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Expectant Management in Twin Pregnancies With Discordant Structural Fetal Anomalies

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Objective: Routine obstetric ultrasound increasingly leads to the detection of structural fetal anomalies. In twin pregnancies with one anomalous twin, counseling on management strategies is complicated. *Patients and methods:* Twin pregnancies (n = 212) were referred to a tertiary center between January 2007 and July 2009. In a retrospective analysis, twins discordant for a structural fetal anomaly were compared to twins without anomalies in the prenatal ultrasound. Outcome parameters were survival and gestational age at birth. *Results:* Anomalies were seen in at least one fetus of 30 twin pairs. The two pregnancies in which the anomalies were concordant were terminated. Selective feticide was performed in three cases of major but non-lethal anomalies in dichorionic twins. The remaining 25 cases were managed expectantly. In three of these cases, spontaneous fetal demise of the affected fetus was observed. In five cases with major (lethal) anomalies, the pregnant women and their partners opted for non-intervention comfort care after birth for the affected fetus. Median gestational age at delivery was 257 days for twins without structural anomalies and was 254 days (n = 22) for twins with one anomalous fetus. This was not significantly different (Mann Whitney U, p = .69). Again, no difference was found for median gestational age at delivery in normal vs. discordant anomalous dichorionic twins if subdivided for chorionicity (Mann Whitney U, p = .68). *Conclusion:* In this cohort we describe the request for expectant management by pregnant women and their partners of those twins discordant for major (lethal) anomalies. Expectant management was not associated with increased risk of premature delivery. Fetocide was only opted for in a small number of cases with severe but non-lethal anomalies in dichorionic twins.

■ **Keywords:** twin pregnancy, structural anomalies, neonatal outcome

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 their chorionicity should also be detected. Second, a Standard Anomaly Scan (SAS) at 18–22 weeks' gestational age is offered to all women since January 2007 with the primary aim of detecting neural tube defects. All pregnant women are offered Down's syndrome screening, using NT-measurement combined with serum PAPP-A and free β-hCG.

Twin pregnancies are at increased risk for adverse pregnancy outcome compared to singletons. In particular, monozygotic twins are at increased risk for structural fetal anomalies compared to singleton pregnancies, in which predominantly congenital heart defects, neural tube defects and skeletal malformations are present (Bahtiyar et al., 2007; Hall, 2003). In both dizygotic and monozygotic pregnancies, discordance (only one fetus affected) for structural anomalies occurs. In case of discordance for fetal anomalies in twin pregnancies, counseling on management options is complex. Selective fetocide 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 birth (Evans et al., 1999). Complete termination of the

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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 twin 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

All multiple pregnancies between January 1, 2007 and July 1, 2009 were selected in the ultrasound database of our tertiary referral center. The database consisted of data on standard anomaly scans from patients booked for routine antenatal care in our center and patients who were referred from local regional hospitals 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 lambda sign at the inter-twin membrane-placental junction (Sepulveda et al., 1996).

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, abdominal (wall), urinary tract, face and skeleton. Major anomalies were considered those unusual anatomic features that are of serious medical or cosmetic consequence to the patient, that is, 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 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 only monochorionic diamniotic and dichorionic twin pregnancies with complete known outcome were included. Triplets and mono-amniotic twin pregnancies were excluded. Twins were classified 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 a vanishing twin before 20 weeks of pregnancy was present. In the discordant cases only one fetus demonstrated a structural anomaly 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*) or 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 $< .05$ were considered significant.

Results

In total, 231 multiple pregnancies, were scanned during the study period, with follow-up data on the outcome of the pregnancies in 98% of the cases. Five cases, without fetal anomalies on ultrasound, were lost to follow-up and thus excluded from further analysis. Triplets (8) and mono-amniotic twin pregnancies (6) were excluded from further analysis. Of the 212 twin pregnancies, 61 monochorionic-diamniotic (MCDA) and 151 dichorionic (DC) twin pregnancies were analyzed. Table 1 describes maternal and pregnancy characteristics of the MCDA and DC twin pregnancies for maternal age, gestational age at the time of the ultrasound examination, parity and mode of conception. Structural anomalies were seen in 30 twin pregnancies (5 monochorionic and 25 dichorionic).

In nine out of 30 twin cases (30%), pregnant women and their partners opted for invasive testing after the ultrasound diagnosis of a fetal anomaly. All the cases were classified as major anomalies. None of the cases with a minor fetal anomaly opted for invasive testing. In three of these cases in which karyotyping was performed, this took place within the same session as the fetocide. In a congenital cystic adenomatoid malformation (CCAM) case with hydrops, karyotyping was performed during thoracoamniotic shunting. In two pregnancies anomalies were concordant in MC twin pregnancies, namely conjoint

TABLE 1

Maternal and Pregnancy Characteristics

Total number of twin pregnancies		212
Mean ± *SD* maternal age at US (years)		33.9 ± 4.4
Median (range) GA at US (days)		140 (80–241)
Parity (%)	Primipara	49.5
	Multipara	47.2
	Not reported	3.3
Conception (%)	Naturally conceived	67.5
	OI/IUI	5.2
	IVF/ICSI	23.6
	Not reported	3.7

Note: GA = gestational age; IUI = intra uterine insemination; IVF = in vitro fertilisation; ICSI = intra cytoplasmatic sperm injection; OI = ovulation induction; *SD* = standard deviation; US = ultrasound.

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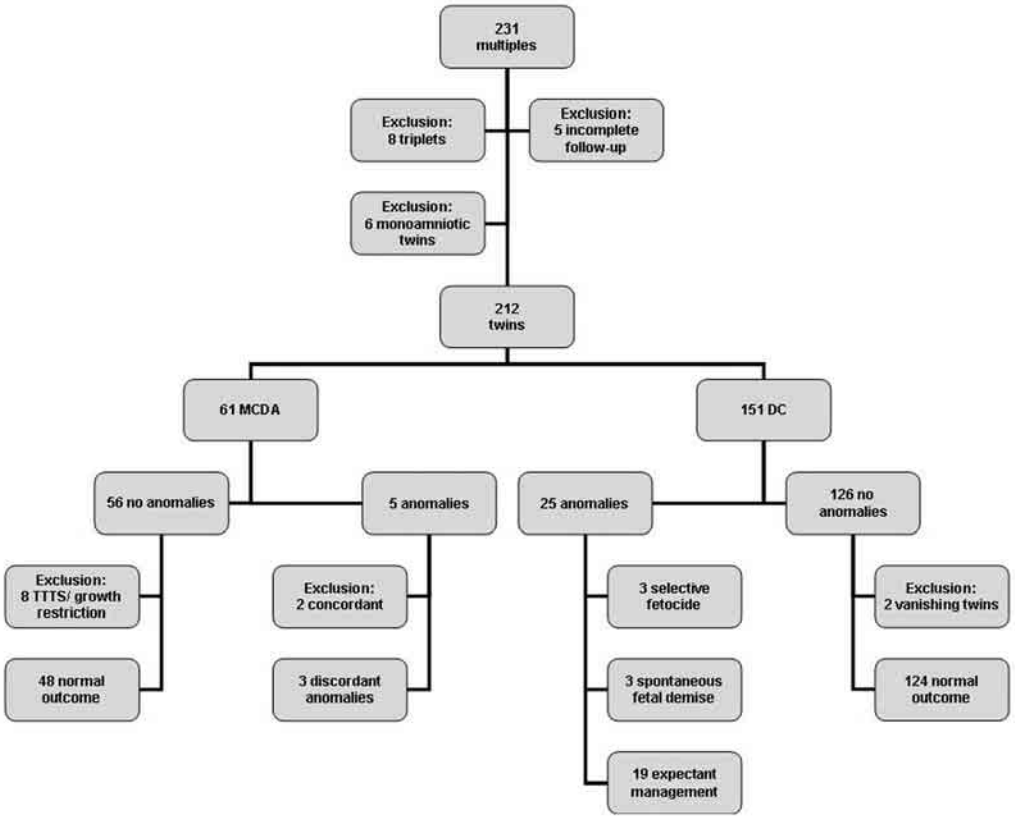

FIGURE 1
Flowchart inclusion and exclusion criteria of the studied population and outcome data.

twinning and concordant Trisomy 13. These two pregnancies were excluded from further outcome analysis, since the complete pregnancy was terminated on request of the parents (see Figure 1). Of the 28 remaining cases, 26 demonstrated isolated fetal anomalies and two demonstrated multiple anomalies. Table 2 gives an overview of the anomalies (28) subdivided for chorionicity for the twin pregnancies and classification as a major (18) or minor anomaly (10). The most common anomalies were of the skeleton ($n = 6$), urinary tract ($n = 6$) and central nervous system ($n = 5$).

Conception mode was comparable, in any case not higher, in the group with anomalies compared to those without anomalies, namely 17% IVF/ICS in the anomalous group compared with 25% in the normal outcome group. Median gestational age at detection of the all anomalies was 19+6 weeks of gestation, ranging from 69 days till 189 days of gestation. In only one case diagnosis was made after 24 weeks of gestation (in the Netherlands termination of pregnancy is possible till 24 weeks of gestation), namely at 27+0 weeks of gestation and in this case multiple anomalies were found. In this case parents had refrained from any previous ultrasound. All suspected fetal anomalies were confirmed after birth, and only in one case a anomaly was missed, namely in the case of bowel obstruction, a tetralogy of Fallot was missed in the same affected MC twin, while the co-twin demonstrated no anomalies.

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 three cases of severe but non-lethal anomalies in DC twins (two spina bifida cases and one bladder extrophy). No pregnancy loss was observed after the procedure and all three pregnancies delivered at term. No requests for complete pregnancy termination were seen in the case of discordant anomalies.

Conservative Management in Discordant Twins

In total, 25 pregnancies (30, minus two terminated pregnancies and three selective fetocides) were managed conservatively after parental counseling. In three cases (multiple anomalies (discordant trisomy 13) and two cases of exomphalus), spontaneous fetal demise of the affected twin occurred at 22+0, 14+4 and 17+1 weeks of gestation, respectively.

Median gestational age at delivery for all twins without structural anomalies (257 days, $n = 172$) and all twins with one anomalous fetus (254 days, $n = 22$), this was not significantly different (Mann Whitney U, $p = .69$). Subdivided

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TABLE 2

Classification of Structural Anomalies in Twins — Subdivided for Chorionicity and Classified as a Major or Minor Anomaly

Anomaly	MCDA	DC	Total	Major	Minor
Central nervous			**5**	**5**	
Spina bifida		3			
Ventriculomegaly/hydrocephalus		2			
Cardiovascular			**3**	**3**	
Hypoplastic left heart		2			
Atrial-ventricular septal defect		1			
Thoracic			**1**	**1**	
Cystic adenomatoid malformation	1				
Abdominal (wall)			**4**	**3**	**1**
Exomphalos		2			
Bowel obstruction/atresia		1			
Intraabdominal cyst	1				
Urinary tract			**6**	**3**	**3**
Obstructive uropathy mild		2			
Obstructive uropathy severe		1			
Cystic renal disease unilateral		1			
Cystic renal disease bilateral		1			
Bladder extrophy		1			
Facial			**1**	**1**	
Clefting		1			
Skeletal			**6**		**6**
Deformities of feet (talipes)	1	4			
Other (arthrogryposis multiplex)		1			
Multiple anomalies			**2**	**2**	
I — heart defect, exomphalos, polydactyly, polycystic kidneys (Trisomy 13)		1			
II — ventriculomegaly, obstructive uropathy, talipes		1			
Total	**3**	**25**	**28**	**18**	**10**

Note: DC = dichorionic; MCDA = monochorionic diamniotic.

for chorionicity median gestational age at delivery for dichorionic twins without structural anomalies was 258 days (n = 124) compared with 253 for a discordant anomaly in a dichorionic twin (n = 19) (Mann-Whitney U, p=0.68) (see Table 3).

For monochorionic twins with a discordant anomaly, less data were available for statistical analysis; however, median gestational age at delivery was 255 days for the normal group and the three discordant fetal anomaly cases were delivered at 247, 254 and 256 respectively.

Excluded from this analysis for the normal monochorionic group without structural anomalies were eight MC twin cases complicated by twin-to-twin transfusion syndrome or severe growth restriction that required laser therapy or umbilical cord coagulation and for the dichorionic group two cases of vanishing twin before 20 weeks of gestation (see Figure 1).

In five cases with likely lethal anomalies, pregnant women and their partners opted for neonatal non-intervention comfort care for their infant (see Table 4). The

TABLE 3

Gestational Age Distributions at Delivery — Subdivided for Normal and Discordant Anomalous Twins and Specified for Dichorionic Twin Pregnancies

	No anomalies (MC+DC) n = 172	Disc. anomalies (MC+DC) n = 22	No anomalies (DC) n = 124	Disc. anomalies (DC) n = 19
Median GA at delivery (days)	257	254	258	253
Before 24 weeks (n) (%)	6 (3.4%)	1 (4.5%)	4 (3.2%)	1 (5.3%)
Before 28 weeks (n) (cum %)	10 (5.8%)	1 (4.5%)	7 (5.6%)	1 (5.3%)
Before 32 weeks (n) (cum %)	23 (13.4%)	3 (13.6%)	17 (13.7%)	3 (15.8%)
Before 36 weeks (n) (cum %)	71 (41.3%)	10 (45.5%)	51 (41.1%)	9 (47.3%)

Note: cum = cumulative; DC = dichorionic; Disc = discordant; GA = gestational age; MC = monochorionic.

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TABLE 4

Outcome of Expectant Management in Five Cases With Severe or Lethal Discordant Anomalies

	GA at delivery (weeks)	Delivery mode	Sex	Birthweight (grams) and percentile	Outcome
I	38+0	CD, breech	F	2926 (p20–50)	Uneventful
DC		CD, breech	M	2108 ($p < 2.3$)	ND, bilateral multicystic kidney disease
II	39+0	CD, breech	F	2575 (p5–10)	Uneventful
DC		CD, breech	F	2200 ($p < 2.3$)	ND, hypoplastic left heart syndrome
III	35+2	CD, CP	F	2095 (p20–50)	Uneventful
MC		CD, CP	F	1815 (p5–10)	ND, CCAM * intra uterine thoraco-amniotic shunt
IV	36+1	Vag, CP	M	2426 (p20–50)	Uneventful
DC		Vag, breech	M	2247 (p10–16)	ND, hypoplastic left heart
V	37+4	CD, breech	M	2450 (p2.3–5)	Uneventful
DC		CD, CP	M	2000 ($p < 2.3$)	ND, bilateral dysplastic kidneys, megacystis

Note: CCAM = congenital cystic adenomatoid malformation; CD = cesarean delivery; CP =cephalic position; DC = dichorionic; GA = gestational age; MC = monochorionic; ND = neonatal death; Vag = vaginal delivery.

gestational age at diagnosis for these five cases were: case I 12+0, case II 19+0, case III 19+5 , case IV 20+4 and case V 14+5 weeks. In all cases diagnosis was thus confirmed before 24 weeks of gestational and parents had all options available to them. In all five cases, these neonates died shortly after birth, four cases within 24 hours and one case 16 days after birth. Their co-twins, without anomalies, had good outcomes in all cases.

Discussion

In this multiple pregnancies cohort, 30 anomalous twin pregnancies were found from the total of 212 twin pregnancies (14%). This retrospective cohort study confirms the known increased risk on fetal anomalies in multiple pregnancies (Bahtiyar et al., 2007; Hall, 2003). 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 subheading.

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. 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 weeks 9–12, 5.4%; weeks 13–18, 8.7%; weeks 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 gestation and 7.8% between 29–32 weeks of gestation (Evans et al., 1999). Combined data lead to a complication risk a 2 > 1 procedure leads before 28 weeks of almost 12%, and before 32 weeks of almost 20%. In other studies, overall loss rates are reported at less than 5%; however, no loss report are given in terms of selective termination before and after 20 weeks of gestation (Eddleman et al., 2002; Stone et al., 2008). Due to the presence of vascular anastomoses in the placenta of monochorionic twins, KCL is not an 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 fetocide (Rustico et al., 2005).

Conservative Management

In case of lethal or severe malformations, the risk of selective termination to the normal co-twin should be weighed against the risk of the continuing development of the affected twin. The possibility of expectant management can be addressed in counseling patients in case of lethal malformations. However, expectant management is being criticized because of a possible association with premature birth (Alexander et al., 1997; Malone et al., 1996; Nassar et al., 2000). In the study of Malone et al., the mean GA at delivery of twins with one anomalous fetus ($n = 14$) was 33+6 weeks compared to 35+6 weeks in the control group of twins ($n = 78$). Very early delivery occurred in only one of the 14 anomalous twins at 28 weeks of gestation. The risk of delivery at 36 weeks or less was 78.6% for single

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anomalous twins vs. 59% for the control group (Malone et al., 1996). A larger case-series reports on 18 twins discordant for major anomalies and 38 twins discordant for minor anomalies (Alexander et al., 1997). A significant lower gestational age at delivery was found (32 weeks vs. 35 weeks). Nassar et al. 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 gestation (Nassar et al., 2000). 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 group (Lust et al., 2008). 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 (Chang et al., 2004; Heydanus et al., 1993). 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 weeks in uncomplicated group vs. 35.07 weeks in the group with a single anomalous fetus), low birth weight and neonatal outcome (Sun et al., 2009). 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-twin (Ong et al., 2006).

In our study, median gestational age at delivery was not significantly different for both normal twins and twins with a single anomalous fetus, also if subdivided for chorionicity. 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. 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 five cases with major severe or lethal anomalies patients opted for non-intervention, comfort care for the affected fetus. In all five cases, the outcome of the unaffected co-twin was good, whereas all affected twins died shortly after birth, as expected. We emphasize that in case of anomalous fetus (also in singleton pregnancies) extensive collaboration between obstetricians, pediatrics and genetic counsellors is needed during the pregnancy and after birth. In our center in all cases, specific psychological care is actively offered to all parents. In all cases with neonatal death after expectant management, the parents stated that they were comforted by the opportunity to see their child and to hold it until nature took its course, although they were in severe grief for the lost of their child.

For future studies structured follow-up of the unaffected twin is desirable also including long-term follow-up. In the three conservatively managed cases, spontaneous fetal demise of the affected fetus was observed. Fetal fetocide was only opted for 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 randomized setting are not available. However, in our opinion expectant management is a feasible management option for severe or lethal anomalies if requested by the patients.

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