

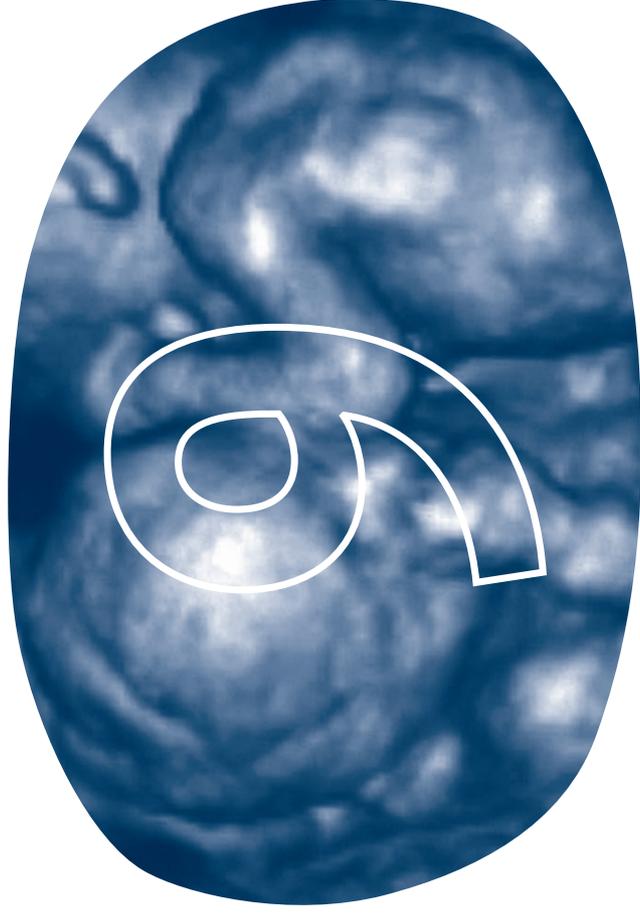
Table 1 Median MoM free β -hCG and PAPP-A in uncomplicated MC twin pregnancies and MC twin pregnancies complicated by TTTS

	MC uncomplicated (n 39)	MC TTTS (n 12)	p-value
Median MoM free β -hCG	1.53	1.99	0.32
Median MoM PAPP-A	1.69	1.94	0.51

MC – monochorionic; **MoM** – Multiple of the Median; **TTTS** – Twin-to-Twin Transfusion syndrome; **hCG** – human Chorionic Gonadotropin; **PAPP-A** – pregnancy associated plasma protein-A

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Expectant management in multiple pregnancies with discordant structural fetal anomalies

Submitted

Abstract

• • • Objective

Routine obstetric ultrasound increasingly leads to the detection of structural fetal anomalies. In multiple pregnancies with one anomalous twin, counselling on management strategies is complicated.

• • • Patients and methods

Twin pregnancies (n=23) referred to a tertiary center between January 2007 and July 2009. In a retrospective analysis, twins discordant for a structural fetal anomaly were compared with twins without anomalies on prenatal ultrasound. Outcome parameters were survival and gestational age at birth.

• • • Results

Anomalies were seen in at least one fetus of 34 twin pairs (8.5%), predominantly central nervous system (n=5), skeletal (n=7), urinary tract (n=6) and cord anomalies (n=5). Multiple anomalies were present in 4 fetuses of which 3 had trisomy 13. Selective feticide using potassium chloride was performed in 3 cases of major but non-lethal anomalies in dichorionic twins. The remaining 29 cases were managed expectantly. In 3 of these cases, spontaneous fetal loss was observed. In 5 cases with major (lethal) anomalies pregnant women and their partners opted for non-intervention comfort care for the affected fetus. Median gestational age at delivery for twins without structural anomalies (255 days) and twins with one anomalous fetus (256 days fetus (n=26), this was not significantly different (Mann-Whitney U, p=0.65).

• • • Conclusion

In this cohort we experienced the request for expectant management by pregnant women and their partners of those twins discordant for major (lethal) anomalies. Feticide was only opted in a small number of cases with severe but non-lethal anomalies in dichorionic twins.

Introduction

Obstetric ultrasound is becoming routine in pregnancy care, with increasing frequencies in all trimesters of pregnancy with various indications. In the Netherlands, two scans are standard in each pregnancy. A viability and dating scan is conducted in the first trimester, at which multiple pregnancies and its chorionicity should also be detected. Secondly, a Standard Anomaly Scan (SAS) at 18-22 weeks' gestational age is offered to all women since January 2007 with primary aim to detect neural tube defects. Additionally, all pregnant women are offered Down syndrome screening, with first trimester combined screening as policy of choice.

Twin pregnancies are at increased risk for adverse pregnancy outcome compared with singletons for both fetal and maternal conditions. In particular monozygotic twins are at increased risk for structural/fetal anomalies compared with singleton pregnancies, in which predominantly congenital heart defects, neural tube defects and skeletal malformations are more frequently seen^{1,2}. In both dizygotic and monozygotic pregnancies, discordance (only one fetus affected) for structural anomalies occurs. In case of discordance for fetal anomalies in multiple pregnancies, counselling on management options is complex. Selective feticide involves an invasive procedure with inherent risk of complications and loss of the unaffected co-twin. In addition, the presence of a dead co-twin may increase the risk for preterm birth³. Complete termination of a multiple pregnancy is generally only opted for in case of concordant anomalies. Finally, expectant management of the pregnancy is an uncertain choice and still bears the usual risks of multiple pregnancies like preterm birth and increased incidence of preeclampsia. Our aim was to analyze the outcome of multiple pregnancies with discordant structural anomalies in a consecutive cohort of twins referred for ultrasound examination following the implementation of the SAS in the Netherlands.

Patients and Methods

The ultrasound database of our tertiary referral center was searched for multiple pregnancies between January 1st 2007 and July 1st 2009. The database consisted of standard anomaly scans from patients booked for routine antenatal care in our center and patients who were referred for diagnostic targeted ultrasound because of suspected fetal anomalies. All pregnancies were dated on last menstrual period, confirmed or adjusted by first trimester crown-rump length measurement. In cases of assisted reproduction, ovum-pick-up date or insemination date determined the gestational age. Chorionicity was always classified at first-trimester ultrasound by absence or presence of a λ -sign at the inter-twin membrane-placental junction⁴. All ultrasound data were analyzed for the presence or absence of fetal anomalies and classified to anomalies of the central nervous system, cardiovascular system, thorax, abdomen (wall), urinary tract, face, skeleton and placenta/cord/membranes. Major

anomalies were considered those unusual anatomic features that are of serious medical or cosmetic consequence to the patient, i.e. anomalies that require intervention or surgery or had significant impact on neonatal morbidity and mortality. All scans were performed by experienced staff using a Voluson E8 with a 4-8 MHz abdominal transducer or a 6-12 MHz transvaginal transducer (GE Medical Systems, Kretz, Austria). If fetal anomalies were suspected, patients were counseled concerning associated risk for chromosomal anomalies, where appropriate in case of a structural anomaly and informed about the iatrogenic risks of invasive testing. After counseling they opted for, or refrained from invasive testing. Pregnancy outcome was obtained from our electronic medical records. For analysis twins were subdivided for chorionicity and classified as normal if both fetuses demonstrated no anomalies at ultrasound and no history of Twin-to-Twin Transfusion syndrome or severe growth restriction that required intervention or vanishing twin was present. In the discordant cases only one fetus demonstrated fetal anomalies at ultrasound. If both fetuses were affected those pregnancies were classified as concordant and excluded from further analysis. Primary outcome measurements were survival percentage of the healthy twin and gestational age at delivery.

• • • Statistical analysis

In this observational retrospective cohort study patient characteristics of all pregnancies are presented as mean (SD), median (range) values and percentages as appropriate. Differences between the groups (normal vs. fetal anomaly) were tested for significance with non-parametric tests. Statistical analyses were performed using SPSS version 15.0 (Chicago, IL, USA). *p*-values <0.05 were considered to be significant.

Results

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In total 231 multiple pregnancies comprising 470 fetuses, were scanned during the study period, with follow-up data in 94% of the cases. Table 1 shows an overview of the classification of chorionicity of the 231 multiple pregnancies. Table 2 describes maternal and pregnancy characteristics of the group for maternal age, gestational age at the time of the ultrasound examination, parity and mode of conception. Table 3 gives an overview of the anomalies subdivided for chorionicity for the twin pregnancies and classification as major or minor anomaly. Mean gestational age at detection of the anomalies was 19-20 weeks of gestation. In 38 twin fetuses (34 twin pregnancies), structural anomalies were detected. Of these structural anomalies, 18 were classified as single major anomalies. In four fetuses, multiple anomalies were seen (see Table 3 and 4). Anomalies were most common of the skeleton (n=7), urinary tract (n=6), central nervous system (n=5) and umbilical cord (n=5). Of the 4 fetuses with multiple congenital anomalies, 3 had trisomy 13. In 9/34 (26%) twin cases, pregnant women and their partners opted for invasive testing after the ultrasound diagnosis of a major fetal anomaly. In none of the cases with a minor fetal anomaly pregnant women and their partners opted for invasive testing. In 4 of the cases with a major fetal anomaly karyotyping was performed within the same

Table 1 Classification of chorionicity

	Chorionicity	n
Twins (223)	-MCMA	6
	-MCDA	62
	-DC	155
Triplets (8)	-MCTA	2
	-DCTA	3
	-TCTA	3

MCMA – monochorionic monoamniotic; **MCDA** – monochorionic diamniotic; **DC** – dichorionic; **MCTA** – monochorionic triamniotic; **DCTA** – dichorionic triamniotic; **TCTA** – trichorionic triamniotic

Table 2 Maternal and pregnancy characteristics

	n	231
Mean ± SD maternal age at US (years)		33.8±4.5
Median GA at US (days) (range)		140 (57-241)
Parity		
primipara (%)		48
multipara (%)		49
not reported (%)		3
Conception		
naturally conceived (%)		65
OI/IUI (%)		7
IVF/ICSI (%)		23
not reported		5

OI – ovulation induction; **IUI** – Intra Uterine Insemination; **IVF** – In Vitro Fertilisation; **ICSI** – Intra Cytoplasmatic Sperm Injection

session as the fetocide. In a congenital cystic adenomatoid malformation (CCAM) case with hydrops, karyotyping was performed during thoraco-amniotic shunting. In total 8/231 multiple pregnancies were triplets. In a monochorionic triamniotic triplet, two individual fetuses had ventriculomegaly. One of these fetuses had an increased nuchal translucency with a normal male karyotype. This pregnancy ended in spontaneous birth at 24+0 weeks of gestation, with neonatal demise of both twins. In the 7 other triplet pregnancies, no fetal anomalies were detected. Triplets were excluded from further analysis. All suspected fetal anomalies were confirmed after birth. In one case, a complete situs inversus with a small ventricular septum defect was not detected prenatally in a monoamniotic twin. Furthermore in a case of a dilated bowel, a tetralogy of Fallot was missed in a MC twin.

Table 3 Overview of isolated structural anomalies in twins subdivided for chorionicity and classified as major or minor anomaly

Anomaly	MC	DC	Total	Major	Minor
Central nervous					
- Neural tube defects: spina bifida		3			
- Ventriculomegaly/hydrocephalus		2	5	5	
Cardiovascular					
- Hypoplastic left heart		2			
- Atrial-ventricular septal defect		1	3	3	
Thoracic					
- Cystic adenomatoid malformation	1	1	1	1	
Abdominal (wall)					
- Exomphalos		2			
- Bowel obstruction/atresia		1			
- Intraabdominal cyst	1		4	3	1
Urinary tract					
Obstructive uropathy					
- mild		2			
- severe		1			
Cystic renal disease					
- unilateral		1			
- bilateral		1			
Bladder exstrophy		1	6	3	3
Facial					
- clefting		1	1	1	
Skeletal					
- Deformities of feet (talipes)	2 (cond)	4			
- other (athrogyposis multiplex)		1	7		7
Placenta/cord/membranes					
- single umbilical artery (SUA)	2	3	5		5
Other					
- conjoint twin	2 (cond)		2	2	
Total	8	26	34	18	16

Cond – concordant; **DC** – dichorionic; **MC** – monochorionic

Table 4 Twins with multiple congenital anomalies and outcome

Case	Anomalies	Karyotype	Outcome
I disc DC	AVSD, exomphalos, polydactyly, polycystic kidneys	T13 disc	Spontaneous demise at 21 weeks
II+III cond MC	Holoprosencephaly, facial clefting, polycystic kidneys, polydactyly	T13 cond	Induced labour at 22 weeks
IV disc DC	Ventriculomegaly, obstructive uropathy, talipes, SUA	Normal male Karyotype	CD at 34+2

AVSD – atrio ventricular septal defect; **Cond** – concordant; **DC** – dichorionic; **disc** – discordant; **MC** – monochorionic; **SUA** – single umbilical artery; **CD** – caesarean delivery

... Selective fetocide /pregnancy termination in discordant twins

Selective fetocide with intracardiac potassium chloride was performed on request of the pregnant women and their partners in 3 cases of severe but non-lethal anomalies in DC twins (2 spina bifida /1 bladder exstrophy). No pregnancy loss was observed after the procedure and all 3 pregnancies delivered at term. In two MC pregnancies (concordant trisomy 13 and conjoint twin), the complete pregnancy was terminated on request of the parents. No requests for complete pregnancy termination were seen in case of discordant anomalies.

... Conservative management in discordant twins

The remaining 29 pregnancies were managed conservatively after parental counselling. In 3 cases (discordant trisomy 13 and 2 cases of exomphalos without fetal karyotype), spontaneous fetal demise of the affected twin occurred at 22+0, 14+4 and 17+1 weeks' gestation, respectively. In 5 cases with likely lethal anomalies, pregnant women and their partners opted for neonatal non-intervention comfort care for their infant. These neonates died shortly after birth, four cases within 24 hours. Their co-twin, without anomalies, had good outcome in all cases (see Table 5). Median gestational age at delivery were not significantly different for twins without structural anomalies (255 days) and twins with one anomalous fetus without fetal loss (256 days (n=26)) (Mann-Whitney U, p=0.65). Subdivided for classification of the anomaly: 258 days for a minor anomaly (n=14); median 254 days for major anomaly (n=12) (Table 6). Excluded from this analysis in the normal group were 10 MC twin's cases complicated by Twin-to-Twin Transfusion syndrome or severe growth restriction that required laser therapy or umbilical cord coagulation and two cases of late vanishing twins.

Table 5 Outcome of expectant management in 5 cases in with severe or lethal discordant anomalies

GA at delivery	Delivery	Sex	Birth weight (gram) and percentile	Outcome
I DC	CD, breech	♀	2926 (p20-50)	Uneventful
	CD, breech	♂	2108 (p<2.3)	ND, bilateral multicystic kidney disease
II DC	CD, breech	♀	2575 (p5-10)	Uneventful
	CD, breech	♀	2200 (p<2.3)	ND, hypoplastic left heart syndrome
III MC	CD, CP	♀	2095 (p20-50)	Uneventful
	CD, CP	♀	1815 (p5-10)	ND, CCAM * intra uterine thoraco-amniotic shunt
IV DC	Vag, CP	♂	2426 (p20-50)	Uneventful
	Vag, breech	♂	2247 (p10-16)	ND, hypoplastic left heart
V DC	CD, breech	♂	2450 (p2.3-5)	Uneventful
	CD, CP	♂	2000 (p<2.3)	ND, bilateral dysplastic kidneys, megacystis

CCAM – congenital cystic adenomatoid malformation; **CD** – caesarean delivery; **CP** – cephalic position;

DC – dichorionic; **GA** – gestational age; **MC** – monochorionic; **ND** – neonatal death; **Vag** – vaginal delivery

Table 6 Gestational age distributions at delivery subdivided for twins without anomalies and minor/major anomalies

	No structural anomalies n 177	Minor anomalies n 14	Major anomalies n 12	p
Median (range) GA at delivery (days)	255 (154-280)	258 (162-273)	254 (224-273)	0.24
- Before 24 weeks (n) (%)	7 (3.9 %)	1 (7.1%)	0 (0%)	0.57
- Before 28 weeks (n) (%)	11 (6.2 %)	1 (7.1%)	0 (0%)	0.62
- Before 32 weeks (n) (%)	25 (14.1 %)	3 (21.4 %)	0 (0%)	0.35
- Before 36 weeks (n) (%)	75 (42.4 %)	5 (35.7 %)	5 (41.6 %)	0.62

Discussion

In this multiple pregnancies cohort, 38 anomalies were found in 446 twin fetuses (8.5%), of whom 18 were classified as major and in four cases had multiple anomalies. This retrospective cohort study confirms the known increased risk on fetal anomalies in multiple pregnancies¹². In multiple pregnancies with severe or lethal anomalies, the pregnant women and their partners are faced with more difficult considerations than in singleton pregnancies. Management options in twin pregnancies with anomalies are either selective fetocide of the anomalous twin, complete termination of the pregnancy or expectant management. All these options affect the live born changes for the unaffected fetus and are discussed in the following paragraph.

... Selective fetocide

Selective fetocide is associated with the unwanted risk of pregnancy loss of the unaffected 'normal' co-twin. The technique of selective fetocide is dependent on the chorionicity of the multiple pregnancies. In dichorionic twin's, intracardiac or intraumbilical injection of potassium chloride (KCl) is currently the best option to initiate fetal asystole. Evans et al. (1999) studied multiple pregnancies in which selective termination by KCl was performed in case of chromosomal/structural or mendelian disorders with an overall complete pregnancy loss before <24 weeks of 7.5% in all procedures. Loss rates of this procedure for gestational age were in week 9-12: 5.4%; week 13-18: 8.7%; week 19-24: 6.8% and > 25 weeks: 9.1%. Analyzing only twin pregnancies with 2 to 1 selective reduction, the overall loss rate before 24 weeks was 7.0%, and after 24 weeks 0.9%. Besides the loss rate, 2 to 1 selective reduction is also associated with a 4.6% premature delivery rate between 25-28 weeks of gestation³. Combined data lead to a complication risk in a >21 procedure before 28 weeks of almost 12%, and before 32 weeks of almost 20%. In other studies, overall direct loss rates are reported of less than 5%, however, no loss reports are given in selective termination before and after 20 weeks of gestation^{5,6}. Due to the presence of vascular anastomoses in the placenta of monochorionic twins, KCl is no option for selective termination. A technique in which the arterial and venous flows in the umbilical cord of the affected twin are occluded completely and permanently is needed. Different techniques are used for selective fetocide in MC twins including endoscopic ligation, laser coagulation or bipolar coagulation of the umbilical cord of the affected twin, and intraabdominal coagulation of the umbilical vessels using interstitial laser or radiofrequency ablation. The method of choice is mainly dependent on local experience and parental preference since the literature is not conclusive on the best method for selective fetocide⁷.

... Conservative management

In case of lethal or severe malformations, the risk of selective termination to the normal co-twin should be weighted against the risk of the continuing development of the affected twin. The possibility of expectant management can be addressed in counselling patients in case of lethal malformations. However, expectant management is being criticized because of a possible association with premature birth⁸⁻¹⁰.

In the study of Malone et al. (1996), the mean GA at delivery of twins with one anomalous fetus (n=14) was 33+6 weeks compared with 35+6 weeks in the control group of twins (n=78). Very early delivery occurred in only 1 of the 14 anomalous twins at 28 weeks of gestation. The risk of delivery at 36 weeks or less was 78.6% for single anomalous twins vs. 59% for the control group⁸. A larger case-series reports on 18 twins discordant for major anomalies and 38 twins discordant for minor anomalies. A significant lower gestational age at delivery was found (32 weeks vs. 35 weeks)¹⁰. Nassar et al. (2000) found that one anomalous fetus in a twin pregnancy significantly increases the risk of preterm delivery at <37 weeks gestation. However, no difference was found in rate of delivery before 34 weeks of gestation⁹. For lethal anomalies such as anencephaly, a recent review on 86 DC twin cases with discordant anencephaly found a median GA at delivery of 38.0 weeks in cases after selective termination and 36.0 weeks in the cases with expectant management. Survival of the normal co-twin was not different in the selective termination group and expectant management group¹¹. Since anencephaly is associated with decreased swallowing of the fetus, the development of polyhydramnios as additional risk factor for premature delivery is more likely with anencephaly than with other structural anomalies. Others report no significant association between discordant anomalies in twins and outcome^{12,13}.

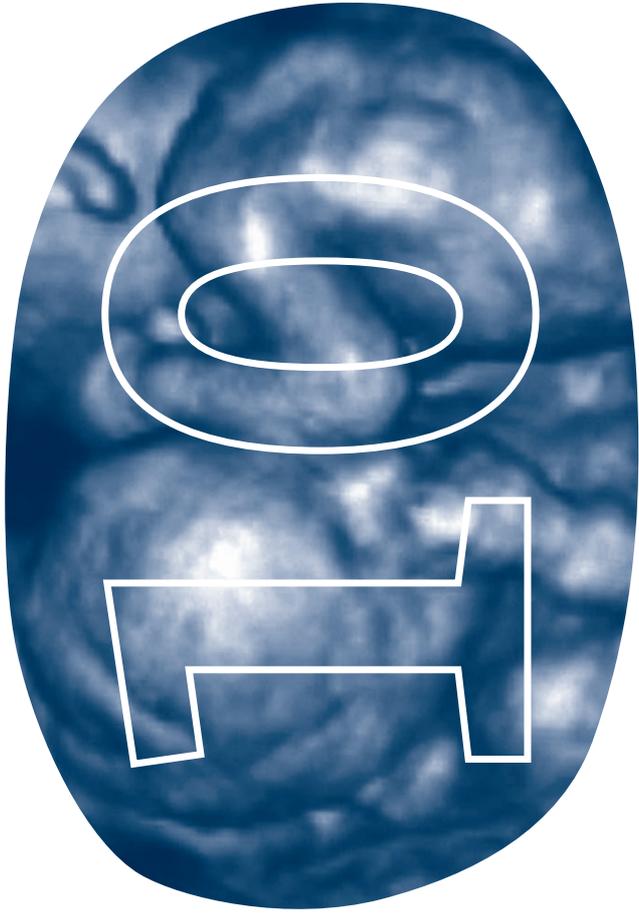
The most recent report on this topic with 3307 single affected fetus in twins, found a weak but statistically significant association with gestational age at birth (35.84 week in uncomplicated group vs. 35.07 weeks in the group with a single anomalous fetus), low birth weight and neonatal outcome¹⁴. Although this study was published in 2009, it describes a cohort from 1995-1997. Furthermore, the study was not subdivided for chorionicity. Moreover, birth weights were not corrected for gestational age. Overall in expectant management of MC twins caution is advised since spontaneous loss or intrauterine death of the affected fetus can cause demise or severe morbidity in the co-twin¹⁵.

In our study, median gestational age at delivery was not significantly different for both normal twins and twins with a single anomalous fetus. A possible explanation is that our report describes a more recent population with different strategies aimed to delay premature birth and early identification of premature birth, such as routine measurement of cervical length in multiples. All papers correspond in one way that although some report an overall increase in premature delivery rates, it is not associated with extreme premature birth with associated morbidity and mortality for the unaffected co-twin. Selective fetocide is both associated with loss related to the procedure but also with increased premature delivery rates. The complication risk of 20% before 32 weeks described by Evans et al is comparable with the data of our study: spontaneous loss rate of 3/29=10.3% in case of a single anomalous twin managed expectantly and the risk of delivery before 28 weeks (1/26=3.8% minor+major) and 32 weeks (3/26=11.5%). In our study, we find a tendency of patient choice towards conservative management of those twins discordant for very severe or lethal anomalies to avoid the risk of selective fetocide for the unaffected co-twin.

In 5 cases with major severe or lethal anomalies patients opted for non intervention, comfort care for the affected fetus. In all 5 cases, the outcome of the unaffected co-twin was good, whereas all affected twins died shortly after birth. For future studies structured follow up of the unaffected twin is desirable also including long term follow up. In 3 conservatively managed cases, spontaneous fetal loss was observed. For fetal fetocide was only opted in a small number of cases with severe but non-lethal anomalies in DC twins. Termination of the complete pregnancy was only performed in MC twins with concordant anomalies. Currently, data on selective and conservative management in a randomised setting are not available. However, in our opinion expectant management is a feasible management option in severe or lethal anomalies if requested by the patients.

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General discussion and perspectives