Monochorionic Diamniotic Twin Pregnancy; a Retrospective Study on Twin-twin Transfusion Syndrome and Related Disorders

Kanako MITSUZUKA, Atsuko TOGO, Yasuhira KANNNO, Tomoaki NARAYAMA, Hirofumi KASHIWAGI, Masaru HAYASHI, Yumiko GOTO and Hitoshi ISHIMOTO

Department of Obstetrics and Gynecology, Specialized Clinical Science, Tokai University School of Medicine

(Received November 29, 2019; Accepted April 3, 2020)

Objective: We assessed the clinical characteristics and perinatal outcome of disorders specific to monochorionic diamniotic (MD) twin pregnancies, focusing on twin-twin transfusion syndrome (TTTS) and related disorders, such as selective intrauterine growth restriction (sIUGR), inter-twin amniotic fluid discordance (AFD), and twin anemia polycythemia sequence (TAPS).
Methods: We retrospectively reviewed 69 cases of MD twin pregnancies delivered after 22 weeks at our institution from January 2009 to September 2013.
Results: TTTS occurred in 9 cases (13%). There was a total of 11 cases (16%) of MD twins with sIUGR in this period. One case developed TTTS. All 3 cases (4%) of AFD in this study developed TTTS or sIUGR.
Conclusion: AFD should be recognized as predictors of TTTS or sIUGR. Further studies on TTTS-related disorders allow a more precise subgroup categorization that enables optimal management.

Key words: monochorionic diamniotic twin pregnancies, twin-twin transfusion syndrome, selective intrauterine growth restriction, inter-twin amniotic fluid discordance

INTRODUCTION

Monochorionic diamniotic (MD) twin pregnancies are at greater risk for perinatal morbidity and mortality compared to dichorionic diamniotic twin pregnancies because of disorders specific to MD twin pregnancies, such as twin-twin transfusion syndrome (TTTS). TTTS occurs in approximately 15% of MD twin pregnancies [1, 2]. There is a robust amount of data on the clinical characteristics of TTTS and its management, including the efficacy of fetoscopic laser photocoagulation (FLP) [3–8]. However, there is a relative paucity of information on TTTS-related disorders, such as selective intrauterine growth restriction (sIUGR), inter-twin amniotic fluid discordance (AFD), and twin anemia polycythemia sequence (TAPS). Management of TTTS cases without FLP treatment and TTTS-related disorders has not been established. The aim of our study was to review our experience and to assess clinical characteristics and perinatal outcome of disorders specific to MD twin pregnancies, with a focus on TTTS and related disorders, such as sIUGR, AFD, and TAPS.

METHODS

MD twin pregnancies delivered after 22 weeks between January 2009 and September 2013 at our institution were retrospectively reviewed. We excluded cases with spontaneous pregnancy loss before 22 weeks of gestation. The study protocol was approved by the local Institutional Review Board for Clinical Research, and written informed consent was waived because of the retrospective design. MD twin pregnancies were confirmed in all cases on first-trimester ultrasound. Our standard management program for MD twin pregnancies included biweekly (before 30 weeks of gestation) and weekly (after 30 weeks of gestation) ultrasounds combined with patient reporting of symptoms. All patients with TTTS diagnosed before 26 weeks of gestation were referred to another institution for FLP, except for one case (a 24-week-acute-onset TTTS referred from a nearby tertiary center that necessitated immediate delivery). TTTS was defined as the presence of oligohydramnios (defined as a maximal vertical pocket [MVP] of ≤ 2 cm) in one sac and polyhydramnios (a MVP of ≥ 8 cm) in the other sac. Cases of TTTS were classified using the Quintero staging system. The various criteria are as follows: Stage I, bladder of donor fetus is still visible; Stage II, bladder of donor fetus is no longer visible; Stage III, abnormal Doppler studies (absent/reverse end-diastolic velocity in the umbilical artery, absent/reverse flow in the ductus venosus or pulsatile flow in the umbilical vein) and/or echocardiographic abnormalities; Stage IV, hydrops in either fetus; and Stage V: demise of one or both twins. sIUGR was defined as an estimated fetal weight below the 10th percentile in the smaller twin. AFD was defined as a MVP of ≥ 7 cm in one sac, a MVP ≤ 3 cm in the other sac, which is usually quoted in Japan. TAPS was diagnosed postnatally in cases of anemia in

Atsuko TOGO, Department of Obstetrics and Gynecology, Specialized Clinical Science, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-91-4343 E-mail: atsuko.tou5@gmail.com

one twin and polycythemia in the other at birth. It was defined as a large intertwin hemoglobin discordance (> 8 g/dL) without AFD, in addition to at least of one of the following conditions: reticulocyte count ratio > 1.7, and/or placenta with only small (diameter < 1 mm) vascular anastomoses [9].

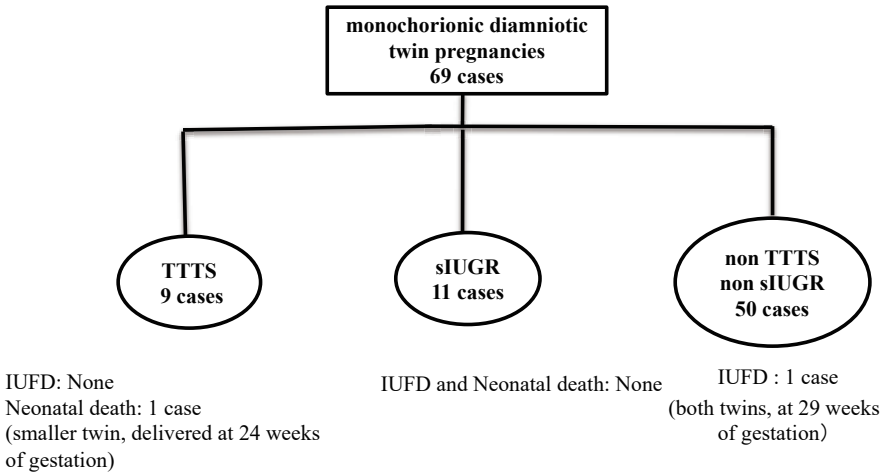
The following neonatal data were recorded: gestational age at birth, birthweight, birthweight discordance, and Apgar scores. Birthweight discordance was assessed in surviving pairs of twins and was calculated in the following manner: [(birthweight of the larger twin−birthweight of the smaller twin)/birthweight of the larger twin] × 100%. The following neonatal outcome measures were recorded: tracheal intubation, catecholamine treatment, anemia at birth, hypervolemia, heart failure, neonatal death, and neurological complications. Tracheal intubation was defined as the placement of a tube into the trachea to maintain open and effective airways. Chronic lung disease (CLD) was defined as an oxygen requirement greater than that obtainable from room air beyond 28 days of age, and was indicated by an abnormal x-ray scan. Catecholamine treatment was defined as the use of dopamine, dobutamine, noradrenalin, and/or adrenalin. Anemia was defined as a hemoglobin level < 12 g/dL [10]. Hypervolemia was defined as positive fluid balance > 7% of body weight [11]. Heart failure was defined as severe when catecholamines and/or intubation was required [12]. Neurological complications were defined as the presence of intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and cerebral palsy (CP). IVH was defined in accordance with the classification of Volpe [13]. PVL was defined as the presence of periventricular white matter echo-densities (periventricular area almost as bright as the choroid plexus) or echo-lucencies (cystic PVL), and was graded as suggested by de Vries *et al*. [14]. CP was defined as a chronic disorder of the central nervous system, characterized by aberrant control of movement or posture, appearing early in life and not resulting from progressive disease [15]. After birth, neurological assessment and cranial ultrasound scans were performed in all the surviving cotwins. In cases of suspected cerebral injury, magnetic resonance imaging (MRI) was performed.

RESULTS

This study included 69 MD twin pregnancies. Mean maternal age was 32.1 ± 4.6 years (range 21 to 42 years), and the mean gestational age at delivery was 35.1 ± 3.2 weeks (range 24 + 3 to 37 + 5 weeks). All MD twins were delivered by cesarean section. Premature delivery occurred in 47 cases (68%). A summary of perinatal outcomes are shown in Fig. 1. Intrauterine fetal death (IUFD) occurred in 1 case (1%), which did not involve TTTS, sIUGR, or severe structural anomalies, and both fetuses died. Eight cases (12%) had maternal complications, 3 cases (4%) had hypertensive disorder of pregnancy (HDP), 1 case (1%) had HELLP syndrome, 3 cases (4%) had gestational diabetes mellitus (GDM), and 1 case (1%) had renal dysfunction. Major congenital structural anomalies occurred in 2 out of 138 fetuses (1%). There was a case where 1 fetus had tetralogy of Fallot and the other had a cleft lip and palate.

TTTS occurred in 9 cases (13%). Mean gestational age at diagnosis was 23.0 ± 3.8 weeks (range 17 + 0 to 29 + 6 weeks) and the mean gestational age at delivery was 32.1 ± 5.0 weeks (range 24 + 3 to 37 + 1 weeks). There were 7 cases diagnosed before 26 weeks. Using the Quintero staging system, as previously defined, 3 cases were stage I, 2 cases were stage II, 2 cases were stage III, and 2 cases were stage IV disease. FLP was used for treatment in 6 cases (Table 1) and 3 cases were not treated with FLP (Table 2). Mean gestational age at FLP was 21.7 ± 1.6 weeks (range 19 + 3 to 24 + 5 weeks). All patients diagnosed with TTTS before 26 weeks were referred to another institution for FLP, except for 1 case which was a 24-week acute-onset TTTS referred from a nearby tertiary center that necessitated immediate delivery. In the FLP-treated group, mean gestational age at delivery was 33.5 ± 5.1 weeks (range 25 + 2 to 37 + 1 weeks). There was 1 case of labor pain within 7 days following FLP. In the non-FLP-treated group, mean gestational age at delivery was 29.2 ± 4.1 weeks (range 24 + 3 to 32 + 1 weeks). Neonatal outcomes of the TTTS cases are summarized in Table 3. In the FLP-treated group, there were no instances of neonatal death or cerebral palsy. However, in the non-FLP-treated group, there was 1 case which resulted in neonatal death and cerebral palsy with periventricular leukomalacia. Of 9 donor twins, 8 survived and 1 died during the neonatal period (survival rate of 89%). All recipient twins survived (survival rate of 100%). The survival rate of both twins was 94%.

sIUGR was diagnosed in 11 cases (16%) and the mean gestational age at diagnosis was 26.7 ± 5.4 weeks (range 17 + 1 to 33 + 0 weeks). sIUGR cases were classified into 3 groups based on umbilical Doppler flow according to the type of umbilical artery Doppler diastolic flow in the IUGR twin, Type I: normal, II: persistent absent or reversed end-diastolic velocity (AREDV), and III: intermittent AREDV. There were 10 cases with Type I and 1 case was Type III (Table 4). The incidence of TTTS after an initial diagnosis of sIUGR was 1 out of 10 (10%) in Type I. It progressed into TTTS at 29 weeks of gestation (case No11). Out of the 10 cases of sIUGR we reviewed, the mean gestational age at delivery was 33.3 ± 2.3 weeks (range 30 + 0 to 36 + 4 weeks) and the rate of birth weight discordance was from 23 to 46% (median, 35%). Non-reassuring fetal status (NRFS) in the smaller twin was observed in 5 cases (50%). Rate of birth weight discordance of NRFS cases tended to be higher compared with reassuring status fetal (RFS) cases. In terms of placental findings, placental territory of smaller twin was from 20 to 50% (median 38 ± 8%). In Type III cases, placental territory of the smaller twin was significantly smaller (20%). The incidence of velamentous and marginal cord insertion for the smaller twin were 70% (7/10) and 30% (3/10), respectively. There were no cases of a smaller twin with normal cord insertion. All cases of velamentous cord insertion were diagnosed Type I. Unfortunately, we could not analyze all placental vascular anastomoses in this study. Table 5 shows neonatal outcomes in sIUGR cases. Neonatal death and neurological complications were not observed (survival rate, 100%), but respiratory and cardiac managements were required in the larger twin in 8 cases. Marked cardiac hypertrophy was seen in the larger twin without sign



TTTS = twin-to-twin transfusion syndrome, sIUGR = selective intrauterine growth restriction, IUFD = intrauterine fetal death

Fig. 1 Summary of perinatal outcome

Table 1 Cases of Twin-to-Twin Transfusion Syndrome treated with fetoscopic laser photocoagulation

Case	GA at diagnosis	Quintero stage	Cardiomegaly in recipient	GA at FLP	GA at delivery	Birth weigh (g)	Birth weight discordance(%)
1	21w0d	Ⅱ	No	21w3d	36w2d	2610/1825	30
2	18w2d	Ⅲ	No	19w3d	36w3d	2105/1545	27
3	20w5d	Ⅱ	No	21w2d	28w2d	1324/1274	4
4	20w5d	Ⅰ	No	21w2d	37w1d	2450/1894	22
5	24w2d	Ⅳ	Yes	24w5d	25w2d	882/702	20
6	20w0d	Ⅲ	No	21w0d	36w6d	2744/1552	43

GA = gestational age, FLP = fetoscopic laser photocoagulation

Table 2 Cases of Twin-to-Twin Transfusion Syndrome not treated with fetoscopic laser photocoagulation

Case	GA at diagnosis	Quintero stage	Cardiomegaly in recipient	Background	GA at delivery	Birth weight (g)	Birth weight discordance (%)
1	24w3d	Ⅳ	Yes	Transferred from another hospital	24w3d	940/551	41
2	27w1d	Ⅰ	No	Transferred from another hospital	32w1d	1649/1180	28
3	29w6d	Ⅰ	No	Progressed from sIUGR	30w5d	1390/894	36

GA = gestational age, sIUGR = selective intrauterine growth restriction

Table 3 Neonatal outcomes of Twin-to-Twin Transfusion Syndrome

	Treated with FLP (n = 6)		Without FLP (n = 3)	
	Donor	Recipient	Donor	Recipient
Tracheal intubation	2	2	3	3(→1 CLD)
Catecholamine treatment	2	1	1	2
Anemia	0	0	1	0
Hypervolemia	0	0	0	1
Heart Failure	0	0	0	1
Neonatal death	0	0	1	0
Neurological complications	0	0	0	1 (PVL, CP)

FLP = fetoscopic laser photocoagulation, CLD = chronic lung disease,
PVL = periventricular leukomalacia, CP = cerebral palsy

Table 4 Clinical and placental character of selective intrauterine growth restriction cases

Case	Type	GA at diagnosis (weeks)	NRFS in smaller twin	GA at delivery (weeks)	Birth weight (g)	Birth weight discordance (%)	Cord insertion for smaller twin	Placental territory of smaller twin (%)
1	1	29	Yes	33	1887/1119	41	marginal	40
2	1	17	No	34	1973/1520	23	velamentous	40
3	1	33	No	36	2500/1750	30	marginal	40
4	1	29	Yes	30	1308/815	38	velamentous	40
5	1	29	Yes	30	1464/792	46	velamentous	40
6	1	23	Yes	32	1591/911	43	velamentous	40
7	1	18	No	31	1736/1176	32	velamentous	50
8	1	24	No	31	1531/1134	26	velamentous	40
9	1	27	No	36	2696/1873	31	velamentous	30
10	3	34	Yes	34	1950/1112	43	marginal	20
11*	1	25	Yes	30	1390/894	29	normal	50

GA = gestational age, NRFS = nonreassuring fetal status
*Progressed into TTTS at 29 weeks of gestation

Table 5 Neonatal outcomes of selective intrauterine growth restriction cases

	Larger twin	Smaller twin
Tracheal intubation	6*	5*
Catecholamine Treatment	7*	2*
Anemia	0	2*
Hypervolemia	0	0
Heart Failure	1#	0
Neonatal death	0	0
Neurological complications	0	0

*Type Ⅲ cases included, #a case with "cardiomegaly in the larger twin"

Table 6 Clinical characteristics of Amniotic Fluid Discordance cases

Case	GA at Diagnosis	MVP (mm)		Abnormal UA Doppler	Disease Progression	Birth Weight Discordance (%)	Recipient cardiomegaly
		Recipient	Donor				
1	17w0d	78	12	No	TTTS stage III (18w2d)	26	No
2	24w1d	71	11	No	TTTS stage IV (24w2d)	17	Yes
3	21w3d	73	24	No	sIUGR type I (25w3d)	21	No

GA = gestational age, MVP = maximum vertical pocket, UA = umbilical artery
TTTS = twin-to-twin transfusion syndrome, sIUGR = selective intrauterine growth restriction

of TTTS at 29 weeks of gestation in 1 case (No7), and the outcome of the larger twin was more serious than the smaller twin. AFD was identified in 3 cases (4%). Characteristics of AFD are listed in Table 6. Two of the 3 cases (67%) progressed to TTTS. One was Quintero stage III, and the other was stage IV when they first fulfilled the diagnostic criteria for TTTS. The third case of AFD progressed to sIUGR. There were no cases of TAPS identified at birth.

DISCUSSION

TTTS, which occurs in approximately 15% of MD twin pregnancies, is associated with very high perinatal mortality and morbidity [1, 2]. The pathophysiology of TTTS relies on an unbalanced circulating blood flow from the donor twin to the recipient twin via placental anastomoses. Untreated TTTS cases result in perinatal death in 90% of cases and impaired neurological development in up to 50% of survivors due to prematurity or intrauterine death of the other twin [2]. Several treatments, such as amniodrainage, septostomy, selective feticide, and FLP aim to improve the prognosis [3]. FLP has been established as the primary treatment for a monochorionic twin pregnancy associated with TTTS between 16 and 26 weeks of gestation. Retrospective studies have noted that FLP resulted in higher survival rates and lower rates of neurological complications [1, 4–6].

In our study, a total of 69 MD twin pregnancies were included. TTTS occurred in 9 cases (13%) and

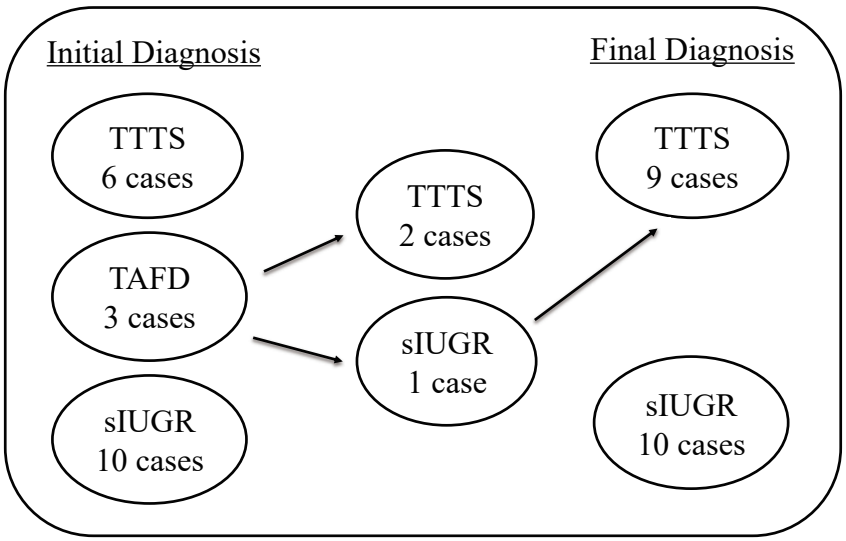
those TTTS cases without FLP treatment were associated with a poorer prognosis. A total of 11 cases of MD twins with sIUGR were followed over the period of this study. More neonates required tracheal intubation and catecholamine treatment in the larger twin group, compared to the smaller twin group. All 3 AFD cases included in this study developed to TTTS or sIUGR. We suggest that AFD should be recognized as a predictor for TTTS or sIUGR.

In our study, TTTS cases without FLP, which resulted in the neonatal death of a recipient and chronic lung disease of a donor, were associated with a poor prognosis. From these results, it is essential to recommend FLP as a treatment for patients with TTTS. Some studies have shown that the survival of both fetuses was affected by the Quintero stage [7, 8]. Although early detection is important, TTTS often progresses rapidly, making it difficult to detect all early cases of TTTS with bi-weekly surveillance. Previous studies have demonstrated that a crown-rump length (CRL) discrepancy, nuchal translucency (NT) discrepancy, and abnormal blood flow in the ducts venosus in the first trimester are predictive markers for the development of TTTS [16–20]. It is important to identify high-risk cases of developing TTTS to allow referral to another institution for earlier FLP treatment. Recently, FLP treatment for TTTS after 26 weeks of gestation has been reported [21–23]. Valsky *et al.* compared the outcomes of 28 TTTS cases treated with FLP between 28 + 0 and 28 + 6 weeks of gestation with 324 cases treated between 15 + 0 and 25 + 6 weeks during a 3-year period. This study showed that FLP for TTTS after 26 weeks of gestation had similar outcomes to cases treated with FLP before 26 weeks [21]. Nakata *et al.* performed a prospective study investigating all cases of TTTS with an MVP ≥ 10 cm in the recipient between 26 and 28 weeks of gestation [22]. These studies described that FLP may be a therapeutic option for TTTS after 26 weeks, especially at 26–28 weeks of gestation. The use of FLP for treatment of TTTS is expected to expand.

sIUGR affects about 10–25% of MD twin pregnancies [24]. The pathophysiology of sIUGR is the presence of unequal placental sharing and unbalanced blood-flow through the placental anastomoses, which is the main factor responsible for perinatal outcome. Gratacos *et al.* compared the prognoses in sIUGR cases diagnosed in the 2nd trimester using a classification based on the characteristics of umbilical artery (UA) Doppler diastolic flow in the IUGR twin as previously mentioned [25]. They reported that Type II and Type III pregnancies delivered significantly earlier and the fetal weight discordance was markedly higher in comparison with Type I cases. Deterioration of the smaller twin occurred in 90% of Type II pregnancies, 10.8% of Type III pregnancies, and 0% of Type I pregnancies. The prevalence of parenchymal brain lesions on neonatal ultrasound scans in the larger twin was observed in 19.7% of Type III pregnancies, 3.3% of Type II, and 0% in Type I [25]. Several reports have demonstrated the outcome of sIUGR according to this classification [26–28]. Ishii *et al.* described that the outcome of sIUGR with an abnormal UA Doppler was markedly poor, while a normal Doppler seemed to be associated with a good prognosis [26]. In our retrospective study, neonatal death and neurological complications were not observed in our sIUGR cases. However, deterioration of the smaller twin occurred in 5 cases (50%) that were Type I and 1 case of Type III. During the neonatal period, respiratory and cardiac managements were required in 7 cases (70%) of the larger twin group and in 5 cases (50%) of the smaller twin group. An abnormal Doppler flow of the UA in the IUGR twin may be an important indicator for prognosis in sIUGR. In addition, some studies demonstrated MD twins with velamentous cord insertion were at an increased risk of birth-weight discordance compared with a normal insertion group [29, 30]. Cambiaso *et al.* reported a highly significant association between birth-weight discordance and discordance cord insertions that defined if the cord insertions of both fetuses were normal and velamentous or marginal [30]. In our study, the incidence of velamentous and marginal cord insertion for the smaller twin were 70% (7/10) and 30% (3/10), respectively. Normal cord insertion for the smaller twin was not found in any of our cases. We couldn't compare with outcome of smaller twin with normal cord insertion. It is possible to image the placental cord insertion from the first trimester. Several reports have also demonstrated that CRL discrepancy in the first trimester is another useful prognostic maker for the development of sIUGR [19]. Assessing these factors may help predict adverse perinatal outcomes. Current treatment for these disorders includes expectant management, termination of pregnancy, or umbilical cord occlusion. Recently, several reports have described FLP as a treatment method for sIUGR with AREDV in the UA [31–33]. They advocated that FLP treatment for sIUGR may be beneficial when it is accompanied by AREDV in the UA and severe oligohydramnions of the twins. The application of FLP for sIUGR may improve its prognosis.

AFD is defined as a condition that does not satisfy the diagnostic criteria for TTTS. Some reports have described perinatal outcomes in MD twin pregnancies with AFD. Huber *et al.* reported that AFD in combination with sIUGR and AREDF in the UA in one fetus of an MD twin pregnancy represented an extremely high-risk condition for adverse pregnancy outcome [34]. In our study, AFD was diagnosed in 3 cases, 2 of those cases progressed to TTTS and 1 case progressed to sIUGR and then to TTTS at 29 weeks of gestation (Fig. 2). This indicates there is overlap between AFD, TTTS, and sIUGR. AFD may be a risk factor for TTTS and sIUGR. Previous reports have demonstrated AFD detected early in the second trimester was useful for predicting severe TTTS development [35–37]. Van Mieghem *et al.* identified moderate amniotic fluid discordance as a predictive factor for TTTS and sIUGR. Sensitivity and specificity for the development of TTTS were 77% and 91%, respectively. They were 90% and 81%, respectively, for the development of sIUGR [35]. Yamamoto *et al.* reported a sensitivity and specificity of 70% and 91%, respectively, when using an inter-twin amniotic fluid difference ≥ 4 cm between 16 and 18 weeks of gestation [36]. Management protocols for AFD without signs of TTTS are still controversial.

Application of FLP for the treatment of AFD has been challenging. Ozawa *et al.* performed FLP on 11 cases of AFD with AREDV in the UA [37]. The surviv-



TTTS = twin-to-twin transfusion syndrome, AFD = aminiotic fluid discordance
sIUGR = selective intrauterine growth restriction

Fig. 2 Summary of diagnosis progression

al rates of the donor and the recipient twins were 27% (3/11) and 100% (11/11), respectively. They concluded that FLP dose not seem to be a promising treatment for AFP with AREDV in the UA. The establishment of a management protocol for patients with AFD is desirable. In our study, the number of cases was too small to analyze statistically, but all cases progressed to TTTS or sIUGR. Based on these results, AFD should be recognized as a predictor for TTTS or sIUGR and managed strictly for early detection of both outcomes.

One of the main limitations of this study is the small number of cases in each disease, especially in AFD where a larger evaluation is required. Further studies, including evaluation of prognostic factors in the first trimester, are required to allow a more precise subgroup categorization that enables optimal management on TTTS-related disorders.

CONCLUSIONS

TTTS and TTTS-related disorders are most likely overlapping pathological conditions. AFD should be recognized as a potential predictor of TTTS and sIUGR.

ACKNOWLEDGEMENTS

We would like to acknowledge staff members of the neonatal intensive care unit at the Tokai University School of Medicine Hospital.

CONFLICT OF INTEREST

We have no conflicts of interest to declare.

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