Fetoscopic interventions in complicated monochorionic twin pregnancies

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Timely diagnosis of twin-to-twin transfusion syndrome by biweekly ultrasound and patient instructions

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2

Abstract

Objective: To assess the value of serial ultrasound examinations together with patient instructions to report the onset of symptoms in achieving timely detection of twin-to-twin transfusion syndrome (TTTS) in a cohort of monochorionic diamniotic twin pregnancies, and to evaluate sonographic TTTS predictors.

Methods: Timely detection of TTTS was defined as diagnosis before severe complications of TTTS occurred, such as preterm prelabour rupture of membranes, very preterm delivery (24-32 weeks of pregnancy), fetal hydrops, or intrauterine fetal death. During a 2-year period, a prospective series of 23 monochorionic twin pregnancies was monitored from the first trimester until delivery. At least every 2 weeks we performed ultrasound and Doppler measurements (nuchal translucency thickness, presence of membrane folding, estimated fetal weight, deepest vertical pocket, bladder filling, and Doppler waveforms of the umbilical artery, ductus venosus, and umbilical vein). Measurements of TTTS cases were compared with those of non-TTTS cases matched for gestational age. Furthermore, patients were informed about the symptoms caused by TTTS, and instructed to consult us immediately in case of rapidly increasing abdominal size or premature contractions.

Results: In all four TTTS cases, the diagnosis was timely. At the time of diagnosis, one case was at Quintero Stage 1, two at Quintero Stage 2, and one at Quintero Stage 3.Two of the TTTS cases became apparent after the patients' feeling of rapidly increasing girth. The identification of TTTS predictors was successful with respect to one parameter: isolated polyhydramnios in one sac, without oligohydramnios in the other, preceded the ultimate diagnosis of TTTS in two of the four TTTS cases. All other ultrasound measurements of TTTS cases, prior to the diagnosis of TTTS, were within the range of measurements of non-TTTS cases.

Conclusions: Biweekly ultrasound examinations, with special attention to amniotic fluid compartments of both fetuses, combined with detailed patient instructions to report the onset of symptoms resulted in timely diagnosis of all TTTS cases and appears to be a safe program for monitoring monochorionic twin pregnancies.

Introduction

Twin-to-twin transfusion syndrome (TTTS) occurs in 15% of monochorionic diamniotic twin pregnancies.[1] The syndrome is caused, at least partly, by unbalanced blood flow through vascular placental anastomoses between the twin fetuses, and presents sonographically as an oligo/polyhydramnios sequence. TTTS has been classified into five stages according to Quintero *et al.*[2] Untreated, it is associated with extremely high mortality and morbidity rates.[3-6] In a recent randomised comparison with serial amniodrainage, treatment by fetoscopic laser coagulation of the placental vascular anastomoses was associated with higher perinatal survival rates, more advanced gestational age at delivery and better neurological outcome.[7] Moreover, perinatal survival rates after laser therapy were higher in TTTS stage 1 or 2 than in stage 3 or 4.[7;8] Increasingly, therefore, attention is being paid to the timely diagnosis and treatment of TTTS.

Several studies have focused on the identification of sonographic markers that could forecast the development of TTTS. Sebire *et al* found that pregnancies with increased nuchal translucency thickness in the first trimester and folding of the intertwin membrane in the second trimester are at increased risk of developing TTTS.[1;9;10] Also, the presence of a velamentous umbilical cord insertion and sonographic absence of arterioarterial anastomoses have been found to be more common in pregnancies with TTTS.[11;12] The observation of such TTTS predictors could thus lead to increased surveillance during the pregnancy and hence to the timely detection of TTTS. Absence of these factors, however, does not guarantee that TTTS will not develop.

Symptoms and staging of TTTS are clearly defined, which makes the syndrome, if present, easy to diagnose.[2] Little is known, though, about the optimal surveillance strategy of monochorionic twins in order to detect TTTS before severe complications occur. The first objective of this prospective study was to assess the value of biweekly ultrasound examinations together with patient instructions to report the onset of symptoms in achieving timely detection of TTTS in a cohort of monochorionic diamniotic twin pregnancies. Timely detection was defined as diagnosis before the occurrence of severe

complications of TTTS. Patients were instructed to consult us if they had the impression of rapidly increasing abdominal girth or premature contractions, in which case an ultrasound examination was performed within 24 hours. The second objective of this study was to assess the prognostic value of nuchal translucency thickness, folding of the intertwin membrane, estimated fetal weight (EFW) and ultrasound markers used for Quintero-staging in the development of TTTS (TTTS-predictors).

Methods

We performed a longitudinal, prospective study of all monochorionic diamniotic twin pregnancies referred to our obstetrical unit during a 2-year period (September 2002 - September 2004). Inclusion criteria were: gestational age below 16 completed weeks and no signs of TTTS at initial ultrasound examination, an absent lambda sign and thin dividing membrane on ultrasound (considered to be evidence of monochorionic diamniotic twinning), and absence of fetal abnormalities. In all cases, gestational age was based on the first day of last menstrual period and confirmed by ultrasound examination in the first or early second trimester. Placental pathological examination was used to confirm monochorionicity after birth.
The study involved serial abdominal ultrasound and Doppler examinations, carried out at least every 2 weeks from when the twin pregnancy was first discovered until delivery. In cases of abnormal ultrasound findings that raised the suspicion of future development of TTTS, the examination frequency was increased. Ultrasound examinations were performed by one of two experienced sonographers. Nuchal translucency thickness was measured only once in the first trimester in cases presenting before 14 weeks, and the following parameters were measured at each examination: folding of the intertwin membrane; EFW; deepest vertical pocket (DVP) of amniotic fluid for each fetus; bladder filling (viewed three times with 10-min intervals and classified as normal, collapsed or enlarged); end-diastolic flow (EDF) of the umbilical artery (UA) (recorded as present, absent or reversed); A-wave in the ductus venosus

(DV) (recorded as present, absent or reversed); flow pattern of the intrahepatic part of the umbilical vein (UV) (classified as pulsatile or non-pulsatile). All measurements were performed in the absence of fetal movements using an Acuson Sequoia (Acuson, Mountain View, California, USA) ultrasound machine with a 4.0- or 6.0-MHz-probe.

TTTS was diagnosed by the presence of oligo/polyhydramnios sequence in the absence of other causes. Polyhydramnios and oligohydramnios were defined as a DVP of amniotic fluid of >8 cm at ≤20 weeks (or >10 cm at >20 weeks) and <2 cm, respectively. TTTS severity was assessed based on Quintero's established criteria[2]: Stage 1, isolated oligo/polyhydramnios sequence; Stage 2, absent visible bladder of the donor twin; Stage 3, critically abnormal Doppler results (absent/reversed EDF of the UA, absent/reversal of flow during atrial contraction in DV, or pulsatile flow pattern of the intra-hepatic part of the UV); Stage 4, hydrops in either fetus; Stage 5, demise of one or both twins. Timely detection of TTTS was defined as diagnosis before the occurrence of severe complications of TTTS, such as preterm prelabour rupture of membranes, very preterm delivery (24-32 weeks of pregnancy), fetal hydrops, or intrauterine fetal death. TTTS diagnosed <26 weeks was treated by fetoscopic laser coagulation of communicating placental vessels. This was always combined with a single amniodrainage procedure. TTTS diagnosed >26 weeks was treated by (repeated) amniodrainage procedure(s). Additionally, patients were informed about the symptoms caused by TTTS and were instructed to consult us immediately in the case of rapidly increasing girth or premature contractions. In this case, sonography was performed as soon as possible (within 24 hours). The institutional review board approved this study and all patients gave informed consent. Pregnancies affected by TTTS were referred to as "TTTS cases", and those not complicated by TTTS were referred to as "non-TTTS cases". In order to identify TTTS predictors, sonographic measurements of TTTS cases were compared with the mean value of non-TTTS cases matched for gestational age. The range of values obtained from non-TTTS cases was considered to be normal. Values of TTTS cases outside this range were considered abnormal.

Results

During the 2-year period, 25 consecutive monochorionic diamniotic twin pregnancies were managed prospectively at our hospital. One pregnancy was excluded from the study because of fetal malformation (lower urinary tract obstruction) followed by selective feticide by cord coagulation. One patient refused to participate in the study because of concerns about the safety of frequent scanning. The remaining 23 patients were included. In total, 268

Table 1 *Pregnancy characteristics for cases with and without twin-to-twin transfusion syndrome (TTTS)*

Characteristic		TTTS (n=4)	non-TTTS (n=19)
Maternal age (years, median (range))		35.0 (33-40)	34.0 (23-39)
Parity (median (range))		4 (1-5)	2 (1-4)
Gestational age (weeks, median (range) at:			
-	initial US examination	12.6 (11.3-14.6)	12.3 (11.0-15.6)
-	TTTS diagnosis	23.4 (16.9-29.1)	-
-	delivery	32.2 (18.3-37.0)	36.1 (19.1-38.7)
Pregnancies (n (%)) with:			
-	double perinatal survival	3 (75%)	18 (95%)
-	single perinatal survival	0 (0%)	0 (0%)
-	no perinatal survival	1 (25%)*	1 (5%)†

**TTTS treated with uncomplicated laser therapy at 16+6 weeks. At 17+6 weeks' gestation, abrupt double intrauterine death was diagnosed. Autopsy was refused. †Sudden double intrauterine death at 19 weeks. At autopsy, one of the fetuses was found to have a frontonasal malformation and left cardiac ventricular hypertrophy with abnormal pulmonary venous return. The other twin was unaffected. US, ultrasound.*

ultrasound examinations of 23 twin pairs were performed. Median number of ultrasound examinations per patient was 12 (range, 4-17).
Four pregnancies (17%) were complicated by TTTS and were diagnosed before the occurrence of severe complications. They were treated by either fetoscopic laser coagulation (n=2), amniodrainage prior to laser therapy 4 weeks later (n=1), or amniodrainage alone (n=1). Two of these four TTTS-cases became apparent after the patient experienced rapidly increasing girth, which made them ask for an extra scan between regular visits. None of the 19 patients without TTTS presented between regular visits with similar complaints. Clinical details of TTTS cases and non-TTTS-cases are given in table 1. All ultrasound findings prior to the diagnosis of TTTS in the four TTTS-cases are given in table 2.

Nuchal translucency thickness >95th centile in at least one of the fetuses was found in 2/16 pregnancies (13%).[13] None of these pregnancies was complicated by TTTS. Folding of the intertwin membrane was seen at least once in six pregnancies (26%), of which one developed TTTS. One other pregnancy with membrane folding had large discrepancies in amniotic fluid (polyhydramnios without oligohydramnios and without other signs suggestive of TTTS) and fetal size that persisted until delivery but did not require any form of treatment.The other 4 cases with membrane folding had an uneventful course. Isolated polyhydramnios without further signs of TTTS was diagnosed in three (13%) pregnancies, of which two went on to develop TTTS. The third pregnancy with polyhydramnios in one sac (maximum DVP, 15.8 cm) was the one mentioned above with intertwin membrane folding that did not develop other signs of TTTS during pregnancy. Prior to the diagnosis of TTTS, TTTS and non-TTTS cases did not differ in: EFW, bladder filling, EDF of the UA, A-wave of the DV, and pulsations of the UV.
The first TTTS case had 2 normal ultrasound examinations until diagnosis of TTTS at 16+6 weeks. At this time, during a routine visit, oligo/polyhydramnios sequence was observed, with a DVP of 1.0 cm and 7.3 cm for donor and recipient, respectively. Also, the donor's bladder was collapsed and the recipient's bladder was enlarged. The flow in the UV was pulsatile. Despite

Table 2 *All ultrasound (US) findings prior to the diagnosis of twin-to-twin transfusion syndrome (TTTS)*

	Case 1	Case 2	Case 3	Case 4
1st ultrasound examination	GA: 12+6, CRL: 7.4/7.4, NT: 0.19/0.14, MF: -, DVP: 3.3/2.9, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 12+2, CRL: 4.5/5.0, NT: 0.12/0.13, MF: -, DVP: 2.4/2.1, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 14+4, EFW: 113/102, MF: -, DVP: 2.9/4.0, BF: -/-, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 11+2, CRL: 4.6/4.5, NT: 0.11/0.15, MF: -, DVP: 3.5/3.5, BF: -/-, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
2nd ultrasound examination	GA: 14+6, EFW: 113/101, MF: -, DVP: 2.2/3.2, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 14+2, CRL: 7.2/8.4, MF: -, DVP: 3.2/2.9, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 17+0, EFW: 182/182, MF: -, DVP: 4.8/6.4, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 13+2, CRL: 6.9/6.9, MF: -, DVP: 3.9/4.3, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
3rd ultrasound examination		GA: 16+0, EFW: 145/161, MF: -, DVP: 3.8/3.5, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 19+2, EFW: 312/339, MF: -, **DVP:** 3.8/**9.1**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 15+1, EFW: 115/112, MF: -, DVP: 5.8/4.4, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
4th ultrasound examination		GA: 18+0, EFW: 202/219, MF: -, DVP: 3.7/4.1, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 19+4, MF: -, **DVP:** 4.7/**11.2**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 17+1, EFW: 182/182, MF: -, DVP: 4.2/5.9, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
5th ultrasound examination		GA: 20+0, EFW: 296/314, MF: -, DVP: 4.8/5.1, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 20+3, MF: -, **DVP:** 4.7/**10.9**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 18+1, EFW: 181/198, **MF:** +, DVP: 3.4/6.9, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
6th ultrasound examination			GA: 20+4 (after AR), MF: -, DVP: 4.7/6.5, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 19+1, **MF:** +, **DVP:** 4.0/**8.8**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
7th ultrasound examination			GA: 21+0, EFW: 369/375, MF: -, DVP: 3.5/9.8, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 20+1, EFW: 237/339, **MF:** +, DVP: 3.8/8.6, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+

8th ultrasound examination			GA: 22+2, EFW: 439/474, MF: -, DVP: 6.0/10.0, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 21+1, **MF:** +, DVP: 5.0/6.8, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
9th ultrasound examinationn			GA: 23+2, EFW 477/559, MF: -, **DVP:** 4.7**/10.8**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 22+1, EFW 370/-, **MF:** +, DVP: 4.9/8.4, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
10th ultrasound examination			GA: 24+2, MF: -, **DVP:** 2.6**/11.9**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+	GA: 24+1, EFW: 652/606, **MF:** +, DVP: 4.3/8.9, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+
11th ultrasound examination				GA: 26+1, EFW: 716/780, MF: -, **DVP:** 5.6**/10.2**, BF: nl/nl, UA EDF: +/+, pulsatility UV: -/-, DV A-wave: +/+

US findings at diagnosis of TTTS are not included in the table. Values presented in twins as " / " represent values of the future donor / recipient. Abnormal values are indicated in bold. -, absent; +, present; AR, amnioreduction; BF, bladder filling; CRL, crown-rump length (cm); DV, ductus venosus; DVP, deepest vertical pocket (cm); EFW, estimated fetal weight (g); GA, gestational age; MF, membrane folding; nl, normal; NT, nuchal translucency thickness(cm); UA-EDF, umbilical artery end-diastolic flow; UV, umbilical vein.

the DVP of the recipient being <8 cm, the combination of a collapsed and an enlarged bladder together with a critically abnormal Doppler suggested a TTTS Quintero Stage 3. Treatment by laser coagulation of the communicating placental vessels (three arteriovenous anastomoses from donor to recipient) was performed. There were no complications during the procedure. However, at 17+6 weeks' gestation, 1 week after treatment, an abrupt double intrauterine fetal death was diagnosed.

In the second case, TTTS was diagnosed at 22+1 weeks. All five previous ultrasound examinations had been unremarkable. At the regular, biweekly scan at 22+1 weeks' gestation, the DVP of Twin A and Twin B measured 3.7 and 11 cm, respectively. Throughout the 45-min examination, Twin A showed a collapsed bladder and Twin B had normal bladder filling. Doppler measurements were normal. Despite the donor's DVP measuring >2 cm, we considered this case (due to the absence of bladder filling in the donor twin) to be Quintero Stage 2. Treatment with fetoscopic laser coagulation of communicating placental vessels was performed (three arteriovenous anastomoses from donor to recipient and 1 arteriovenous anastomosis from recipient to donor). Spontaneous delivery occurred at 31+5 weeks.

In the third case the first ultrasound examination was at 14+4 weeks' gestation, too late for appropriate nuchal translucency thickness measurement. The first two scans, at 14+4 and 17+0 weeks, showed normal values for both fetuses. Ultrasound examination at 19+2 weeks revealed one of the twins to have a DVP of 9.1 cm, which increased to 11.2 cm at 19+4 weeks. There was, however, no oligohydramnios in the other sac (DVP, 3.8 and 4.7 cm, respectively) and bladder filling and Doppler measurements were within normal ranges for both fetuses. There were no fetal anomalies explaining the increase in amniotic fluid. At 20+3 weeks, effacement of the cervix prompted amniodrainage of 1100 mL and placement of a cerclage. In the next weeks, the recipient twin's DVP increased from 6.5 to 11.9 cm, whereas the donor twin did not develop oligohydramnios. The bladder filling and Doppler studies of both fetuses remained normal. At 24+5 weeks, 3 days after the last ultrasound examination, the woman contacted us with complaints of abdominal distension. At this time, a fetus with polyhydramnios (DVP, 13.5 cm)

and enlarged bladder was seen in one sac; while in the other sac a stuck twin with oligohydramnios (DVP, 0.5 cm) and normal bladder filling was identified (Quintero Stage 1). Laser coagulation of the communicating placental vessels (four arteriovenous anastomoses from donor to recipient) was performed. At 37+0 weeks, labour was induced.

The fourth case was diagnosed at 29+1 weeks. The four ultrasound scans obtained between 11+2 and 17+1 weeks of gestation were uneventful. At the next six weekly ultrasound examinations, between 18+1 and 24+1 weeks' gestation, we observed folding of the intertwin membrane. Other sonographic measurements were unremarkable. The patient came to the hospital between regular visits at 29+1 weeks, one week after the last examination, because of rapidly increasing abdominal size. On ultrasound examination, a stuck twin with oligohydramnios (DVP, 0.8 cm) and collapsed bladder was noted. The recipient twin had polyhydramnios (DVP, 14.0 cm) with an enlarged bladder. Doppler measurements were all normal. A diagnosis of TTTS Quintero Stage 2 was made. Previous ultrasound examinations had already shown an accumulation of amniotic fluid in the recipient's sac (DVP measuring 10.2 cm and 11.7 cm at 26+1 and 28+1 weeks). The amniotic fluid compartment of the donor twin, however, had remained within normal ranges during these previous examinations (5.6 cm at 26+1 and 7.7 cm at 28+1 weeks). Because the gestational age was >26 weeks, this patient was treated by repeated amniodrainage. She delivered spontaneously at 32+4 weeks.

The fetal loss rate was 25% (2/8) for TTTS cases and 5% (2/38) for non-TTTS cases (Table 1). All 42 fetuses that were born alive were structurally normal. At autopsy, one of the demised fetuses of the non-TTTS group was found to have a frontonasal malformation and left cardiac ventricle hypertrophy with abnormal venous pulmonary return. Its demised co-twin was unaffected. For the two fetuses that died after laser therapy, the parents refused autopsy. Monochorionicity of all placentas was confirmed histological.

Discussion

Our study evaluated prospectively the natural history of monochorionic diamniotic twin pairs with regard to the development of TTTS during fetal life. We succeeded in the timely diagnosis of TTTS cases by a program of frequent (biweekly) ultrasound examinations and patient instructions to report the onset of symptoms, diagnosing all TTTS cases before severe complications of TTTS were encountered: there were no cases of preterm prelabour rupture of membranes or very preterm deliveries caused by polyhydramnios, and no cases of fetal hydrops or fetal death. Patient instructions turned out to be highly relevant for the timely detection of TTTS; two of the four TTTS cases in our series became apparent the patient experienced rapidly increasing girth. None of the 19 patients without TTTS presented between their regular scheduled visits with similar complaints. Despite the anxiety during pregnancy that may be associated with patients being informed extensively on all the risks that may be involved with monochorionic twinning, we consider explicit patient instructions to be crucial for the timely detection of TTTS.

We identified the DVP of amniotic fluid was identified as being a TTTS predictor. In two of the four TTTS cases we found isolated polyhydramnios in one sac, without oligohydramnios in the other and with normal bladder filling of both fetuses, preceding the ultimate diagnosis of TTTS. Another pregnancy with polyhydramnios that lacked coexistence of oligohydramnios, however, did not develop TTTS. Polyhydramnios alone must certainly be considered an important sign, possibly indicative of the future development of TTTS, but it should not invariably lead to invasive treatment. We think it is very importance to locate the intertwin membrane and to measure the DVP of each fetus routinely at least every 2 weeks. Accumulation of amniotic fluid should alert obstetricians and lead to increased sonographic surveillance.

None of the other sonographic parameters was found to showed to be predictive of future TTTS. As polyhydramnios in TTTS is thought to originate mainly from excessive urine production of the recipient twin, it could be hypothesized that urinary bladder filling should also be increased. However, prior to diagnosis of TTTS, no differences in fetal bladder size between future

donor and recipient twins were detected in this study. It would be interesting to investigate more extensively whether a discrepancy in fetal urinary production precedes the development of an oligo/polyhydramnios sequence. To explore this properly, a more detailed approach is required.[14]

Although EFW differences have long been abandoned in diagnosing TTTS, there still exists a general belief that donor twins should be smaller than recipients. Formerly, a growth discordance of ≥20% has been used as a diagnostic criterion of TTTS. Such a birth weight difference, however, is seen as frequently in monochorionic as in dichorionic twins.[15] Consequently, a difference in EFW is not considered a mandatory feature of TTTS. Similarly, the Quintero staging system criteria do not include fetal biometry.[2] Differences in EFW are thus not expected to be of any help in forecasting TTTS. This was demonstrated in our study by the EFW of the donor twin exceeding that of the recipient twin in three of the four TTTS cases.

As stated in Quintero *et al*'s criteria, the more advanced stages of TTTS are characterized by critically abnormal Doppler studies of the UA, DV or UV.[2] Assuming that TTTS is the result of long-lasting circulatory imbalance and not a sudden incident, Doppler studies could be expected to deteriorate progressively in the weeks before TTTS is diagnosed. However, in our study we were unable to show differences between TTTS cases and non-TTTS cases in Doppler studies performed prior to the scan revealing TTTS.

We could not confirm findings of previous studies in which ultrasound markers such as nuchal translucency thickness and folding of the intertwin membrane were associated with the development of TTTS. Sebire *et al* suggested that the likelihood ratio of an increased fetal nuchal translucency for the prediction of TTTS was 3.5.[1] Although we found an increased nuchal translucency thickness in at least one fetus in 2/16 pregnancies (13%), which is similar to the frequency in Sebire's series, all four cases that later developed TTTS had normal nuchal translucency thickness values. Another association found by Sebire *et al* was the occurrence of folding of the intertwin membrane with subsequent development of TTTS.[10] In their study, folding occurred in 28% of monochorionic twin pregnancies and resulted in TTTS in 52% of the cases. We found a similar rate (26%) of folding of the intertwin membrane, but only

one of these six pregnancies (17%) was subsequently complicated by TTTS. Interestingly, 3/17 patients without intertwin membrane folding also developed TTTS. Matias *et al* proposed a role for the combination of increased nuchal translucency thickness and abnormal DV flow patterns in anticipating TTTS.[16] This could not be established in our study, since none of the fetuses showed absent or reversed flow of the DV during atrial contraction.

We realise that our study population was relatively small, which may well be the reason for our not confirming findings of larger studies. Our study, though, was unique for its prospective, longitudinal approach. The rarity of monochorionic twinning hampers prospective research in this area. A series of 23 patients may seem rather undersized, but should be considered relatively large in this context. Moreover, we think our study population is representative of a normal monochorionic diamniotic twin cohort. The 17% incidence of TTTS in our series is comparable with the reported 15%.[1] Another potential weakness was the lack of a control group, which leads us to refrains from drawing conclusions about the advantages of a monitoring program. Nevertheless, information on how to manage monochorionic twins is urgently needed and we think our study contributes realistic data to this information gap.

In conclusion, based on our study results, we think combined use of sonography and maternal symptom monitoring forms a safe program for monitoring monochorionic twin pregnancies. Hence, for the timely diagnosis of TTTS cases, we advise biweekly ultrasound examinations, with special attention being paid to the amniotic fluid compartments of both fetuses, combined with detailed patient instructions.

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