

Twin amniotic fluid discordance below 26 weeks of gestation for predicting adverse outcomes

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Aim: To identify the threshold of monochorionic twins with amniotic fluid discordance (TAFD) below 26 weeks for predicting progression to adverse outcomes. **Method:** A retrospective study involving 68 women of monochorionic twins that do not meet fetoscope laser photocoagulation criteria was conducted. The TAFD was calculated as the vertical pocket of Twin 1 minus that of Twin 2, and the maximum TAFD in any period from 14 weeks to below 26 weeks was identified. We then calculated the ratio of the vertical pocket of Twin 1 to that of Twin 2 as the maximum TAFD ratio. We attempted to elucidate the cut-off value of the maximum TAFD ratio for adverse outcomes including cases that progressed to twin-twin transfusion syndrome (TTTS) after 26 weeks, twin anemia-polycythemia sequence, or neurologic abnormalities. **Results:** There were 21 cases of selective intrauterine growth restriction (sIUGR), 4 cases of twins that developed TTTS, one case of twins that developed TTTS with neurologic abnormalities, and 4 cases of twins that developed neurologic abnormalities. The median maximum TAFD ratio of the study group was 1.5. ROC curve analysis showed that a maximum TAFD ratio of 1.9 was the optimal cut-off value. In cases where the maximum TAFD ratio was greater than 1.9, the odds ratio for adverse outcomes was 15.4 when considering the presence of sIUGR. All cases of twins with neurological abnormalities had a maximum TAFD ratio greater than 1.9. **Conclusion:** Maximum TAFD ratio greater than 1.9 below 26 weeks increased adverse outcomes in monochorionic twins.

Keywords

MD twins; Amniotic fluid discordance; Twin-twin transfusion syndrome; Neurological abnormalities; 2nd trimester

1. Introduction

The prognosis of twin-twin transfusion syndrome (TTTS) of monochorionic twins has been improved by fetoscope laser photocoagulation (FLP) [1, 2]. According to a recent review of FLP for TTTS in Japan, a 70% survival rate of both twins and a 90% survival rate of at least one twin has been achieved [3]. However, it is true that 11~14% of living twin children have an adverse neurological outcome after FLP [3]. In overseas reports, the proportion of adverse neurological outcome was 14~18%, almost the same as in Japan [4, 5]. Investigations into the effects on neurological outcome after FLP are still ongoing [6]. Although FLP is currently the optimal treatment for TTTS, the achievement of intact survival of TTTS has yet to be realized.

On the other hand, even if the conventional criteria of FLP for TTTS are not met, monochorionic twins with amniotic fluid discordance (TAFD) have been found to be at risk of adverse outcomes. For example, constant TAFD with absent or reversed end-diastolic flow of umbilical artery is strongly associated with adverse perinatal outcomes in terms of both overall and intact survival [7]. TAFD without meeting the criteria for FLP is also strongly associated with twin anemia-polycythemia sequence (TAPS) [8]. Although it might be possible to expand the indication of FLP to TAFD on the basis of adverse outcomes with the presence of TAFD, treatment with FLP is not so promising in cases of TAFD bordering on TTTS [9]. The obstacles in achieving intact survival have yet to be overcome in the case of monochorionic twins with TAFD. At this time, there is no doubt that monochorionic twins that do not meet the criteria for FLP treatment need to be carefully examined in an effort to identify at-risk cases that require close observation to identify future disabilities.

Under the current conventional criteria of FLP for TTTS, up to 26 weeks is given as the period to determine whether to engage in FLP for TTTS [10]. Identifying TAFD thresholds below 26 weeks of gestation to predict adverse outcomes for monochorionic twins that do not meet FLP criteria may help in management strategies after 26 weeks of gestation and follow-up twins after birth. Therefore, we conducted this study to identify the threshold of TAFD below 26 weeks of gestation for predicting progression to adverse outcomes including neurologic abnormalities.

2. Materials and methods

Approval of this clinical study was obtained from a suitably constituted ethics committee at the University of Miyazaki (#2019-0-0562). We underwent a retrospective study of pregnant women with monochorionic diamniotic twins (MD twins) who were managed at the University of Miyazaki Hospital Perinatal Center from January 2010 to May 2019. The University of Miyazaki is a tertiary center in Miyazaki Prefecture, Japan. The University Hospital has dealt with a number of high-risk cases and in this instance 182 cases of twins were investigated during the designated period.

Diagnosis of MD twins was basically performed by transvaginal ultrasonography by 10 weeks of gestation. From 10 weeks onward, membranous diagnoses were made with reference to number of placentae, sex of the twins, and characteristics of the intertwin membrane such as “T-sign” for monochorionic twins. Cases comprising MD twins without congenital anomalies were selected. After 16 weeks, ultrasound examination for MD twins was performed once every 2 weeks. If there seemed to be an AFD, we performed weekly ultrasound examination. We excluded cases with TTTS cases who underwent FLP, cases with twin reversed arterial perfusion (TRAP) sequence, and cases with unknown amniotic fluid volume less than 26 weeks from the study group. The conventional criteria employed for FLP was as follows: MVP of at least 8 cm in Twin 1 and 2 cm or less in Twin 2 at 16 weeks or more and less than 26 weeks of gestation [3, 11].

From 26 weeks onward, the diagnosis of TTTS was made by the presence of a maximum vertical pocket (MVP) of at least 8 cm in Twin 1 and 2 cm or less in Twin 2, regardless of the gestational age at diagnosis [12]. Pregnancy was terminated in cases diagnosed with TTTS after 26 weeks and cases of pregnancy with hypertension syndrome involving persistent severe hypertension (blood pressure > 160/110 mmHg), oligouria (< 500 mL/day), low platelet count (< 100,000/mm³), HELLP syndrome (hemolysis, elevated liver enzyme and low platelets), pulmonary edema or eclampsia. In cases of persistent non-reassuring fetal heart rate patterns in at least one twin or cases involving an MD-twin score of 3 points after 26 weeks of gestation, pregnancy was also terminated. The MD-twin score consists of five abnormal variables including fetal weight discordance (intertwin estimated fetal weight discordance above 25%), amniotic fluid discordance (MVP of at least 8 cm in Twin 1 or 2 cm or less in Twin 2), hydrops fetalis, abnormal umbilical cord insertion (marginal or velamentous cord insertion), and abnormal fetal heart rate pattern (occasional late deceleration, occasional severe variable deceleration, sinusoidal, or loss of variability). Each abnormal variable was assigned a value of 1. We have adopted management using MD-twin scores after 26 weeks of gestation, and a total score of 3 or more will increase the number of adverse outcome cases including neurologic abnormalities [13].

From the medical charts of women with MD twins, the following maternal and perinatal demographic data were collected: maternal age, parity (primipara), history of assisted reproductive technology (ART) including artificial insemination with the partner’s semen and embryo transfer, the gestational age (weeks) at which the TAFD was determined, BMI before conception, gestational age at delivery (weeks), presence of selective intrauterine growth restriction (sIUGR), and presence of placental vascular anastomosis such as AA: arterio-arterial anastomosis (AA), veno-venous anastomosis (VV), or arterio-venous anastomosis (AV). The presence of anastomosis was confirmed by observing the filling pattern of colored milk into the contralateral circulation. The number

of anastomoses was expressed as AA × number (n). sIUGR was defined as an intertwin estimated fetal weight discordance above 25%. The calculation was performed as follows: (weight of the larger twin-weight of the smaller twin)/weight of the larger twin × 100 [9]. The TAFD was calculated as the MVP of Twin 1 minus the MVP of Twin 2 (cm) according to the method of Van Mieghem *et al.* [14]. The maximum TAFD in any period from 14 weeks to below 26 weeks, which did not meet the TTTS criteria, was identified. We then calculated the ratio of the vertical pocket of Twin 1 to that of Twin 2 as the maximum TAFD ratio. Since gestational age is associated with amniotic fluid volume [15, 16], the ratio of MVP between twins was used to minimize the involvement of gestational age.

Adverse outcomes were investigated and included evaluations of cases that progressed to TTTS after 26 weeks, cases with twin anemia polycythemia sequence (TAPS), cases in which either of the twins died in utero or newborn after 26 weeks, cases that progressed to cerebral palsy (CP) or mental retardation (MR), and cases diagnosed with hypoxic-ischemic encephalopathy (HIE) or periventricular leukomalacia (PVL) by neonatal MRI. Independent pediatric neurologists that were blinded to the current study performed the neurodevelopmental assessment of a child with CP and MR. Assessment was performed by an independent pediatric neurologist using the Enjoji Scale of Infant Analytical Development or the Kyoto Scale of Psychological Development 2001 at 1 year of age or older [17].

We initially divided the study into two groups according to MD twins with adverse outcomes or without, and then compared the demographic data between groups. To determine the optimal cut-off value of the maximum TAFD ratio below 26 weeks for extracting adverse outcome cases from the study group was calculated using Receiver Operating Characteristic Curve (ROC) analysis. For comparison, the optimal cut-off the value of maximum TAFD (cm) was also calculated. After determining the optimal cut-off value, the odds ratio of maximum TAFD ratio for predicting progression to adverse outcomes after 26 weeks was then examined. Furthermore, the odds ratio was corrected by taking into account the presence of sIUGR, which seems to be related to neurologic outcome [18]. For these purposes, a χ^2 test and multiple logistic regression analysis were performed. Comparisons between groups were made using the χ^2 test or Mann-Whitney U test. Data are expressed as a median (interquartile range) or percentage (n/N). Probability values < 0.05 were considered significant.

3. Results

Eighty-eight cases of MD twins were identified during the study period. There was one case of MD twins in which one twin had a congenital anomaly. Ten cases of MD twins with TTTS that had developed by 26 weeks of gestation, 3 cases of MD twins with TRAP sequence, and 6 cases of MD twins with unknown amniotic fluid volume less than 26

Table 1. Characteristics of study group.

Study cases	68	Adverse outcome cases*	Without	P
		9	59	
Maternal age (years)	31.5 (27.8~35.0)	31.0 (29.0~34.0)	32.0 (27.5~35.0)	0.58
Primipara	45.6% (31/68)	44.4% (4/9)	45.8% (27/59)	0.94
History of ART	13.2% (9/68)	0% (0/9)	15.2% (9/59)	0.21
BMI before conception	20.5 (19.2~22.7)	21.1 (18.2~22.3)	20.5 (19.3~22.9)	0.60
Gestational age of diagnosis of maximum TAFD (weeks)	23.3 (20.9~24.7)	24.3 (18.0~23.6)	23.1 (21.0~24.7)	0.32
Maximum TAFD (cm)	2.2 (1.3~2.9)	3.4 (2.8~4.2)	2.0 (1.2~2.6)	< 0.01
Maximum TAFD ratio	1.5 (1.3~1.9)	2.5 (1.9~3.3)	1.5 (1.3~1.8)	< 0.01
Gestational age at delivery (weeks)	34.9 (31.2~36.9)	30.0 (27.9~31.0)	35.0 (32.1~37.0)	0.01
sIUGR	30.9% (21/68)	55.6% (5/9)	27.1% (16/59)	0.09

Results are expressed as median (interquartile range) or percentage (n/N). Comparisons between groups were made using the χ^2 test or Mann-Whitney U test. ART: assisted reproductive technology, TAFD: monochorionic twins with amniotic fluid discordance, sIUGR: selective intrauterine growth restriction, *: cases that progressed to twin-twin transfusion syndrome after 26 weeks or neurologic abnormalities.

weeks were also identified. Excluding these 20 cases, 68 cases of MD twins were included in the study group.

The median maternal age of the study group was 31.5 years (interquartile range, 27.8~35.0 years) and the percentage of primipara pregnancies was 45.6% and that of ART was 13.2%. The gestational age of diagnosis of maximum TAFD was 23.3 weeks (interquartile range, 20.9~24.7 weeks). The median maximum TAFD and the median maximum TAFD ratio were 2.2 cm and 1.5, respectively. The median gestational age at delivery was 34.9 weeks (interquartile range, 31.2~36.9 weeks). There were 21 cases of MD twins (30.9%) in which one twin had sIUGR. There were 9 cases of MD twins with adverse outcomes in the study group (Table 1).

There were no significant differences between MD twins with adverse outcomes and MD twins without adverse outcomes in terms of maternal age, parity, history of ART, BMI before conception, or presence of sIUGR (Table 1). The timing of diagnosis of maximal TAFD was not significantly different between groups. There were significant differences between groups in terms of maximum TAFD, maximum TAFD ratio, and gestational age at delivery ($P < 0.01$, $P < 0.01$ and $P = 0.01$, respectively).

There were 4 cases of MD twins that developed neurologic abnormalities, 4 cases of MD twins that developed TTTS after 26 weeks, and one case of MD twins that progressed to both TTTS and neurologic abnormality (Table 2). There were no cases of TAPS during the study period. In four cases of MD twins that developed TTTS after 26 weeks, there was one case of MD twins with selective FGR. In four cases of MD twins that developed neurologic abnormalities, all cases were MD twins with selective FGR. Of these, two infants with neurologic abnormalities were smaller co-twins and the remaining four were larger co-twins. In the case of twins that developed to TTTS with neurologic abnormalities, the neurologically abnormal infant was the larger co-twin and showed 10.8 cm of the maximum TAFD (maximum TAFD ratio = 5.9), which was close to the FLP criteria. AV anas-

tomosis in adverse outcome cases was more relevant at the maximum TAFD ratio of ≥ 1.9 (Table 2).

The optimal cut-off value of the maximum TAFD ratio below 26 weeks for predicting progression to adverse outcome cases of MD twins was calculated using ROC curve analysis. As seen from the ROC curve in Fig. 1, the area under the curve (AUC) was 0.81 with statistical significance (95% confidence interval: 0.65~0.97), and the shortest distance from the upper left corner and the maximum product of sensitivity and specificity was at 1.9 (sensitivity 0.78, specificity 0.81). On the other hand, the AUC of the maximum TAFD (cm) was 0.79 (95% confidence interval: 0.62~0.95) and lower than that of the maximum TAFD ratio. The optimal cut-off value of the maximum TAFD was 2.8 cm.

In cases where the maximum TAFD ratio was greater than 1.9, the odds ratio for adverse outcome was 15.3 (95% confidence interval: 2.8~83.8). When considering the presence of sIUGR, the odds ratio for adverse outcome was 15.4 (95% confidence interval: 2.3~104.1). There was no association with the presence of sIUGR (odds ratio: 1.0, 95% confidence interval: 0.2~5.7). All cases of MD twins with neurologic abnormalities had a maximum TAFD ratio greater than 1.9.

4. Discussion

Our study represents the first reported attempt to set a cut-off value of the maximum TAFD ratio below 26 weeks of gestation that covers predicting neurological prognosis of MD twins. When the cut-off value of the maximum TAFD ratio below 26 weeks of gestation was 1.9, all cases of MD twins with neurologic abnormalities and more than half of MD twins that progress to TTTS after 26 weeks could be extracted. Using the maximum TAFD ratio as an index in lieu of the maximum TAFD (cm) was superior in setting the cut-off value for detecting cases of MD twins with adverse outcomes. Apart from TTTS, it has been shown that sIUGR is involved in adverse outcomes including neurologic abnormalities [18], and we showed that a maximum TAFD ratio

Table 2. Details of adverse outcome cases in study group.

Case	Maximum TAFD (cm)	Maximum TAFD ratio	Gestational age at diagnosis of maximum TAFD (weeks/ days)	Gestational age at delivery (weeks/days)	TTTS	sIUGR	Birth weight of twins (g)	Neurologic abnormalities		Vascular anastomosis
								Smaller or larger co-twin	type	
1	1.1	1.2	22/2	35/0	+	–	1988/2108	–	–	AA × 1
2	2.2	1.6	23/4	29/4	+	–	980/1111	–	–	VV × 1
3	2.8	2.0	22/1	31/0	–	+	1090/1240	Smaller	HIE/MR	NA
4	3.4	2.5	24/5	31/3	–	+	1152/1472	Larger	PVL, CP	AA × 1, AV × 1
5	3.4	3.0	16/2	30/0	+	+	1054/1422	–	–	–
6	3.7	1.9	23/3	30/6	–	+	1122/1492	Larger	PVL	AA × 1, VV × 1, AV × 1
7	4.2	3.6	14/5	27/6	+	–	824/1024	–	–	AA × 1, AV × 1
8	4.8	3.3	18/0	26/1	–	+	494/686	Smaller/Larger	MR/PVL, MR	AA × 1, AV × 1
9	10.8	5.9	24/5	24/4	+	–	812/1172	Larger	PVL, CP	AV × 1

TAFD: monochorionic twins with amniotic fluid discordance, TTTS: twin-twin transfusion syndrome, sIUGR: selective intrauterine growth restriction, HIE: hypoxic-ischemic encephalopathy, MR: mental retardation, CP: cerebral palsy, PVL: periventricular leukomalacia, NA: not available, AA: arterio-arterial anastomosis, VV: veno-venous anastomosis, AV: arterio-venous anastomosis.

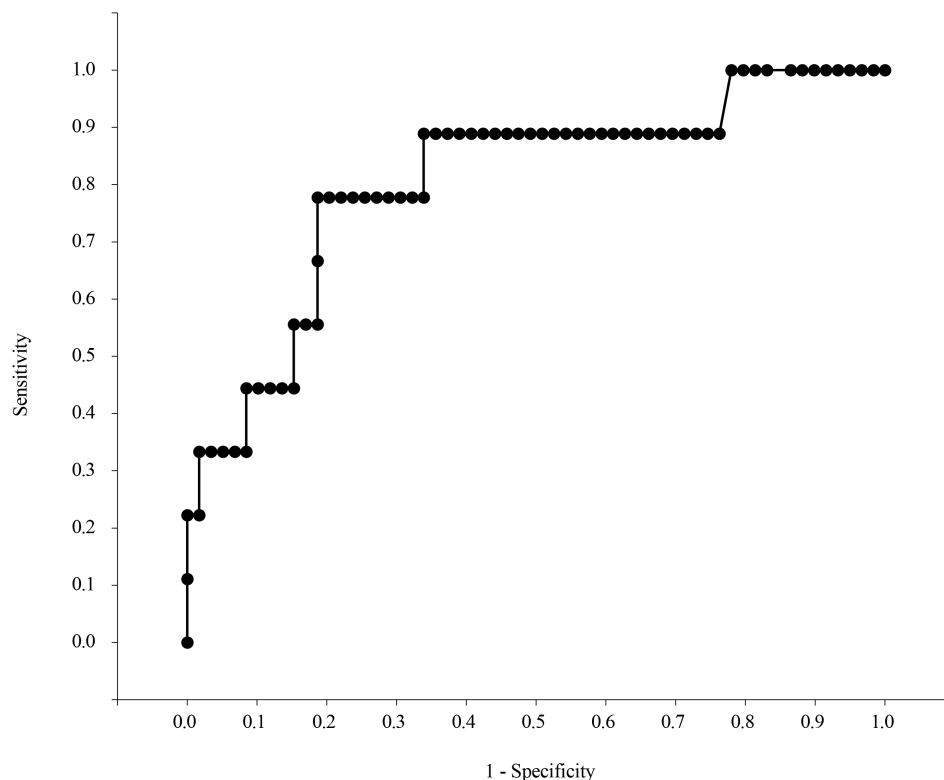


Fig. 1. ROC curve of maximum TAFD ratio for distinguishing adverse outcome cases in the study group. The AUC was 0.81 with statistical significance (95% confidence interval: 0.65–0.97), and the shortest distance from the upper left corner and the maximum product of sensitivity and specificity was at 1.9 (sensitivity 0.78, specificity 0.81), TAFD: monochorionic twins with amniotic fluid discordance.

greater than 1.9 is more strongly involved in adverse outcomes even considering the presence of sIUGR. In fact, in our study, MD twins with sIUGR alone did not increase the odds ratio for adverse outcomes. The clinical significance of TAFD that does not meet the diagnostic criteria of TTTS

below 26 weeks of gestation is presently under investigation. Identifying MD twin pairs with a maximum TAFD ratio greater than 1.9 is more sensitive and specific to predict adverse outcomes compared to identifying MD twin pairs with sIUGR.

To date, there are no effective screening tests to determine adverse outcomes for monochorionic twins in the first trimester [19]. At the early second trimester of 16 to 18 weeks of gestation, it has been reported that intertwin differences in anthropometric measurements such as abdominal circumference, femur length, head circumference, and fetal weight could not predict progression to TTTS, or composite neonatal outcomes including respiratory distress syndrome, intraventricular hemorrhage, an Apgar score less than 7, necrotizing enterocolitis, early-onset sepsis, and neonatal death [20]. In our study, identifying MD twin pairs with sIUGR does not appear to be an effective screening measure for predicting adverse outcomes although, clearly, findings such as AFD and abnormalities in blood flow of umbilical cord and fetus should be considered in lieu of anthropometric measurements. For example, constant TAFD with absent or reversed end-diastolic flow of umbilical artery is strongly associated with adverse perinatal outcomes in terms of both overall and intact survival, where TAFD is defined as ≤ 3 cm of the MVP of Twin 1 and ≥ 7 cm of the MVP of Twin 2, excluding TTTS [7]. Of course, while the aforementioned research attempts to expand the indications for FLP, treatment with FLP is not so promising in cases of TAFD bordering on TTTS [9]. Additionally, adverse outcomes of infants occurred among our MD twins that did not meet the above TAFD definition. Although our study did not compare the efficacy of predicting adverse outcomes of MD twins between blood flow assessment and TAFD, TAFD assessment is a promising tool for effectively identifying MD twins that need to be observed in the future.

In our examination, adverse outcome cases increased with a maximum TAFD ratio greater than 1.9. No other report has evaluated prognosis using the “ratio” of MVP between twins. On the other hand, in our examination, adverse outcome cases with neurological abnormalities also increased with maximum TAFD of at least 2.8 cm, and other reports also concentrated on a TAFD of 3 cm as the threshold. It has been reported that a TAFD of at least 3.1 cm in less than 20 weeks has an 86% chance of progressing to TTTS [14]. There are also reports that TAFD values of at least 3.0 cm are apt to become TAPS [8]. Recently, it was reported that TTTS did not develop in a large infant with subsequent neurological abnormality, and that no abnormalities in fetal blood flow showed for up to 32 weeks, and that the AFD gradually broadened followed by the emergence of abnormalities in blood flow [21]. Thus, the AFD may be due to premature disturbance of fluid dynamics of MD twins, resulting in irreversible changes at the tissue level before observable fetal or umbilical blood flow abnormalities occur.

With changes in the physiological state of amniotic fluid balance in TTTS, it is thought that there are firstly major changes in urine production and amniotic fluid circulation via the transplacental route [15]. On the donor twin, arteriovenous anastomosis causes a decrease in blood pressure, resulting in a decrease in urine output. In our cases, AV anas-

tomosis was observed in 4 out of 6 infants with neurological abnormalities. At the same time, reduced colloid osmotic pressure of the donor twins impairs the pathway through the placenta which is the primary source of amniotic fluid, and promotes reduced amniotic fluid volume [15]. Since these changes occur at the early second trimester, it makes sense to capture early physiological changes due to fetofetal transfusion via AV anastomosis in MD twins.

This study has some limitations. Since the number of adverse outcome cases is relatively small, investigation of a larger number of suffered cases of MD twins is necessary. Secondary, we did not perform detailed umbilical and fetal blood flow measurements. Additional studies are needed to determine whether blood flow abnormalities occur before any changes in amniotic fluid volume are observed. Furthermore, AV anastomosis may have an effect on AFD, it is necessary to examine the results including those without adverse outcomes.

In conclusion, we demonstrated that a maximum TAFD ratio greater than 1.9 in periods below 26 weeks increases adverse outcomes including neurologic abnormalities in monochorionic twins. Using the maximum TAFD ratio as an index in lieu of the maximum TAFD (cm) was superior in setting the cutoff value for detecting cases of MD twins with adverse outcomes in our study. Further studies of MD twins are required to determine the prognostic impact of second trimester AFD. It is also necessary to advance these studies in an effort to facilitate improvements in outcomes in monochorionic twins.

Author contributions

MF and SF designed the research study. HS advised on how to proceed with the clinical research. MF and SF collected and analyzed the data. MF and SF wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare no competing interests.

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