is only one other study which compared the outcome of a prenatal and postnatal group with isolated TEV[4]. They only assessed the percentage of cases requiring surgery in both groups, which was 55 and 60%, respectively. Detailed analyses of age at surgery, type of surgery and admission period have not been previously reported.

During embryologic limb development the foot passes through three different positions. At first the foot is in a straight line with the leg. Then at the 30-mm stage the foot passes to a marked equinovarus-adductus position which is eventually followed at the end of the embryologic phase to only a slight equinovarus-adductus position[13]. It is believed that the arrest of bone growth between the 30 and 50 mm stage of the embryo will result in congenital TEV[14]. Therefore the majority of congenital TEV should be detectable at the 18-22 week anomaly scan. Tillet et al.[10] assumed that the reason why orthopedic surgeons still see cases of isolated TEV at birth that have not been diagnosed prenatally, is the possibility of a transient TEV in pregnancy[15]. However, studies investigating the detection rate of TEV[4,11] reached a maximum detection rate at the end of their investigation period of 35% and 64%, respectively. Although an obvious learning curve was demonstrated and experience would most likely continue to rise, even tertiary centers present false negative figures between 3 and 29% for bilateral TEV where, in the prenatal period, a unilateral TEV was assumed[9,16,17]. It is therefore highly plausible that still a number of cases of isolated TEV may only be detected at birth.

The male preponderance in isolated TEV present in both our prenatal and combined postnatal group confirms data from neonatal studies where the male female ratio is 2:1[18].

Although the present study concentrated on TEV requiring surgery, it is remarkable that only two fetuses (10%) with a prenatal diagnosis of isolated TEV received redressement treatment only, whereas in the other 90% this was followed by surgery. This is a much higher percentage than the 48-72% requiring surgery reported in other studies of prenatally detected isolated TEV[4,6,9,10]. In the study by Woodrow et al.[8] only 18% of isolated cases needed surgery which was performed well beyond the first year of life. This discrepancy is most likely the result of different treatment modalities. Furthermore, in our clinic, the necessity for surgery is defined by radiographic and clinical examination at the end of the redressement treatment period. Only a completely corrected foot will not require surgery. To stimulate normal

motor development in neonates with a TEV, it is policy in the Netherlands to obtain a stable plantigrade foot by the time the infants start to walk. This approach has led to the present management with surgery being carried out between the age of 4 and 9 months[12]. Also, in the present study, only three patients (4%) in the isolated group suffered a recurrence which is comparable to other studies with surgically treated isolated TEV[19,20].

In the prenatal group, 66% of the fetuses were diagnosed with a complex TEV whereas this was only 16% of the postnatal group. The significant distribution difference in proportion of isolated and complex TEV cases between the prenatal and postnatal group appears to be caused by the severity of the associated anomalies in the former group, resulting in a high incidence of termination of pregnancy, intrauterine and neonatal death. Previous prenatal studies [3,7,17,21] have shown similarly high figures but reports from countries with a longstanding experience in ultrasound screening demonstrate a more equal proportion of isolated and complex TEV cases[5,9]. It is likely that this is the result of more experience in the detection of congenital anomalies and as a consequence an increase in those isolated anomalies which are more difficult to detect.

In our prenatal complex TEV group, there were six cases (15.4%) with a chromosome anomaly. For complex TEV cases similar percentages were reported in previous studies with no chromosomal anomalies in isolated cases[5,9,17]. The majority of chromosomal anomalies represented trisomy 18 and triploidy. In the present study a case of hydrops associated with trisomy 21 was documented. Trisomy 21 is not typically related to TEV, as opposed to TEV hyperflexibility of the joints is a feature of this chromosomal anomaly[22]. The combination of complex TEV and trisomy 21 has been reported in a number of prenatal studies[5,16,17,21]. When a TEV is established prenatally, the present study clearly demonstrates that the ultrasonographer should be aware of the fact that in more then 50% of cases associated anomalies may be present. If the resolution of the ultrasound scan and the experience of the sonographer allow exclusion of additional anomalies in case of isolated TEV, we agree with Malone et al.[23] that there is no indication for karyotyping.

Of the survivors with a complex TEV, the associated anomalies mainly represented musculoskeletal abnormalities and neural tube defects. These anomalies generally cause a stiff TEV which explains why the postero-medial release operation was required in all but one case to obtain a plantigrade foot. For both the prenatal and the postnatal group of complex TEV, the treatment was commenced in our Pediatric Orthopedic department and no difference was observed in timing and nature of surgery, period of admission and recurrence rate.

Infants from both the prenatal and postnatal complex TEV group showed 75 and 80% bilateral TEV, respectively. This confirms data by Bakalis et al.[5] and Treadwell et al.[21] who also detected bilateral TEV in the majority of prenatal complex TEV cases. Similarly to a previous report[24], isolated TEV in our postnatal group was bilateral in approximately 50% of cases. However,

in the prenatal group of isolated TEV, only 17% revealed the unilateral form and a significant difference was established in the proportion of unilateral and bilateral cases between the prenatal and postnatal isolated TEV cases. Detection of a relative minority of isolated unilateral TEV cases was also shown in other studies[4,16]. This low detection rate of isolated unilateral TEV is probable the result of inexperience in recognising congenital anomalies. Maffulli[25] considered prenatal detection of TEV only of prognostic relevance in complex cases. This is at variance with the present study, which has demonstrated that there is a prognostic advantage in the prenatal detection of isolated TEV.

It can be concluded that prenatal detection of isolated TEV results in earlier and less complicated postnatal surgery and a shorter admission time, provided treatment is arranged in a pediatric orthopedic center. After prenatal detection of a complex TEV survival is low and determined by associated anomalies: outcome of TEV treatment is not dependent on timing of diagnosis.

TABLE 1 The delivery and treatment data for isolated TEV of the prenatal group and the postnatal group A, referred directly for redressement and surgery and group B, referred for first surgery after redressement treatment is started elsewhere.

	Prenatal group N=17	Postnatal group A N=39	Postnatal group B N=25	P
GA at delivery (weeks)	39 ± 2	39 ± 2	39± 3	NS
Birth weight (g)	3193 ± 430	3359 ± 656	3211 ± 789	NS
Male/female	13/4	27/12	16/9	NS
Unilateral TEV	3	24	12	*<0.01
Bilateral TEV	14	15	13	
Age at surgery (month)	6.3 ± 2.4	6.7 ± 2.9	8.6 ± 2.4	**<0.01
				***<0.01
Type of treatment				
Postero-lateral release	10	20	1	**<0.001
Postero-medial release	7	19	24	***<0.001
Duration of admission	2.4 ± 1.7	2.8 ± 1.9	5.0 ± .4	**<0.001
(days)				***<0.001
Recurrence	0	3	0	

Values represent means ± SD. TEV, talipes equinovarus; GA, gestational age; ns, not significant; g, gram

* p value for significant difference between the prenatal group and the combined postnatal groups A and B

** p value for significant difference between the prenatal group and the postnatal group B

*** p value for significant difference between the postnatal group A and the postnatal group B

TABLE 2 Associated anomalies and outcome in the prenatal and postnatal group with complex TEV

Associated anomalies	TOP	IUD	NND	Alive	Alive
	Prenatal group				Postnatal group
Central nervous system					
Exencephaly	2	-	-	-	-
Spina bifida	2	-	2	3	3
Encephalocele	1	-	-	-	-
Walker Warburg	1	-	-	-	-
Chromosomal					
Triploid	1	1	-	-	-
Trisomy 18		2	-	-	-
Trisomy 21	1	-	-	-	-
Marker chromosome with ventriculomegaly	-	1	-	-	-
Abdominal wall defect					
Canthrell pentalogy	-	-	1	-	-
Limb bodywall complex	1	-	-	-	-
Skeletal dysplasia					
Chondrodysplasia punctata	1	-	-	-	-
Achondrogenesis type II	1	-	-	-	-
Atelo-osteogenesis type II	1	-	-	-	-
Uorgenital anomaly with oligohydramnios					
Obstructive uropathie	-	-	1	-	-
Polycystic renal dysplasia	-	1	-	-	-
Meckel Gruber syndrome	2	-	-	-	-
MCA					
Multiple vertebral anomalies with tethered cord, rib agenesis, anal atresia and dextrocardia	-	-	-	1	-
Hypoplastic right heart syndrome with pulmonary stenosis and transposition of the great arteries, multiple vertebral anomalies, horseshoe kidney	-	-	-	-	1
Arthrogryposis	1	-	1	1	4
Myotonic dystrophy	-	-	2	-	-
Hydrops	4	-	1	-	-
Larsen syndrome	-	-	-	-	2
Diaphragmatic hernia	-	-	1	-	-
Cleft lip/palate	-	-	-	1	-
Totaal	19	5	9	6	10

TEV, talipes equinovarus; TOP, termination of pregnancy; IUD, intrauterine death; NND, neonatal death; MCA, multiple congenital anomalies

TABLE 3 The delivery and treatment data for complex TEV of the survivors of the prenatal and the postnatal group.

	Prenatal group N=6	Postnatal group N=10	P
GA at delivery (weeks)	39 ± 1	39 ± 1	NS
Mean birth weight (g)	3440 ± 431	3031 ± 510	NS
Unilateral TEV	2	2	NS
Bilateral TEV	4	8	
Number with surgery	6	10	NS
Age at surgery (month)	11.6 ± 5.6	14.6 ± 9.4	NS
Type of treatment			
Postero-lateral release	0	1	NS
Postero-medial release	6	9	NS
Mean duration of admission (days)	4.5 ± 1.6	5.2 ± 1	NS
Recurrence	1	0	

Values represent means ± SD. TEV, talipes equinovarus; GA, gestational age; g, gram.

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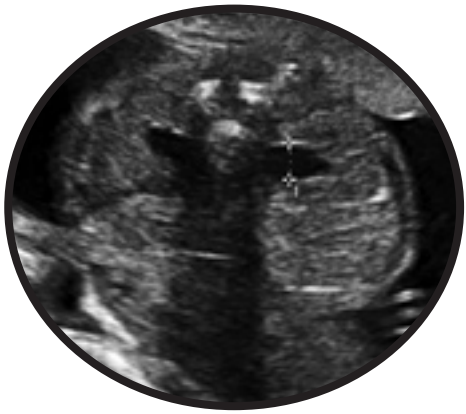
5 Diagnosis of urinary tract anomalies

Fetal kidneys and urinary bladder filling can be visualised as early as 12-14 weeks of gestation. Renal tract abnormalities whether at urethral or at urethral level will provide well-defined images by medical ultrasound. Whereas assessment of renal function during fetal life has been limited, grading of urinary tract dilation appears to be helpful in determining which infant will need postnatal evaluations (chapter 5. 1).
Abnormal renal morphology may not only be the result of urinary tract obstruction, it may also reflect abnormal development of the kidney itself, as is the case in multicystic dysplastic kidney. The postnatal outcome of this renal abnormality is determined by associated renal or non-renal structural pathology rather than the size or location of the renal anomaly itself (chapter 5. 2)



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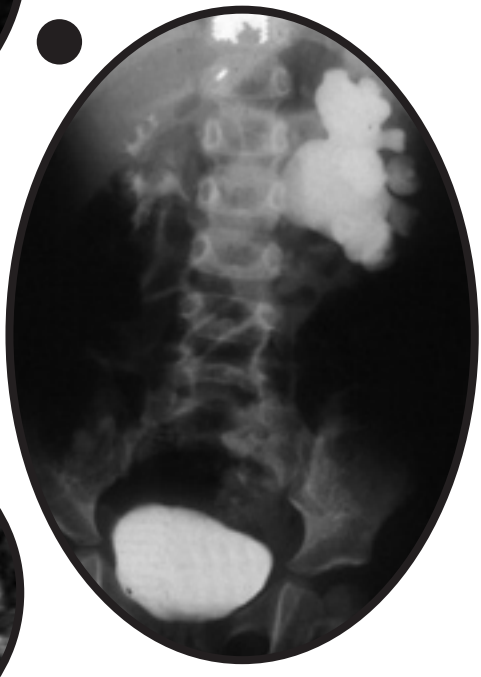

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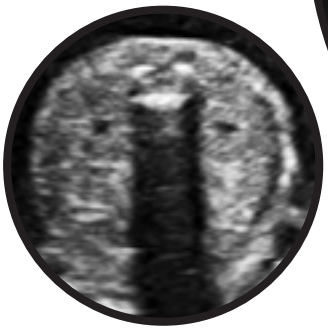

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1 Transverse image of the normal fetal abdomen with the spine at 12 o'clock. Right and left adjacent to the spine the kidney's are visible with a normal size pyelum.
2 Transverse image of the fetal abdomen with the spine at 12 o'clock. Right and left adjacent to the spine the kidney's are visible with a dilated pyelum of the left kidney.
3 Intra-venous pyelogram in infant showing the left kidney with pelviureteric junction obstruction.

5.1

Mild renal pyelectasis in the second trimester; determination of cut-of levels for postnatal referral.

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Abstract

Objective To establish guidelines for postnatal referral of fetuses presenting with mild pyelectasy in the second trimester of pregnancy.

Methods: In a retrospective study 87 fetusus with a renal pelvis anterior posterior (RPAP) diameter of ≥4 mm and ≤10 mm before 28 weeks of gestation were included. All patients had a third trimester scan and fetuses with an RPAP diameter of ≥10 mm were referred for postnatal assessment. The family practitioner of all infants with an RPAP of <10 mm in the third trimester was contacted for follow up information. The RPAP diameter most predictive of renal pathology was determined with receiver-operating characteristics (ROC) curve analysis for both the first and second scans.

Results: In 36 of 87 infants, 49 abnormal kidneys were diagnosed. Seven infants required surgery on 8 renal tracts. The ROC curves of the first scan, second scan and differences between scans resulted in an area under the curve of 0.60, 0.87 and 0.85, respectively. The sensitivities and specificities for a cut-off level of 8, 9 and 10 mm at the second scan are 80%, 71% and 61% and 79%, 90% and 93% respectively. At a cut-off level of 10 mm, only cases of insignificant dilatation and a case of vesicoureteric reflux (VUR) requiring surgery were not detected.

Conclusion: After establishing a diagnosis of mild pyelectasy before 28 weeks a second scan is mandatory to determine which infants need postnatal evaluation. A cut-off level of 8 mm has a low specificity but includes most cases of pathology. A cut-off level at 10 mm detects most significant pathology, however VUR may be missed.

Introduction

The fetal kidneys and bladder are readily visualised during prenatal scanning due to the collection of urine. In the second trimester, many consider the renal pelvis dilated when the renal pelvic anterioposterior (RPAP) diameter is ≥4 mm[1–5]. Mild pyelectasis is associated with an increased risk of associated pathology or chromosomal defects[6,7]. The Society of Fetal Urology introduced a scheme to grade excessive accumulation of fluid within the fetal kidneys[8]. From grade III upwards, when the renal pelvis is dilated with at least almost all calyces visible, there appears to be no doubt that infants should be referred for postnatal assessment and treatment in order to minimize renal injury and scarring[9]. In the case of mild pyelectasis, when only the renal pelvis with one or two calyces at most is visible, the need for postnatal assessment is less clear. RPAP cut-off levels varying from ≥5 mm at any stage in pregnancy[10,11] to ≥8 mm[1] in the third trimester are recommended for referral for postnatal assessment. This results in sensitivities ranging from 70%[4] to 100%[11,12]. Langer et al.[13] and Sairam et al.[14] have recommend postnatal referral only when the renal pelvis is ≥10mm in the third trimester. These varying recommendations are confusing for doctors in the prenatal assessment of potential pathology and the advice they should give to parents, and they may lead to an unnecessarily large burden for pediatric urological clinics. Previous studies have included patients presenting in both the second and third trimester[12,13], or included moderate as well as mild pyelectasis in the analysis[10,11]. Although Sairam et al.[14] evaluated the natural history of fetal hydronephrosis in a large prospective study, no follow up of infants with an antenatal RPAP <10 mm in the 3rd trimester was obtained. In the present study, fetuses presenting with mild second trimester pyelectasis and available third trimester and postnatal follow-up were investigated in order to establish clear guidelines for postnatal referral to a pediatric urology unit and to determine the risk of uropathy at different cut-off levels for renal pelvic size.

Methods

From the 1st of January 1996 until the 31st of December 1999 all women with a singleton pregnancy and an RPAP diameter of ≥4 mm and ≤10 mm before 28 weeks of gestation were selected from the database of our tertiary referral center. Only kidneys with renal pelvis dilatation without calyceal dilatation were included. A third-trimester ultrasound scan was mandatory for inclusion. Fetuses with obvious obstructive uropathy as presented by a dilated urinary bladder and keyhole urethra at the first scan were excluded, as well as fetuses with associated or chromosomal anomalies.
All fetuses with an RPAP diameter of ≥10 mm in the third-trimester scan were referred to a pediatric urologist for assessment. Postnatal ultrasound scans

were performed at the end of the first week. The postnatal cut-off level for a normal renal pelvis is <10 mm. However, caliectasis or ureterectasis were considered abnormal regardless of the size of the renal pelvis. Generally, when the renal pelvis exceeded 15 mm or calyceal dilatation was present, a Tc-99 mercaptoacetyltriglycine (MAG3) scan and micturating cystourethrogram (MCU) were performed.
The family practitioner of all infants with an RPAP of <10mm in the third trimester was contacted for follow-up information on possible renal tract anomalies and urinary tract infections. If referral to the pediatrician was indicated, this person was approached for further information on follow-up.
Statistical comparison of percentages was carried out using the Chi-Square test. Continuous data were compared with the Mann-Whitney *U*-test. Sensitivities and specificities for various cut-off levels were calculated and graphically displayed using receiver-operating characteristics (ROC) curves. Logistic regression analysis was applied to determine the predictive chance of pathology for each RPAP diameter at the first and second scan. In case of bilateral pathology, both renal pelves were analyzed separately.

Results

Of the 6087 fetuses in the database 101 (1.7%) were found to have a RPAP diameter of ≥4 mm and ≤10 mm before 28 weeks of gestation. Three of these fetuses had a dilated bladder and keyhole urethra due to posterior urethral valves and were therefore excluded. In six cases associated anomalies were seen including hydrops (N=2), omphalocele (N=1), ventriculomegaly (N=2), and a cardiac anomaly (N=1). In two of these six fetuses a genetic syndrome was diagnosed at post mortem or after delivery. Trisomy 18 was diagnosed in two fetuses with multiple anomalies. The mean maternal age of the study population was 31.2 (range, 19-44) years (SD 4.8). Three women were lost to follow up. Eighty-seven newborns with 174 renal units were available for the final analysis. Due to the retrospective design of the study, follow-up ranged from at least 1 year to 5 years.
The mean gestational age at the second and third trimester scan was 21.6 weeks (SD 2.5) and 32.5 weeks (SD2.3). There were 65 males and 22 females, of which 26 (40%) and 10 (45%) showed anomalies in 37 and 12 renal units, respectively. There was no significant difference in the number of abnormal kidneys between males and females (P=0.65). In Table 1 the postnatal diagnosis is classified according to cases and number of abnormal kidneys. A distinction is made between fetuses with both RPAP diameters <10 mm or at least one RPAP diameter ≥10 mm after 28 weeks of gestation. In the group where both RPAP diameters were <10 mm after 28 weeks' gestation, 43 (81%) showed no evidence of any renal tract anomaly. In 8 infants and 12

renal units a mild idiopathic dilatation, defined as a RPAP ≥10 mm and <15 mm, was established. In one infant, bilateral vesicoureteric reflux (VUR) was diagnosed. A scan at 32 weeks' gestation had shown both RPAP diameters to be 8 mm. In another infant, a unilateral dysplastic kidney was diagnosed at the age of 1 year. The antenatal RPAP diameter was 9 mm at 34 weeks' gestation. A postnatal ultrasound scan had been performed and no anomaly was established.

In the group where at least one RPAP diameter was ≥10 mm after 28 weeks, isolated pelviureteric junction obstruction (PUJO) was diagnosed in 17 renal units in 14 infants (41%). Isolated unilateral VUR existed in two infants. Unilateral VUR was diagnosed once in combination with PUJO and twice with renal duplication. A unilateral kidney cyst was diagnosed in one infant. Mild idiopathic dilatation was seen in six infants in 11 renal units. The RPAP diameter after 28 weeks in these 11 renal units varied between 4 and 18 mm. In 8 infants and 34 renal units there was no evidence of any renal tract pathology. In the total study group, 7 of 87 neonates (8%) underwent surgery, the nature of which is described in Table 2. The RPAP diameters at the first and second scan of all infants requiring surgery are provided in Table 2. In five infants, surgery was performed for PUJO, which involved bilateral pyeloplasty for one of them. In another infant, a partial nephrectomy was performed for renal duplication and VUR. One infant required bilateral endoscopic antireflux surgery and this was the only infant requiring surgery where both RPAP diameters after 28 weeks were <10 mm.

Antibiotic prophylaxis was prescribed to 21 newborn on the first day of life. This involved 18 of 33 newborns with a RPAP diameter ≥10 mm and 3 of 54 newborn with a RPAP diameter <10 mm. Despite this treatment six infants developed urinary tract infections, including two with VUR. In two infants with RPAP diameters of <7 mm at the second scan, a urinary tract infection was diagnosed. Mild idiopathic dilatation was subsequently diagnosed in one case, whereas in the other, no urogenital pathology was established. The predictive chance of all uropathology, decribed in Table 1, is calculated for each RPAP diameter at the first and second scan, and the results are displayed in Figures 1. For the first measurement the risk shows a moderate increase for greater diameters, whereas for the second measurement the risk demonstrates a much steeper rise. In Figure 2, the ROC curves for the RPAP diameter at the first and second scan, and for the RPAP diameter difference between the two scans, are displayed. The areas under the curve were 0.60, 0.87 and 0.85 respectively. When considering the second scan as the best performer (ROC area of 0.87), the sensitivities for a cut-off level of 8,9 and 10 mm were 80%, 71% and 61%, respectively. The specificities for these cut-off values were 79%, 90% and 93%, respectively. At a cut-off level of 10 mm, only cases of insignificant minimal dilatation and a case of VUR requiring surgery were not detected.

Discussion

The prevalence of 1.7% for mild renal pyelectasis in this study is comparable to that of other studies of low- and high-risk populations[10,14,15]. In our high-risk population associated anomalies were seen in 8% of cases. In other studies[16–18] this percentage varied between 3.9 and 31.6%. The relative high percentage of associated anomalies in the present study is likely to be due to the fact that a high-risk population was investigated. Mild renal pyelectasis has an increased risk of aneuploidy, particularly trisomy 21 when another risk factor such as advanced maternal age (≥36 years) or associated anomalies are involved[7]. No case of trisomy 21 was encountered in the present study, but in two cases trisomy 18 was diagnosed. Both fetuses showed multiple associated anomalies at a maternal age of 25 and 32 years, respectively. Encountering mild renal pyelectasis should trigger the investigator to exclude associated anomalies and instigate invasive diagnosis if other risk factors are involved.

Our study confirms that isolated mild renal pyelectasis is significant more common in males than in females. This predominance of affected males has also been observed by others[1,3,16,19] and is in accordance with the postnatal incidence of hydronephrosis where PUJO is the most common diagnosis[20]. In our study, it is evident that from the 174 kidneys with mild renal pyelectasis in the second trimester, 148 kidneys did not reveal significant pathology in the postnatal period. There were 23 kidneys with a mild idiopathic dilatation that did not require surgery and in which there was no evidence of renal impairment. PUJO was diagnosed in 18 of the 174 kidneys; five infants with six renal units needed pyeloplasty. PUJO was the most common diagnosis in the pathology group followed by VUR, as has also been evident in other studies[2,5]. Apart from one case with bilateral VUR and one case with a unilateral dysplastic kidney diagnosed at the age of 1 year, all infants in whom significant uropathology was diagnosed had displayed RPAP diameters of ≥10mm after 28 weeks of gestation.

VUR was diagnosed in six infants. Two infants required antireflux surgery, one of them showed bilateral RPAP diameters in the third trimester of only 8 mm**.** Reported percentages of VUR established after prenatal diagnosis of mild renal pyelectasis vary from 4.1 to 22%[10,16] but many cases of VUR are not detected[16,21,22]. To prevent this, all cases with a prenatal RPAP of ≥5 mm at any stage of pregnancy, would require an MCU[10]. Yerkes et al.[23] demonstrated that adopting such a policy would establish a high prevalence of VUR, whereas most of these cases would resolve without intervention and only require conservative management within 1-4 years. This policy would cause a high burden on medical resources without significantly improving morbidity in infants with mild degrees of VUR. Furthermore, there appears to be a high rate of spontaneous resolution of VUR within the first 2 years[24,25]. The issue of antibiotic prophylaxis in the presence of mild pyelectasis remains unclear in the literature. While Misra et al.[26] advise only to give

prophylaxis in case of bilateral hydronephrosis, others[27] recommend antibiotic prophylaxis when renal calyces are dilated. In the presence of VUR there is consensus about prophylactic therapy. Despite antibiotic prophylaxis, six infants in our study developed a urinary tract infection. In two of these cases VUR had been diagnosed. These figures are higher than those reported by Blachar et al.[27] and only emphasize the importance of prophylactic treatment in order to prevent urinary tract infection and subsequent renal scarring[28]. In two infants with RPAP diameters of <7 mm at the second scan, a urinary tract infection was diagnosed. Only in one case renal pathology in the form of mild idiopathic dilatation was subsequently established. These results are consistent with other studies[2]. Considering these findings we would support the advice from Kent et al.[4] that, if ultrasound examination in the third trimester is considered normal, no further investigations are required. However, the parents should be advised that if the infant develops a fever of unknown origin, a urine culture is necessary and infants with a proven urinary tract infection should be referred for treatment and radiologic work-up, including ultrasound and MCU. Despite the retrospective study design, contrary to other studies, we obtained a complete follow-up of all cases that entered the study, including those with a RPAP diameter in the third trimester of <10 mm. Furthermore, only 3% of cases were lost to follow up. This enabled us to provide a true picture of the incidence of postnatal pathology. The areas under the ROC curves for the first scan, the difference between the two scans, and the second scan indicate that the difference between measurements and the anteroposterior measurement of the pelvis after 28 weeks are both tests with a good prediction. It confirms that a renal pelvis which remains stable in size throughout pregnancy, especially with a RPAP diameter of ≤9 mm, is of little clinical significance[5,13]. In 60% of the patients of our study the RPAP diameter did not exceed 10 mm in the third trimester and in only a few of these cases a minimal dilatation was detected in the postnatal period. However, one case of VUR requiring surgery also belonged to this group. The graph for the predictive chance of pathology for each RPAP diameter at the first scan shows a linear increase with a maximum prediction of 55% at an RPAP diameter of 10 mm. The graph for the predictive chance of pathology for each RPAP diameter at the second scan shows a steeper increase particularly from 8 mm onwards. This information may be of use to both care providers and parents when confronted with a mildly dilated renal pelvis in the second trimester. As observed by others, a second scan in the third trimester is required to distinguish between normal and potential pathologic cases[29,30]. When counselling parents on the ability of ultrasound to detect renal anomalies one should bear in mind that not all cases of urogenital anomalies are identified at a second-trimester scan. Several authors have reported that cases of VUR and some cases of obstructive uropathy may be associated with a normal scan in the second trimester, with a pathological dilatation of the renal pelvis only being revealed in the third trimester or the postnatal

period[21,31]. All parents experience anxiety when confronted with any kind of fetal anomaly and serial investigations may only aggravate this[32] where, in case of mild renal pyelectasis no additional information is obtained[33]. Only, when a significant reduction of the amniotic fluid is detected in the presence of bilateral urinary tract pathology should repeat scans be recommended. In conclusion, after establishing mild renal pyelectasis before 28 weeks' gestation, a second scan is mandatory to determine which infants need postnatal evaluation. A cut-off level of 8 mm will include most cases of pathology, however, with a low specificity. At a cut-off level of 10 mm most significant pathology will be detected. In the presence of a RPAP diameter of <10 mm in the third trimester of pregnancy, postnatal investigations are not recommend. However, cases of VUR may not be detected. Our recommendation is that in case of a proven urinary tract infection further investigations are indicated.

TABLE 1 **Post partum diagnosis of renal anomalies in fetuses with a renal pelvic anteroposterior (RPAP) diameter of ≥4 mm and ≤10 mm before 28 weeks' of gestation and <10 mm or ≥10 mm after 28 weeks of gestation**

	Bilateral RPAP diameters <10 mm after 28 wks gestation (N(%))		At least one RPAP diameter ≥10 mm after 28 wks gestation (N(%))	
Diagnosis	**Fetuses**	**Kidneys**	**Fetuses**	**Kidneys**
PUJO	0	0	14 (41)	17
VUR	1 (2)	2	2 (6)	2
PUJO and VUR	0	0	1 (3)	1
Renal duplication and VUR	0	0	2 (6)	2
Dysplastic kidney	1 (2)	1	0	0
Solitary kidney cyst	0	0	1 (3)	1
Mild idiopathic dilatation	8 (15)	12	6 (18)	11
No pathology	43 (81)	91	8 (23)	34
Total	53	106	34	68

PUJO, pelviureteric junction obstruction; VUR, vesicoureteric reflux.

TABLE 2 **Measurements of the renal pelvic anteroposterior (RPAP) diameters in the first and second scan in all cases where surgery was performed.**

	RPAP diameter at ultrasound scan <28 weeks' gestation (mm)		RPAP diameter at ultrasound scan ≥28 weeks' gestation (mm)			
Gender	**L**	**R**	**L**	**R**	**Postnatal diagnosis**	**Surgery**
F	3	6	3	23	R PUJO	R pyeloplasty
M		8	4	25	R PUJO	R pyeloplasty
M	6	5	8	8	VUR L gr IV, VUR R gr II	Endoscopic antireflux surgery
F	6	8	54	27	Bilateral PUJO	Bilateral pyeloplasty
M	4		31	3	L PUJO and VUR gr II	L pyeloplasty
M	7	3	10	6	Renal duplication and VUR L lower pole gr V	L partial nephrectomy
M	3	5	6	16	R PUJO	R pyeloplasty

F, female; gr, grade; L. left; M, male; PUJO, pelviureteric junction obstruction; R, right; VUR, vesicoureteric reflux.

FIG. 1 **The predictive chance of pathology for each renal pelvic anteroposterior (RPAP) diameter of the first (dashed line) and second (solid line) scan. Equation of the dashed line: $\log_e(\text{odds}) = -3.99 + 4.2 \times \log_2(\text{diameter(mm)})$, with odds representing the odds (P/(100-P)) of the predicted probability (%). Equation of the solid line: $\log_e(\text{odds}) = -7.32 + 2.31 \times \log_2(\text{diameter(mm)})$, with odds representing the odds (P/(100-P)) of the predicted probability P (%).**

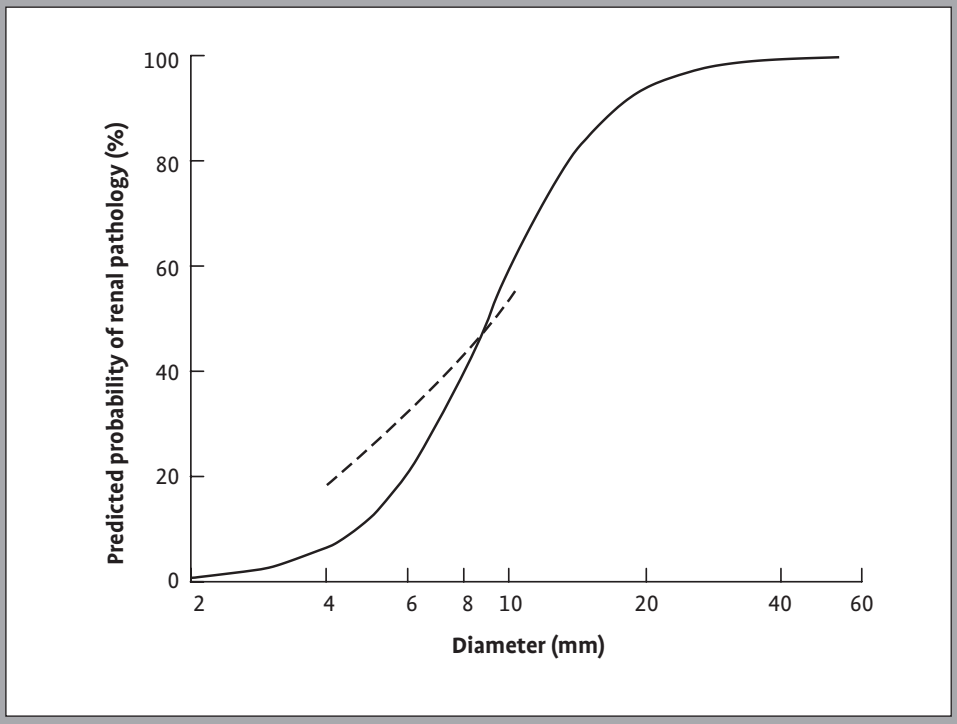
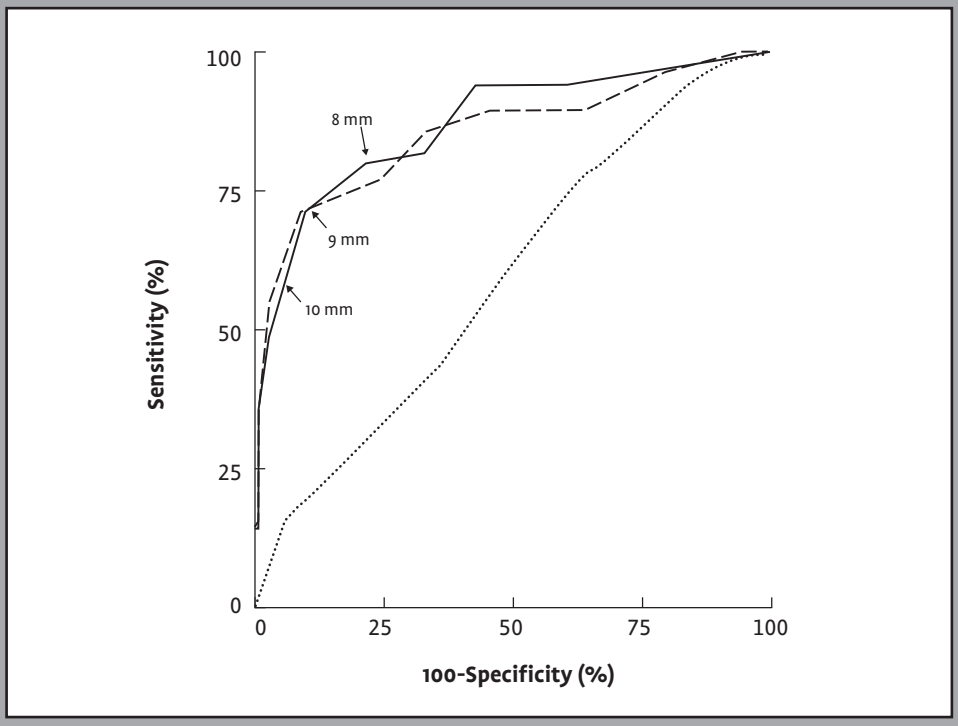


Figure 2 **Receiver-operating characteristics curves for detection of renal pathology according to the renal pelvic anteroposterior diameter measurement at the first scan (dotted line) and the second scan (solid line) and the difference (dashed line) between the two measurements at the first and second scan.**



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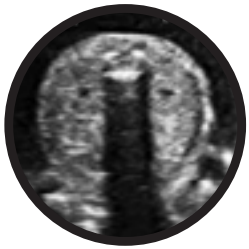

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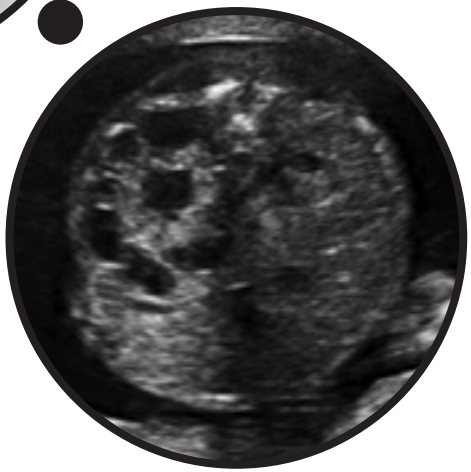

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1 Transverse image of the normal fetal abdomen with the spine at 12 o'clock. Right and left adjacent to the spine the kidney's are visible with a normal size pyelum.
2 Transverse image of the fetal abdomen with the spine at 12 o'clock. The left kidney is normally developed whereas the right kidney shows multiple cysts, consistent with a multicystic dysplastic kidney.
3 Multicystic dysplastic kidney after surgical excision.

5.2

Unilateral multicystic dysplastic kidney: a combined pre- and postnatal assessment

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Abstract

Objectives To review the prenatal assessment of associated renal pathology, non-renal pathology and renal biometry, fetal outcome and postnatal urological management in the presence of unilateral fetal multicystic dysplastic kidney.

Methods A total of 38 singleton pregnancies with fetal unilateral multicystic dysplastic kidney was studied over a 13-year period. Prenatally, fetal biometry, including head and abdominal circumferences and largest longitudinal diameter of the affected and contralateral kidneys, was performed. The amount of amniotic fluid was assessed. Fetal karyotyping was offered in cases of contralateral renal or non-renal pathology. A MAG3 scan and voiding cystogram was performed approximately 4 weeks after delivery to establish renal function and to exclude urinary reflux.

Results Unilateral fetal multicystic dysplastic kidney was left-sided in 53% and right-sided in 47% of cases. The fetus was male in 63% and female in 37% of cases. Associated renal and non-renal pathology existed in 21% and 5% of cases, respectively. The fetal karyotype in these subsets was always normal. The longitudinal diameter of the multicystic dysplastic kidney was above the 95th centile in 87%. There was polyhydramnios in three cases and oligohydramnios in two cases. The prematurity rate was 16%. Postnatal examination revealed a non-functional multicystic kidney in 87% (33/38) of cases. Following surgical removal of the affected kidney, these infants progressed normally. Of the remaining five infants, four died because of associated anomalies and one infant developed normally without surgery.

Conclusions: Fetal outcome is determined by associated renal and/or non-renal structural pathology and not by the size/location of the unilateral multicystic dysplastic kidney or amniotic fluid volume.

Introduction

The multicystic dysplastic kidney (MCDK) is a relatively common form of renal pathology. The MCDK can be unilateral, bilateral or segmental and probably results from atresia of the urethral bud system during embryogenesis[1]. The incidence of MCDK is approximately 1:4300 live births[2,3]. In approximately 20–50%, there are also abnormalities of the contralateral kidney which should also be evaluated. These abnormalities are mostly bilateral multicystic dysplastic kidneys, vesicoureteric reflux, ureteropelvic junction obstruction or renal agenesis[3,4]. Prenatal detection of MCDK allows the pediatric urologist to verify the diagnosis soon after delivery, to monitor the infant for urinary tract infection and to decide on further diagnostic procedures and treatment modalities. We review (i) the prenatal assessment of associated renal pathology, non-renal pathology and renal biometry; (ii) outcome and (iii) postnatal urological management in 38 cases of unilateral fetal MCDK seen in our department over a 13-year period.

Methods

During a period of 13 years, a total of 38 singleton pregnancies was diagnosed with unilateral fetal MCDK. All women were referred to our prenatal center from regional community hospitals for further sonographic analysis. Thirty-four women were referred because of suspected fetal structural pathology at the referring hospital, four women were seen because of a previously affected infant. Details are provided in Table 1. Gestational age at referral was 18–39 weeks (median, 28 weeks). Maternal age ranged between 18 and 41 years (median, 26 years). All ultrasound examinations were carried out on a Toshiba SSA 270 (Toshiba Medical Systems Europe, Zoetermeer, the Netherlands) with 3.5- and 5.0-MHz curvilinear transducers.

Ultrasound evaluation included a detailed anomaly scan of the entire fetus. The diagnosis of MCDK was made from a sagittal and transverse cross-section of the abdomen at the level of the fetal kidneys. MCDK is characterized by normal size, hypoplastic or grossly enlarged kidneys, in which the normal renal parenchyma is replaced by multiple non-communicating cysts that may vary from only a few millimeters to several centimeters in diameter, giving the kidney a distinct hypoechoic appearance[5,6]. The largest MCDK and contralateral longitudinal kidney diameters were measured and data were plotted on the normal reference chart of Romero et al.[7].

Oligohydramnios was defined as a largest fluid pocket of 2 cm or less; polyhydramnios was established when a largest fluid pocket of 10 cm or more was measured. Fetal karyotyping was offered to 12 out of 38 women by means of amniocentesis or cordocentesis because of contralateral renal or non-renal pathology. Fetal biometry included measurement of the biparietal diameter,

head circumference and abdominal circumference. For retrospective data analysis, normal reference charts by Snijders and Nicolaides[8] were used. On the second day following delivery, the infant underwent a confirmatory ultrasound scan of the renal area. A renal scan and voiding cystogram was performed approximately 4 weeks later to establish ipsi- and contralateral renal function and to exclude urinary reflux.

Results

Of our series of 38 patients with unilateral fetal MCDK, 20 (53%) were left-sided and 18 (47%) were right-sided. Twenty-four (63%) fetuses were male and the remaining 14 (37%) were female. Contralateral renal pathology existed in five (13%) out of 38 cases, including three cases of hydronephrosis, one case of ureteral dilatation and one case of renal agenesis. Ipsilateral dilatation of the ureter was established in three (8%) cases. Extrarenal pathology consisted of a case of bilateral cleft lip and a case of combined microcephaly, micrognathia and complicated congenital heart disease.
Fetal karyotyping was carried out through amniocentesis or cordocentesis in 12 cases (31%) because of contralateral renal or non-renal pathology. The chromosome pattern was always normal.
Fetal measurement of longitudinal MCDK diameter was available in 30 cases, with measurements above the 95th centile of the normal reference charts[7] in 26 cases (87%) and within the normal range in four cases (13%).
Measurements of the contralateral kidney length were carried out in 20 cases, of which six (30%) were above the 95th centile, 12 (60%) were within the normal range and two (10%) were below the 5th centile, one because of renal dysplasia.
Fetal abdominal circumference data were available in 32 out of 38 patients. The fetal abdominal circumference was situated above the 95th centile of the normal reference chart[8] in seven cases (22%), was within the normal range in 21 cases (65%) and was below the 5th centile in the remaining four cases (13%).
The amniotic fluid volume was normal in 32 cases (84%). Oligoanhydramnios was established in two cases and polyhydramnios was observed in three cases although the increased amount of amniotic fluid was only temporary in two of these. Amniotic fluid volume was not estimated in one case.
Premature delivery (<37 weeks) took place in six out of 38 cases (16%). Instrumental delivery was performed in nine cases (24%), six of which were cesarean sections because of prolonged labor, fetal distress or breech position. Birth weight was normal in 30 out of 34 cases (88%), below the 2.5th centile in two cases and above the 97.5th centile in two cases. Data on birth weight could not be traced in the remaining four cases.
Postnatal sonographic examination confirmed the presence and location of the MCDK in every case. The infant with multiple congenital anomalies

died soon after delivery. The three cases of prenatally established contralateral hydronephrosis displayed vesicoureteric reflux in two cases and posterior urethral valves in the remaining case. Four infants (11%) developed a urinary tract infection, which was successfully treated. In cases of pre- or postnatal dilatation of the ureter or contralateral kidney, a voiding cystogram was performed 2–4 days following delivery. Renal scintigraphy (diethylenetriaminepenta-acetic acid and recently MAG 3) and voiding cystogram was routinely performed approximately 4 weeks after delivery to determine ipsi- and contralateral renal function and possible renal reflux in the remaining 37 infants. The MCDK was non-functional in 32 cases (86%) but demonstrated some activity varying between 7% and 18% of total renal function in the remaining five cases. Contralateral renal function was normal in all but two infants. In the infant with posterior urethral valves, the contralateral kidney showed dysplasia with diminished function and, in one infant, the contralateral kidney was absent. Vesicoureteric reflux was found in four infants.

Two infants died before surgery was performed (renal failure, epileptic insult). A further two infants were treated expectantly: one infant displayed agenesis of the contralateral kidney and died before the age of 1 year; in the other infant, the MCDK turned out to be so dysplastic that it could not be visualized by ultrasound. This infant subsequently developed normally. In the remaining 33 cases, the MCDK was surgically removed at the age of 3–6 months; in two cases, this included the ipsilateral ureter because of severe vesicourethral reflux. Pathological examination confirmed the diagnosis of MCDK in each case. All infants subsequently progressed normally.

Discussion

MCDK seems to be related to urethral bud abnormalities[9] that lead to abnormal metanephric induction as well as defects involving the genitals, the hindgut and the cloacal derivatives.

The multicystic kidney lacks a discernable pelvis and calices and the abnormality is nearly always associated with atresia at the ureteropelvic junction[10]. Prenatally, the diagnosis of MCDK is only feasible using diagnostic ultrasound.

There is evidence that urological malformations are increasing. This rise may be due to the application of prenatal ultrasound revealing a previously unrecognized group of patients, or reflect the existence of a true increase in the incidence of this entity[11]. Since MCDK is nearly always non-functional, the prognosis depends entirely on the contralateral kidney. In the presence of bilateral MCDK or contralateral renal agenesis, these malformations are nearly always lethal[12].

When both kidneys are involved, the amount of amniotic fluid may be severely reduced because of the virtual absence of fetal urine production.

In the present study, the amount of amniotic fluid was abnormal in five cases. In three cases, there was polyhydramnios which disappeared in two cases during the pregnancy. In the case where polyhydramnios did not disappear, an infant was born with a MCDK, hydroureter and reflux. In one of the two cases of anhydramnios, there was contralateral renal agenesis. The other case was characterized by posterior urethral valves. Kleiner et al.[12], in a series of 27 cases of MCDK, established oligohydramnios in nine and polyhydramnios in two cases. In eight cases, oligohydramnios was associated with bilateral non-functional kidneys; five with bilateral MCDK and three with contralateral renal agenesis. The underlying mechanism for the development of polyhydramnios in the presence of MCDK is unclear.
In the present study, MCDK was left-sided in 53% and right-sided in 47% of cases. These percentages are approximately the same as reported in other studies, where the MCDK tends to be slightly more left-sided[13–15]. In a recent study by Gough et al.[11], left-sided MCDK was established in 63% of cases. In the present study, approximately 90% of the multicystic kidneys were enlarged. The contralateral kidney was enlarged in 30% of cases, 10% of which were a result of hydronephrosis. The remaining 20% represented enlargement of the normal kidney, which most likely reflects a compensatory effect in the presence of a non-functional MCDK. In two cases, the size of the contralateral kidney was below the 5th centile; one of which was the result of a dysplastic kidney. The size of the MCDK was not related to fetal outcome. The contralateral kidney was affected by pathology other than MCDK in 21% of cases, which is similar to a figure of 25% recently established by Lazebnik et al.[16]. However, the percentage of extrarenal abnormalities was five-fold (25%) higher in the latter study compared to our own data (5%), indicating the different populations presented in these studies. In the present study, contralateral renal and extrarenal pathology was associated with a normal fetal karyotype. Both numerical (trisomy 13 and 18) and structural chromosomal abnormalities have been documented by Lazebnik et al.[16] in association with extrarenal pathology. The incidence of extrarenal structural pathology in our study was low (N=2). Whereas, the clinical relevance of fetal chromosome analysis in the presence of contralateral renal pathology is questionable, we advocate fetal karyotyping when extrarenal pathology is established. In the presence of associated renal and/or non-renal structural pathology, the prenatal outcome was poor. Four out of eight infants died because of associated anomalies.
Most cases of MCDK are sporadic malformations. A positive family history is rare, since there is only a small risk of recurrence. However, MCDK may occur as part of the syndrome of hereditary renal A dysplasia (HRA), a predominantly autosomal-dominant abnormality with variable expression[17]. Other inheritance patterns of HRA have been suggested, such as recessive inheritance and X-linked inheritance. MCDK has been described in other syndromes, including the VATER association[18], Williams syndrome[19,49], XXXXX syndrome[20] and branchio-oto-renal syndrome[21]. Since nonrenal

abnormalities also are involved in these syndromes, it is essential to scan the entire fetus when MCDK is diagnosed. Accurate genetic counselling of couples with a family history of MCDK is mandatory.

The most common urological problem after MCDK seen prenatally was dilatation of the ureter (13%) of which 8% was contralateral. Postnatal examination showed that vesicoureteric reflux was the most common urological problem (13%) after MCDK, of which 8% was contralateral. This is somewhat lower than the percentages of contralateral vesicoureteric reflux reported in literature which range between 11% and 28%[16,22,23].

Non-functional MCDK may be removed to avoid the risk of hypertension or malignancy[24], although there is no consensus at present. An expectant non-intervention policy, on the other hand, makes long-term follow-up necessary as the risk of hypertension and malignancy is still uncertain. Cost–benefit studies are presently being carried out, but the outcome depends greatly on the various differences in healthcare systems. Certainly, in those cases with associated pathology of the contralateral kidney, a poorly functioning MCDK does not necessarily have to be removed, although with time most of these kidneys ultimately lose whatever remaining function they initially have. Most pediatric urologists do not feel comfortable to leave a severely dysplastic kidney *in situ*. In these cases, an individual approach is warranted. Because these children only have one functional kidney, which is at risk due to an increased incidence of contralateral abnormalities, a full postnatal evaluation of the urogenital tract has to be carried out and, until these studies are performed, the child should be given antibiotic prophylaxis.

In one infant, the MCDK became so dysplastic that it could no longer be visualized. Earlier follow-up ultrasound studies[16,25,] have documented incomplete or even complete involution of the antenatal MCDK.

It can be concluded that, in the presence of unilateral MCDK, fetal outcome is determined by associated renal and/or non-renal structural pathology and not by the size/location of the unilateral MCDK or amniotic fluid volume. Prenatal knowledge of fetal unilateral MCDK allows optimization of diagnosis and treatment by the pediatric urologist after delivery. Chromosome studies are not needed in cases of isolated fetal unilateral MCDK.

TABLE 1 Referral reasons for fetal anomaly scan

	Number of patients
Suspected renal pathology	30
Dilated bowel loops	1
Fetal cardiac arrhythmia	1
'Double-bubble' phenomenon	1
Suspected urethral stenosis	1
Previous child with	
Dandy Walker syndrome	1
Potter syndrome	1
Congenital heart disease	1
Cleft lip	1

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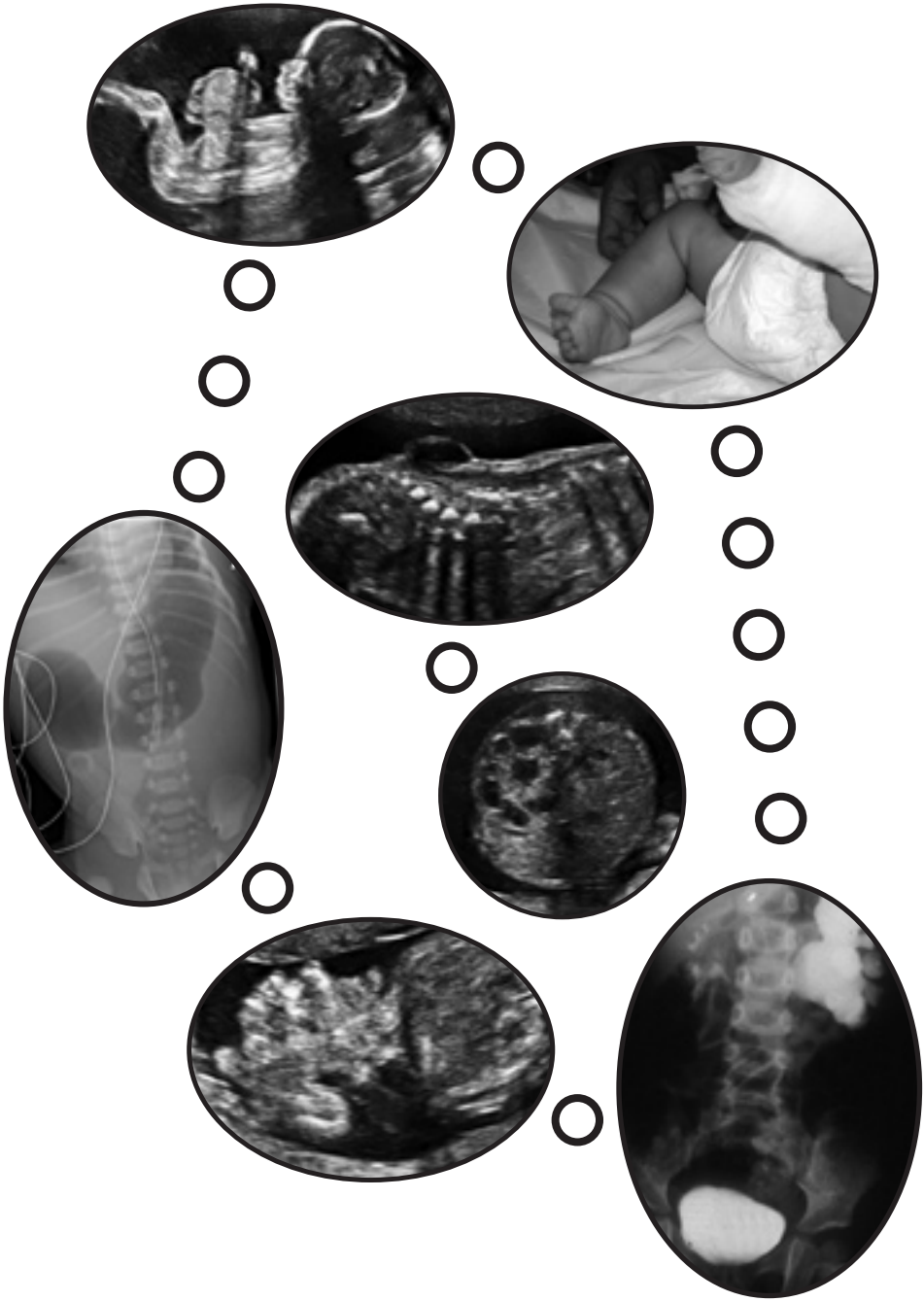

6 General discussion

Introduction

Medical ultrasound is invaluable for the diagnosis of fetal anomalies. Since its introduction in prenatal diagnosis in the 1980's[1], technical progress in ultrasound imaging enabled detection of fetal anomalies with increasing accuracy at earlier stages in pregnancy[2]. Obviously, fetal anomaly scanning would not have been given its prominent position in antenatal care, if it had not resulted in improvement of fetal and maternal welfare. Although a 50% reduction in perinatal mortality was established as a result of ultrasound detection of lethal anomalies, it proved more difficult to demonstrate changes in neonatal morbidity[3]. We therefore approached this subject by looking at the perinatal outcome of a number of different anomalies that were chosen to reflect both lethal and non-lethal anomalies in the context of pre- or postnatal detection. These different situations allow the estimation of the qualitative effect of prenatal detection on mortality and morbidity. Termination of pregnancy for a condition that is lethal postnatally, will not change mortality, when the mortality is not artificially considered separately before or after birth. Morbidity remains unchanged if infants with serious disabilities are allowed to survive. But in these situations mortality will increase if the pregnancy is terminated with as a result a reduction in morbidity. We will now consider the different conditions studied in this thesis separately within this context.

Spina bifida

The spectrum of open isolated spina bifida involves on the one hand a complete rachischisis, with an invariably lethal outcome and on the other hand a minor meningocele without any physical or mental handicap following treatment. The majority of liveborn infants will present with a myelomeningocele and therefore with a certain degree of handicap depending on the spinal level of the defect[4]. Parents faced with this anomaly at a time when management options are still open will in the majority of cases request a termination of pregnancy[5–7]. Not all terminated cases would have resulted in death at birth as a number would have been eligible to treatment. Although improvement in the degree of disabilities or quality of life of affected individuals has been demonstrated, long term morbidity will be unavoidable for the majority of these individuals[8]. One may conclude that prenatal diagnosis of isolated spina bifida prior to 24 weeks of gestation will result in an increased mortality with a decreased morbidity and prevalence of the disease[9]. The audit of prenatal and postnatal diagnosis of isolated open spina bifida in the Netherlands proved that an ultrasound screening policy based on indications will only detect 22% of all cases before 24 weeks of gestation in contrast to the 66% detection rate in the second trimester reported by the Eurocat study[10]. The ultrasound screening policy in the

Netherlands was recently changed to a population based screening policy[11] and it remains to be seen whether as a result of this, the birth prevalence of spina bifida will reduce as much as is reported in other countries[12]. Preconceptional use of folic acid may additionally contribute to a reduction in the prevalence of neural tube defects[13].

Gastrointestinal and abdominal wall defects

Gastro-intestinal and abdominal wall defects represent another group of anomalies for which perinatal outcome was investigated following a prenatal diagnosis or a diagnosis at birth. Gastroschisis and omphalocele are both abdominal wall defects that are easily recognized with prenatal ultrasound.

Gastroschisis

Contrary to omphalocele, gastroschisis is not associated with a high incidence of associated or karyotype anomalies. During pregnancy there is a 10% risk of intrauterine death and another 10% of cases is associated with small bowel atresia which may cause long term morbidity. The timing of the development of associated bowel atresia is not well understood but a recent study reported the development of dilated intra-abdominal bowel loops before 25 weeks of gestation in 8/10 of cases with bowel atresia, suggesting this complication may occur already early in the second trimester[14]. Contrary to spina bifida the majority of parents with prenatal detected cases will continue with their pregnancy. Our study did not reveal a difference in perinatal outcome following a pre- or postnatal diagnosis of liveborn infants, in spite of the fact that 90% of postnatal detected cases was delivered outside our tertiary center. The contribution of prenatal diagnosis to perinatal outcome lies in surveillance protocols with the purpose to detect those cases at risk of intrauterine death or developing complications from intestinal atresia such as perforations. Prenatal diagnosis may thus contribute to a decrease in mortality of this anomaly whereas morbidity will probably remain unaltered.

Omphalocele

As the majority of omphaloceles are either associated with other anomalies or an abnormal karyotype (non-isolated omphalocele) parents often opt for a termination of pregnancy when confronted with this type of anomaly in the second trimester of pregnancy, even if the associated anomalies are not presumed lethal. Isolated omphaloceles form the minority of prenatal detected cases and survival is excellent although again approximately 20% of parents will opt for a termination of pregnancy[15,16]. Surprisingly, in the study presented in this thesis the perinatal outcome of liveborn

infants with prenatally diagnosed isolated omphalocele was considerably worse compared to infants where the anomaly was established only at birth. This was due to larger defects and more liver containing defects in the prenatal subset. Perinatal outcome for liveborn infants with non-isolated omphaloceles did not demonstrate a major difference between the prenatally and postnatally diagnosed infants. Three infants in the postnatal subset died as a result of a concomitant lethal karyotype, however. An indication based ultrasound screening policy will detect those isolated omphaloceles with a more complicated route to recovery. Karyotype anomalies of non-isolated postnatal cases may be missed, with as a result admission to a neonatal intensive care unit and use of medical resources until the aneuploidy is established. From the above data one may conclude that prenatal diagnosis of omphaloceles will contribute to an increase in mortality, at the same time morbidity and the prevalence will be reduced. In our studies of abdominal wall defects only 70% of both omphaloceles and gastroschisis were detected prenatally and a substantial number not before 24 weeks of gestation. Countries with a population based screening policy for congenital anomalies report much higher detection rates[17,18] of these anomalies and as a consequence prenatal diagnosis is likely to have a greater impact on mortality as well as morbidity[19].

Duodenal obstruction

In contrast to the prenatally diagnosed abdominal wall defects, duodenal obstruction (DO) is a gastrointestinal anomaly that presents only with symptoms late in the second or third trimester and in many cases clinical symptoms will only develop after birth. The obstruction can be complete or partial. As is the case with omphaloceles, associated anomalies complicate DO in 50% of cases and another 30% is associated with an abnormal karyotype, particularly trisomy 21. In our study only 30% of cases was detected prenatally of which two prior to 24 weeks of gestation. Both these latter cases were associated with another anomaly or trisomy 21 and the parents requested a termination of pregnancy. Countries with a population based screening policy report a 60% detection rate[20], with the majority of the non-isolated cases detected before 24 weeks of gestation[21]. Both in the isolated and non-isolated form of DO birth weight was significantly lower and prematurity rate significantly higher in the prenatal subsets. For isolated DO this could be explained by the different types of obstruction between the pre- and postnatal subset. Non-isolated DO revealed similar associated anomalies and similar obstructions between both pre- and postnatal subset. The delivery mode was similar for both subsets and other factors such as for instance maternal stress could be responsible for the high prematurity rate of prenatally diagnosed DO. There was no difference in perinatal outcome after surgery between both pre- and postnatal isolated and non-isolated subsets despite the higher prematurity rate in both

prenatal subsets. Adjustment of obstetric management in the prenatal subsets could have contributed to this favorable result. Intrauterine and neonatal death occurred only in the presence of non-isolated DO. In view of the above data one may assume that an ultrasound screening policy based on indications will have a minimal influence on the mortality of the disease whereas the morbidity may improve slightly. If uptake of first trimester screening would be high, a substantial number of Down syndrome cases could be detected. Furthermore a population based ultrasound screening policy could detect approximately 60% of DO cases. Future evaluations of DO are necessary to investigate whether the latter two screening policies have an impact on the mortality, morbidity and prevalence of the anomaly.

Talipes equinovarus (clubfoot)

Compared to the previously discussed abnormalities, talipes equinovarus (TEV) is a more frequently occurring anomaly. Recent prenatal series report an equal occurrence of isolated and non-isolated cases[22,23], the latter in 15% associated with an abnormal, mostly lethal, karyotype. The perinatal outcome of isolated and non-isolated TEV detected prenatally or at birth was investigated. During a 5 year period 131 cases of TEV were studied. Fifty-nine cases (44%) were detected prenatally of which 39 (66%) were non-isolated and only six infants in this latter subset survived. This proportion was different in the postnatal detected subset where only 14% were non-isolated and all these infants survived. Following a prenatal diagnosis of isolated TEV, parents were counseled by a pediatric orthopedic surgeon and after delivery immediate redressement treatment was commenced in the Pediatric Orthopedic Center. Prenatally detected isolated TEV cases received therefore more often a simple type of surgery at an earlier stage with a shorter length of hospital stay compared to isolated cases detected after birth where redressement treatment was commenced in a district general hospital prior to surgery in the Pediatric Orthopedic Center. An indication based ultrasound screening policy would allow less than half of the TEV cases to be detected prenatally, of which the greater part would present with associated anomalies and a poor prognosis. Regions with a population based screening policy for congenital anomalies report higher detection rates[24] with equal proportions of isolated and non-isolated cases[25]. Our data indicated that as long as all infants with isolated TEV are treated in a Pediatric Orthopedic Center prenatal diagnosis for these cases would not be required to reduce morbidity. Generalisation of this finding is, however, critically dependent upon the accurate diagnosis of isolated TEV. Detection of non-isolated cases offers the possibility of additional investigations and adjustment of obstetric management. The mortality and morbidity of non-isolated TEV could thus alter as parents request a termination of pregnancy when confronted with

these anomalies. Although the effect is not estimated to be large, prenatal detection of TEV will lead to an increase in mortality. However, there will be a reduction in morbidity, due to termination of pregnancies in which the TEV is a marker for chromosomal or other associated anomalies.

Urinary tract anomalies

Pyelectasis

Prenatal detection of soft markers such as mild dilatation of the renal collecting system (pyelectasis) has a different impact on the efficacy of prenatal diagnosis. Soft markers are defined as subtle morphological changes that are often transient and have little or no pathological significance. The majority of cases with pyelectasis will resolve during pregnancy or shortly thereafter whereas a minority will develop pathology in need of treatment. When confronted with this knowledge half way through pregnancy, it may create uncertainty for both the pregnant woman and the provider of care but is unlikely to lead to any actions to be taken. Repeated ultrasound scans, to reassure the prospective mother will only increase her anxiety[26]. Boyd et al.[17] reported that soft markers will only marginally increase the detection of anomalies with a substantial increase in the false positive rate. In the working environment, it is impossible to ignore the finding of mild pyelectasis. A management strategy was required in order to determine which fetuses should be referred after delivery for postnatal assessment of the renal system while not unnecessarily increasing the level of anxiety of future parents. The number of infants with a pathologic and normal outcome was determined for different cut-off levels in the third trimester. Our study led to a new protocol for pre- and postnatal surveillance of fetuses with mild pyelectasis. Whilst this approach does not change mortality or morbidity it may change anxiety levels and hence morbidity in the parents.

Multicystic dysplastic kidney

Another relatively easily recognized anomaly is the unilateral multicystic dysplastic kidney (MCDK). The kidney undergoes abnormal development as the connection between the ureteric bud and the methanephros is not properly established. The nephrons produce urine which can not be removed resulting in the formations of many unconnected cysts. This dilated multicystic structure is readily seen by ultrasound and may already be recognized early in the second trimester of gestation. The kidney may shrink in due course and ultimately disappear altogether, sometimes already during pregnancy, but most often later in life. The unilateral nature of the anomaly precludes loss of renal function which is completely taken over by the contralateral kidney. Associated anomalies including contralateral renal malformations determine the prognosis. Our study revealed that vesico-

ureteric reflux is the most common contralateral complication. This may not be recognisable with prenatal ultrasound and a combined pre- and postnatal assessment is therefore indicated. Unilateral MCDK seldom gives rise to clinical symptoms. An indication based ultrasound screening policy will recognize substantially less cases than a population based screening policy where 97% will be detected prenatally[27]. Mortality will not be affected but morbidity will be reduced as contra-lateral renal pathology is recognized and associated complications prevented.

Conclusions

The impact on morbidity and mortality of a population based screening policy can be summarized as follows. In the presence of a lethal anomaly the mortality will not alter but will shift toward an earlier period in gestation. The morbidity associated with an abnormality may be reduced, at least assuming that even with a lethal anomaly infants will survive for a certain period of time. Prenatal termination of non-lethal major anomalies will increase mortality and reduce morbidity. Prenatal management can be adjusted following the detection and continuation of non-lethal major anomalies. Depending on the anomaly, like in gastroschisis, mortality may be reduced, but morbidity will not be altered. Prenatal detection at 18-22 weeks of gestation of major anomalies such a spina bifida, omphalocele and to a lesser extent DO will result in increased mortality and decreased morbidity. For other anomalies such TEV and MCDK, morbidity may be reduced by early commencement of optimal treatment in a pediatric center. Knowledge of the postnatal development of prenatally detected minor anomalies such as mild pyelectasis will ensure selection of those infants at risk of developing pathology. The subsequent prevention of complications carries the capacity to reduce morbidity.

Several studies presented in this thesis demonstrate missed fetal diagnoses in spite of ultrasound investigations. For isolated spina bifida cases established at birth, 12% had been overlooked at a third trimester ultrasound scan in district general hospitals. Furthermore, 39% of prenatal isolated omphaloceles revealed associated anomalies following delivery with consequences for outcome. Of the prenatal cases of duodenal obstruction presumed isolated, 25% revealed additional chromosomal or associated anomalies after delivery. The prenatal isolated subset with TEV contained more infants with bilateral TEV compared to both postnatal subsets. Bilateral TEV is apparently more easily detected by ultrasound than unilateral TEV.

The last three studies were conducted in our tertiary center. The first study underlies the fact that a screening programme can only be successful if carried out by competent sonographers equipped with modern ultrasound machines. Several learning points can be picked up from the false negative diagnoses in a tertiary center. Firstly, rapid postnatal follow up of prenatally

diagnosed anomalies and continuing reporting of postnatal diagnosis obtained from neonatology, pediatric surgery, genetic and post mortem investigations should increase knowledge of the variability in presentation of prenatal anomalies. The increasing number of anomalies detected by prenatal ultrasound will also contribute to the body of knowledge on the natural history of these anomalies. Secondly, continuing education on these subjects for both sonographers in primary care and doctors in prenatal medicine is important for obtaining a high standard upon which future parents can rely. Despite this, it is inevitable that some anomalies will be missed during pregnancy. Health care practitioners should be aware of this inadequacy of prenatal diagnosis when counselling parents.

Suggestions for future research

Relatively few studies[3,24,28-42] have reported on the outcome of congenital anomalies with respect to the timing of diagnosis, the majority of which concerned cardiac anomalies[36,38,40,41]. We propose that the timing of diagnosis of congenital anomalies, whether before of after birth, or early or late in gestation, is further investigated for other organ systems, in order to evaluate the contribution of different prenatal ultrasound screening policies on fetal and maternal welfare. Follow up periods should be longer to evaluate the influence of the timing of detection, and possible change in obstetric management on child development.

Work in this thesis gave rise to a surveillance protocol for fetuses with gastroschisis and a management protocol for mild pyelectasis detected in the second trimester of gestation. Prospective evaluations of these protocols should be performed.

This thesis has concentrated on the medical aspects of pre- or postnatal diagnosis of congenital anomalies. It is generally assumed that prenatal diagnosis of congenital anomalies gives parents and health-care providers the opportunity to prepare for the birth of an infant requiring special attention. Additional information can be acquired and management options can be discussed without the medical or emotional pressure brought about when faced with a critically ill newborn[43]. Parents may experience a different reaction and suffer different degrees of stress when confronted with the fact that their child may not be healthy. It is likely that the use of prenatal diagnosis will only expand. Knowledge about the perception and coping mechanisms of parents, when confronted with the possibility that their child will suffer from a congenital anomaly, is important in order to be able to provide the best possible support during this stressful period. Although a number of studies concerning these matters have been presented[44-47] this field requires more research.

Finally, as stated before, prenatal ultrasound diagnosis has the capability to reduce suffering in infants and parents, although at a price of earlier

mortality. This can only be done when the quality of ultrasound diagnosis is high. It may therefore be questioned if potentially premature release of the procedure in the hands of relatively untrained health professionals like ultrasound technicians or midwifes is effective[48]. This also requires structured training as well as continuing assessment of the role of these professionals. Economic or managerial considerations should not play a role in this before sufficient evaluations have been done.

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Summary / samenvatting

Summary

Ultrasound has made it possible to observe in ever more detail the growth and development of the embryo and fetus. Unfortunately not all embryo's develop normally. In many instances this will result in a miscarriage but if this does not come about the congenital anomalies may be recognized by ultrasound. Minor and major anomalies occur with a frequency of 7 and 2.3%, respectively. Depending on the type of anomaly detection is possible from early, middle or late gestation. However, for a proportion of congenital anomalies such as congenital myopathies or metabolic storage diseases detection by ultrasound is not feasible. In the Netherlands universal population based screening for congenital anomalies was only introduced at the beginning of 2006, which was the reason why prior to this period many congenital anomalies were detected either late in pregnancy or sometimes only at birth. This situation set the scene to investigate whether the outcome of minor and major anomalies is altered by a prenatal detection versus a detection at birth. **Chapter 1** reviews the role of diagnostic ultrasound in Obstetrics and Gynecology and informs on the different types of ultrasound screening policies used to detect congenital anomalies. Targeted screening versus universal population based screening of congenital anomalies using these different methods are discussed. Additionally, the timing of detection is addressed as knowledge of the anomaly before 24 weeks of gestation provides the opportunity for parents to request a termination. Preparing for the birth of a possible critically ill infant in a controlled environment with the presence of a multidisciplinary team is equally important. At the end of the chapter the specific research objective are presented.

Spina bifida is one of the major congenital abnormalities that can be detected by ultrasound. We asked the question what proportion of isolated spina bifida cases an indication based system could detect. The study presented in **chapter 2** revealed that of the isolated spina bifida cases observed over a 4 year period in 3 university hospitals less than 25% was detected before 24 weeks of gestation When faced with the diagnosis at a time that a choice of management in pregnancy is still possible, most parents requested a termination of pregnancy.

The outcome of three major gastrointestinal anomalies diagnosed prenatally or at birth are introduced in **chapter 3**. Two separate abdominal wall defects, gastroschisis and omphalocele, each present a different picture. The association of *gastroschisis* with other anomalies is low but intestinal atresia occurs in 10%. Additionally, approximately 10-15% of all cases die during pregnancy. Perinatal outcome did not reveal a difference for liveborn infants between the pre- and postnatal subset despite the fact that 8/9 postnatal infants were not delivered in our tertiary center, this in contrast to all prenatal diagnosed cases. Intestinal atresia was present in four infants,

three from the prenatal subset and one from the postnatal subset. These four cases experienced more morbidity and a longer length of hospital stay compared to all infants without atresia. The supplementary value of prenatal diagnosis for cases with gastroschisis lies in the recognition of fetuses at risk of a compromising outcome and a surveillance protocol was introduced in order to provide for an optimal outcome.

Omphaloceles are associated with other structural anomalies in 40% of cases and another 50% present with an abnormal karyotype. The defect is classified as isolated (without associated structural anomalies or an abnormal karyotype) or non-isolated. Non-isolated omphaloceles formed 80% of the prenatal cases and the majority (86%) did not survive as a result of termination of pregnancy, intrauterine or neonatal death contrary to the isolated cases where 62% survived. Surprisingly, liveborn infants with a prenatally detected isolated omphalocele displayed a worse outcome compared to infants with a postnatally detected isolated omphalocele. Both the larger sized and more liver containing omphaloceles in the prenatal subset could explain this difference. The outcome for liveborn infants with non-isolated omphaloceles did not reveal a major difference. However, the postnatal non-isolated subset contained three infants who died as a result of a lethal karyotype. An indication based system for prenatal recognition of congenital anomalies could only detect 70% of the abdominal wall defects. Particularly for omphaloceles and to a lesser extent for gastroschisis this policy has consequences for the mortality and morbidity of the disease. Comparable to omphalocele, *obstruction of the duodenum* (DO) is in 50% associated with other structural anomalies and in 30% with an abnormal karyotype, particularly trisomy 21. DO was considered isolated in the absence of other structural anomalies or an abnormal karyotype, whereas in all other cases DO was classified as non-isolated. The DO may be partial or complete and contrary to abdominal wall defects the anomaly is usually only detected by ultrasound late in the second or third trimester. In our study only 28/91 cases (30%) were detected before birth and only two before 24 weeks of gestation. The detection rate is approximately doubled In countries with a population based screening policy where the majority of the non-isolated cases are discovered prior to 24 weeks gestational age. Although liveborn infants from the prenatal isolated and non-isolated subsets had a higher prematurity rate and lower birth weight compared to the postnatal subsets, outcome was similar. The mechanisms responsible for the higher prematurity rate in the prenatal subsets are discussed. With an indication based system for prenatal recognition of congenital anomalies less then half of DO cases are detected before birth and only a minority before 24 weeks of gestation, even in the presence of a substantial number of associated anomalies.

Talipes equinovarus (TEV) is a frequently occurring anomaly and may be isolated or non-isolated. The perinatal outcome of TEV detected prenatally

or at birth is discussed in **chapter 4**. Of the 59 cases detected prenatally, 66% was associated with other structural or chromosome anomalies (non-isolated TEV) and only six infants survived. TEV was detected after birth in 74 infants of which only 13% were non-isolated and all survived. Following the prenatal diagnosis of TEV all infants were treated in a Pediatric Orthopedic Center. The prenatal diagnosis of isolated TEV was associated with less complicated postnatal surgical treatment compared to infants with a postnatal diagnosis where treatment was commenced in a district general hospital. Optimal outcome for infants with isolated TEV is ensured when treatment starts directly after birth in a Pediatric Orthopedic Center.

Anomalies of the urinary tract are presented In **chapter 5**. *Mild dilatation of the renal collecting system* (pyelectasis) is a common finding in second trimester ultrasound. The majority resolves during pregnancy or shortly thereafter. To determine which fetuses should be referred after delivery for postnatal assessment of the renal system, a retrospective study was conducted of 87 fetuses with mild pyelectasis in the second trimester. All fetuses underwent an ultrasound examination in the third trimester and follow up information after birth was arranged. The number of infants with a pathologic and normal outcome was determined for different cut-off levels in the third trimester. This resulted in a new protocol for pre- and postnatal surveillance of fetuses with mild pyelectasis.
The combined pre- and postnatal assessment of 38 cases with a unilateral *multicystic dysplastic kidney* (MCDK) is presented in chapter 5.2. Contralateral renal pathology was revealed in 13% of cases of which the majority demonstrated vesicoureteric reflux. Extrarenal pathology was present in 8%. Outcome was determined by the association of contralateral renal and non-renal pathology and not by the size or location of the unilateral MCDK. Prenatal knowledge of fetal unilateral MCDK allows optimization of diagnosis and treatment by the pediatric urologist after delivery.

Chapter 6 of this thesis is dedicated to the analysis of the different studies and the consequences for perinatal mortality and morbidity. In the presence of a lethal anomaly a population based screening policy will not alter the mortality but shift this toward an earlier period in gestation. The morbidity associated with the abnormality may be reduced. Termination of non-lethal major anomalies will increase mortality and reduce morbidity. Prenatal management can be adjusted following the detection and continuation of non-lethal major anomalies. Depending on the anomaly, for instance in case of gastroschisis, mortality may be reduced, but morbidity will not be altered. Prenatal detection at 18-22 weeks of gestation of major anomalies such a spina bifida, omphalocele and to a lesser extent DO will result in an increase in mortality and a decrease in morbidity of the anomaly. For other anomalies such TEV and MCDK morbidity may be reduced by early commencement of optimal treatment in a pediatric center. Knowledge of

the postnatal development of prenatally detected minor anomalies such as mild pyelectasis will ensure selection of those infants at risk of developing pathology. The subsequent prevention of complications carries the capacity to reduce morbidity.

Samenvatting

Echoscopisch onderzoek heeft het mogelijk gemaakt om de groei en ontwikkeling van het embryo en de foetus met steeds meer detail waar te nemen. Helaas ontwikkelen niet alle embryo's zich normaal. Veelal resulteert dit in een miskraam, maar bij het uitblijven hiervan kunnen eventuele structurele aangeboren afwijkingen door middel van echoscopisch onderzoek worden herkend. Men maakt bij de aangeboren afwijkingen een onderscheid tussen ernstige ('major') en geringe ('minor') afwijkingen. Major aangeboren afwijkingen zijn levensbedreigend, vereisen uitgebreide chirurgie of hebben een ernstige cosmetisch effect. Alle andere afwijkingen worden als minor beschouwd. De frequentie van major en minor aangeboren afwijkingen bij de levend- en doodgeborenen is respectievelijk 2.3% en 7%. Afhankelijk van het soort afwijking is het mogelijk deze vroeg, in het midden of pas laat in de zwangerschap te ontdekken. Een deel van de aangeboren afwijkingen, zoals bij voorbeeld de congenitale spierziekten en stofwisselingsziekten, kan echter niet door middel van echoscopisch onderzoek worden opgespoord. Prenatale screening van de bevolking op structurele aangeboren afwijkingen werd in Nederland begin 2006 geïntroduceerd. Hiervoor werden structurele aangeboren afwijkingen veelal pas laat in de zwangerschap of na de geboorte ontdekt. Deze situatie bood de gelegenheid om te onderzoeken of de uitkomst van minor en major aangeboren afwijkingen verandert na een prenatale diagnose ten opzichte van een diagnose pas bij de geboorte. In **hoofdstuk 1** wordt de rol van het echoscopisch onderzoek in de zwangerschap besproken en wordt informatie gegeven over de verschillende echoscopische screenings methoden om structurele aangeboren afwijkingen op te sporen. Het verschil tussen de toepassing van echoscopie om aangeboren afwijkingen op te sporen bij gericht prenataal onderzoek vanwege een verhoogd risico op aangeboren afwijkingen ten opzichte van prenataal screenings onderzoek van de totale bevolking wordt belicht. Daarenboven komt het tijdstip van detectie van een aangeboren afwijking aan de orde, aangezien bij een diagnose voor een zwangerschapsduur van 24 weken de ouders de mogelijkheid hebben om een verzoek te doen om de zwangerschap te beëindigen. Ook wordt besproken dat een belangrijk aspect van prenatale screening de mogelijkheid is om voorbereid te zijn op de geboorte een eventueel ernstig ziek kind in een gecontroleerde omgeving en in het bijzijn van een multidisciplinair team. Aan het eind van het hoofdstuk worden de afzonderlijke onderzoeksvragen gepresenteerd.

Een *spina bifida* of open rug is een major aangeboren afwijking die door middel van echoscopisch onderzoek kan worden aangetoond. Wij onderzochten welk percentage van de foetussen met een geïsoleerde spina bifida wordt gedetecteerd wanneer het echoscopisch onderzoek op indicatie wordt verricht. De studie in **hoofdstuk 2** laat zien dat van alle casussen met een geïsoleerde spina bifida die over een periode van 3 jaar in drie universiteitsklinieken wer-

den waargenomen minder dan 25% werd ontdekt voor een zwangerschapsduur van 24 weken. Ouders die met deze diagnose waren geconfronteerd op een termijn wanneer nog over het beleid in de zwangerschap mocht worden beslist, kozen voor het merendeel voor een afbreking van de zwangerschap en slechts 2/38 foetussen (5%) bleef in leven. Van de groep die ontdekt werd tussen 24 weken en de geboorte, werden 8 van de 50 zwangerschappen ondanks de late termijn getermineerd omdat de afwijking als lethaal werd beschouwd en 23 kinderen (46%) bleven uiteindelijk in leven. Wanneer de spina bifida bij de geboorte werd vastgesteld (N=65) bleef 79% in leven. De studie toonde aan dat ouders veelal een terminering van de zwangerschap verkozen wanneer deze afwijking voor 24 weken werd aangetoond. Bovendien liet de studie zien dat spina bifida voor de geboorte veelal een ernstiger aspect en somberder prognose heeft dan wanneer deze afwijking pas bij de geboorte aan het licht komt.

In **hoofdstuk 3** wordt de uitkomst besproken van drie major afwijkingen van de buikwand en het maagdarm kanaal die prenataal of bij de geboorte zijn vastgesteld. Twee verschillende buikwanddefecten, gastroschisis en omphalocèle laten ieder een andere uitkomst zien.
Een *gastroschisis* is een paramediaan buikwanddefect, meestal rechts, waardoor de darmen zich vrij in de amnionholte bevinden zonder omgeven te zijn door een vlies. De associatie van gastroschisis met andere structurele afwijkingen is laag maar een darmafsluiting komt bij 10% voor. Intra-uteriene sterfte komt voor bij 10-15%. De perinatale uitkomst toont geen verschil tussen de levendgeboren kinderen met een pre- of postnatale diagnose, ondanks het feit dat 8/9 kinderen met een postnatale diagnose niet in een tertiair centrum zijn geboren in tegenstelling tot alle kinderen met een prenatale diagnose. De toegevoegde waarde van prenatale diagnostiek voor de foetus met een gastroschisis ligt in de mogelijkheid om die foetussen te herkennen die een verhoogde kans hebben op een ongunstige uitkomst. Een bewakingsprotocol werd geïntroduceerd om hiermee een optimale uitkomst te bewerkstelligen.
Een *omphalocèle* is een defect van de buikwand in de umbilicale ring, waarbij abdominale structuren zich buiten de buikwand bevinden, omgeven door een membraan. De afwijking gaat in 40% gepaard met andere afwijkingen en is in 50% geassocieerd met een chromosoomafwijking. De afwijking was geïsoleerd (zonder andere afwijkingen of een chromosoomafwijking) of geassocieerd. De prenatale groep bestond voor 80% uit geassocieerde omphalocèles waarvan het merendeel (86%) niet overleefde als gevolg van een zwangerschapsafbreking, intra-uteriene vruchtdood of neonatale sterfte. Dit in tegenstelling tot de geïsoleerde omphalocèles waarbij 62% in leven bleef. Tot onze verrassing was de uitkomst voor levendgeboren kinderen met een geïsoleerde omphalocèle slechter na een prenatale diagnose in vergelijking tot de kinderen waarbij deze afwijking pas bij de geboorte werd ontdekt. Dit verschil in uitkomst kon verklaard worden doordat de omphalocèles van

de prenatale groep groter bleken en vaker lever bevatten. De uitkomst van levend geboren kinderen met een geassocieerde omphalocèle liet niet een duidelijk verschil zien tussen de pre- en postnataal gediagnosticeerde groep. De postnatale geassocieerde omphalocèle groep bevatte wel 3 pasgeborenen die overleden als gevolg van een letale chromosoomafwijking. Wanneer voor de detectie van aangeboren afwijkingen het echoscopisch onderzoek op indicatie wordt verricht, wordt slechts 70% van de buikwanddefecten prenataal ontdekt. Dit indicatie beleid heeft met name voor de omphalocèle en in mindere mate voor de gastroschisis gevolgen voor de mortaliteit en morbiditeit. Analoog aan de omphalocèle is een obstructie van het *duodenum* (de twaalfvingerige darm) in 50% geassocieerd met andere afwijkingen en in 30% met een chromosoomafwijking, met name trisomie 21. De afwijking werd gerubriceerd als geïsoleerd (zonder andere afwijkingen of een chromosoomafwijking) of geassocieerd. Een obstructie in het duodenum kan partieel of compleet zijn en in tegenstelling tot de buikwanddefecten wordt deze afwijking meestal pas laat in het tweede trimester of in het derde trimester van de zwangerschap met echoscopisch onderzoek ontdekt. In onze studie werden slechts 28/91 (30%) casussen voor de geboorte gedetecteerd waarbij niet meer dan 2 casussen voor de 24ste week van de zwangerschap werden opgespoord. De kans op detectie is verdubbeld in landen met screenings onderzoek op aangeboren afwijkingen van de totale bevolking, waarbij het merendeel van de geassocieerde duodenum obstructies wordt ontdekt voor de 24ste week van de zwangerschap. Hoewel de levendgeboren kinderen met een prenataal bekende geïsoleerde of geassocieerde duodenum obstructie een kortere zwangerschapsduur en lager geboorte gewicht hadden in vergelijking tot de groepen levendgeborenen en dezelfde afwijking, die pas na de geboorte aan het licht kwamen, maakte dit niet uit voor de uiteindelijke uitkomst. De oorzaken voor de hogere prematuriteit bij de prenatale groepen worden besproken. Bij een beleid gericht op indicatie om aangeboren afwijkingen voor de geboorte door middel van echoscopisch onderzoek op te sporen, zal de helft van de casussen met een duodenum obstructie voor de geboorte worden ontdekt en slechts enkelen voor een zwangerschaps termijn van 24 weken, zelfs als er sprake is van geassocieerde afwijkingen.

Een *klompvoet* is een frequent voorkomende afwijking die zich zowel geïsoleerd als geassocieerd presenteert. De perinatale uitkomst van kinderen met een of twee klompvoet(en) ontdekt voor of bij de geboorte wordt besproken in **hoofdstuk 4**. Van de 59 prenataal ontdekte casussen met een klompvoet waren 66% geassocieerd met bijkomende afwijkingen of een chromosoomafwijking (geassocieerde klompvoet). Slechts 6 kinderen van deze groep bleven in leven. Bij de geboorte werd een klompvoet bij 74 kinderen ontdekt. Er was sprake van een geassocieerde klompvoet bij 13% en allen bleven in leven. Nadat de diagnose klompvoet prenataal was vastgesteld, werden alle kinderen behandeld in een orthopedische kinderkliniek. Kinderen met een prenataal vastgestelde klompvoet kregen een eenvoudiger operatie gevolgd

door een kortere opnameduur ten opzichte van kinderen met een klompvoet vastgesteld na de geboorte bij wie de behandeling gestart werd in een algemeen ziekenhuis. De beste uitkomst voor kinderen met een geïsoleerde klompvoet wordt bewerkstelligd als de behandeling direct na de geboorte start in een orthopedische kinderkliniek.

Twee nierafwijkingen worden besproken in **hoofdstuk 5**. Een *milde dilatatie van het nierbekken* wordt frequent gezien in het tweede trimester van de zwangerschap. Het merendeel hiervan verdwijnt vanzelf gedurende de zwangerschap of kort daarna en bij slechts enkele kinderen zal een operatie noodzakelijk zijn. Om te bepalen welke kinderen na de geboorte verwezen moeten worden vanwege een grote kans op afwijkingen aan nieren en urinewegen werd retrospectief een onderzoek gedaan bij 87 foetussen met een milde dilatatie van het nierbekken in het tweede trimester van de zwangerschap. Bij alle foetussen werd het echoscopisch onderzoek van de nieren herhaald in het derde trimester en voor allen was follow-up tot minimaal 1 jaar na de geboorte beschikbaar. Voor de verschillende metingen van het nierbekken in het derde trimester van de zwangerschap kon het aantal kinderen met een normale en pathologische uitkomt worden bepaald. Met deze informatie kon een nieuw protocol voor pre- en postnataal beleid bij foetussen met een milde dilatatie van het nierbekken worden opgesteld.
De gecombineerde pre- en postnatale beoordeling van 38 casussen met een unilaterale *multicysteuze nierdyplasie* komt vervolgens aan de orde. Een multicysteuze nierdysplasie is een nier waarbij het grootste deel van het weefsel is vervangen door cystes waardoor de nier niet functioneert. Contralaterale nierpathologie werd bij 13% waargenomen waarvan het merendeel bestond uit vesico-urethrale reflux. Andere dan nierafwijkingen werd bij 8% aangetroffen. De uitkomst werd bepaald door de contralaterale nierpathologie en de geassocieerde andere afwijkingen en niet door de grootte of plaats van de unilaterale multicysteuze nierdyplasie. De diagnose en behandeling door de kinderuroloog wordt gunstig beïnvloed wanneer deze voor de geboorte reeds op de hoogte is van het bestaan van een unilaterale multicysteuze nierdyplasie.

In **hoofdstuk 6** van dit proefschrift wordt de invloed van de verschillende studies met betrekking tot perinatale morbiditeit en mortaliteit besproken. Bij een letale afwijking zal screenings onderzoek van de totale bevolking naar aangeboren afwijkingen de mortaliteit niet veranderen, maar de termijn hiervan naar een vroeger tijdstip in de zwangerschap verplaatsen. De morbiditeit kan hierdoor wel afnemen. Het afbreken van de zwangerschap bij een niet letale afwijking zal de mortaliteit doen toenemen maar daarmee de morbiditeit verminderen. Het obstetrisch beleid kan worden aangepast nadat een niet letale afwijking is aangetoond en de zwangerschap wordt voortgezet. Afhankelijk van het soort afwijking, zoals bij voorbeeld bij een gastroschisis, kan de mortaliteit worden verlaagd terwijl de morbiditeit nauwelijks

verandert. Het prenataal vaststellen bij een zwangerschapsduur tussen 18 en 22 weken van major aangeboren afwijkingen, zoals spina bifida, omphalocèle en in mindere mate een duodenum obstructie, zal de mortaliteit doen toenemen, waarbij de morbiditeit afneemt. Voor andere afwijkingen, zoals geïsoleerde klompvoeten en unilaterale multicysteuze nierdyplasie, kan de morbiditeit afnemen door na de geboorte vroeg te starten met de behandeling in een centrum voor kindergeneeskunde. Wanneer men op de hoogte is van het postnatale beloop van prenataal vastgestelde minor afwijkingen, zoals een dilatatie van het nierbekken, is het mogelijk alleen die kinderen na de geboorte te verwijzen waarbij een grote kans bestaat op het ontwikkelen van pathologie. Door het voorkomen van complicaties kan de morbiditeit afnemen.

Curriculum Vitae

After secondary school at the Werkplaats Kindergemeenschap in Bilthoven, Titia Cohen-Overbeek (1954) started her medical studies at Leiden University in 1972. During her studies she did practical work in the Tel Hashomer Hospital, Tel Aviv, Israel and in the Department of Pediatrics at the Hammersmith Hospital in London, England. She obtained her medical degree in 1980. From March 1980 until November 1981 she worked as a resident at the department of Obstetrics and Gynecology in the Bronovo Hospital, The Hague. She moved to London in 1981 and worked in family planning clinics for the Lewisham Area Health Authority and Brook Advisory Centers in the South London area. In the meantime she commenced research in the field of Doppler ultrasound and prenatal diagnosis at Kings College Hospital, London, supervised by professor Stuart Campbell, where she remained as a part-time investigator until May 1987. From November 1987 she continued her work in prenatal diagnosis at the Department of Clinical Genetics (head Professor Dr. H. Galjaard) and the Department of Obstetrics and Gynecology, Division of Obstetrics and Prenatal Medicine (Professor Dr. J.W. Wladimiroff, Professor Dr. E.A.P. Steegers) of the Erasmus University Rotterdam. For her work she obtained three awards. The prize for the best clinical paper in volume 11 of Ultrasound in Medicine and Biology in 1985, the Dutch Organon ultrasound prize in 2000 for her contribution to prenatal ultrasound between 1998 and 2000 and the 2nd prize for all posters contributed at the 13th World Congress on Ultrasound in Obstetrics and Gynecology in Paris 2003 for the poster entitled ‘Mild renal pyelectasis in the second trimester; determination of cut-of levels for postnatal referral’. She is married to Adam and the mother of Danielle, Sophie and Ben.

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