Outcome of Pregnancies Complicated by Twin-Twin Transfusion Syndrome in King Chulalongkorn Memorial Hospital

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Objective: *To study perinatal outcomes of pregnancies complicated by twin-twin transfusion syndrome (TTTS), which were treated with the authors' intervention modalities. Maternal outcomes of these populations were also explored.*
Material and Method: *All pregnancies diagnosed TTTS that delivered in King Chulalongkorn Memorial Hospital between January 2000 and November 2009 were enrolled in this descriptive study. Patients' data before August 2008 were retrospectively assessed. Perinatal survival, neonatal morbidities, and maternal outcomes were recorded and analyzed. Antenatal ultrasonographic findings were also analyzed to determine prognostic factors on perinatal outcomes.*
Results: *Twenty-five cases of TTTS were recruited in the present study. Overall perinatal survival was 58% (29/50) with no significant difference in perinatal in among various stages of disease ($p = 0.19$). Survival in stage I-II, stage III, and stage IV were 64.3%, 45.8%, and 75%, respectively. There was no maternal mortality in the present study. The most common maternal morbidity was preeclampsia (6/25; 24%). Progression of disease was the only significant prognostic factor for perinatal mortality ($p < 0.001$).*
Conclusion: *Overall perinatal mortality rate of TTTS in the presented populations was still high (42%). Progression of disease was the only significant prognostic factor for poor perinatal outcome in the preset study. Since the case number of the present study was too small, the conclusion that the prognosis of the conservatively treated TTTS was unrelated to the staging cannot be drawn.*

Keywords: *Twin-twin transfusion syndrome, Perinatal outcomes, Amnioreduction, Prognostic factors*

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Twin-twin transfusion syndrome (TTTS) is a major complication of twin pregnancy that affects 11-15% of monochorionic diamniotic (MCDA) twins[1]. The natural history of this complication is associated with 80-100% perinatal mortality rate and high morbidity rate[2]. This unbalanced perfusion of placental blood flow to both affected fetuses are the causes of volume overload of one fetus (recipient) and volume depletion of the other (donor)[3]. The characteristic feature of this condition can be inspected from the antenatal ultrasound. Several ultrasonographic findings suggestive of TTTS include monochorion, same sex of both fetuses, marked discordance in amniotic fluid volumes and characteristic features of donor (oligohydramnios) or recipient (polyhydramnios). In severe cases, the donor may present with severe growth restriction, hypoxemia and absent or reversed end diastolic flow (AREDF) in the umbilical artery, while the recipient may manifest with cardiomegaly, AREDF in ductus venosus, and hydrops[4,5].

Important management for these patients contains counseling and discussion about the natural course of the disease, prognosis, and plan of treatment. Early detection and transferring to a tertiary hospital are necessary steps of treatment in the public health system. Treatment modalities of TTTS in King Chulalongkorn Memorial Hospital include expectant management, serial amnioreduction, amniotic septostomy and selective feticide. Outcomes

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and prognosis of TTTS are essential information for counselor. Therefore, the authors aimed to study the outcomes of pregnancies complicated by TTTS after our treatment modalities. Perinatal outcomes are primary while maternal outcomes are secondary outcome measures. The authors hope the present study will be the crucial step for further research about TTTS in Thailand in the future.

Material and Method

Our multifetal care clinic has been established in the Division of Fetal Maternal Medicine for 10 years. The study population in the present study included all pregnancies diagnosed as TTTS. The patients who delivered in other hospitals were excluded. The present study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University. The present study design was the prospective collection and assessment of maternal and fetal data between August 2008 and November 2009. Patients' data before August 2008 were retrospectively assessed. Obstetric and neonatal data were recorded in a purpose-design data collection sheet. Outcome measures were perinatal survival, birth weights, Apgar scores, neonatal morbidities and maternal mortality/ morbidities. Antenatal ultrasonographic findings were also recorded and analyzed.

TTTS was diagnosed by antenatal ultrasonographic criteria of monochorionic placenta, same sex of both fetuses, polyhydramnios (DVP > 8 cm) in one and oligohydramnios (DVP < 2 cm) in the other. Intertwin membrane was identified before measurement of DVP in each twin and the measurement was not passed through any part of the fetus (Fig. 1). The recipient was recognized by these features, larger size, polyhydramnios, chronically full bladder, and on occasion, hydrops fetalis. The characteristics of the donor were smaller size, oligohydramnios, absent or tiny bladder volume. The authors classified severity of TTTS by Quintero criteria staging[5]. The diagnosis as TTTS was confirmed by at least two staff members in the division. Fetal weight was estimated by the formula of Hadlock et al[6]. Chrorionicity of placentas were confirmed by pathological examination. Three Ultrasound machines were used in the present study; GE Voluson 730, GE Voluson 730 Expert and GE E8 (GE Medical systems, Milwaukee, Wisconsin, USA) with a 2-7 MHZ curved array transducer.

Gestational age was based on the date of last normal menstrual period if certain date. Gestational age was confirmed by ultrasonography at first or early second trimester. If gestational age by last menstrual period and ultrasonography was > 7 days different, the authors indicated gestational age by ultrasonographic findings.

Regarding Doppler study, the authors obtained the umbilical artery (UA) from each twin at intra fetal location to ensure that this UA study was correctly studied in exact twin. Umbilical vein (UV) or ductus venosus (DV) were undertaken for assessment of severity in each twin as well.

Perinatal death was defined as a fetus that died in utero or within 28 days after birth at any gestation age. Fetal survival was defined as a fetus who could live more than 28 days after delivery. Management and intervention in the presented patients were individualized for their decision after counseling and discussion. Management or intervention options included expectant management, amnioreduction or serial amnioreduction, amniotic septostomy, selective feticide and termination of pregnancy. Endoscopic laser photocoagulation was still unavailable in our institution during the study period. Amnioreduction was performed by using a 21 gauge needle punctured into the sac of recipient and amniotic fluid was released until DVP was less than 8 cm or up to patient tolerance. Amniotic septostomy was performed by making one or a few holes in the intertwin membrane, using 21- gauge spinal needle. Selective feticide was performed in one case, using bipolar diathermy.

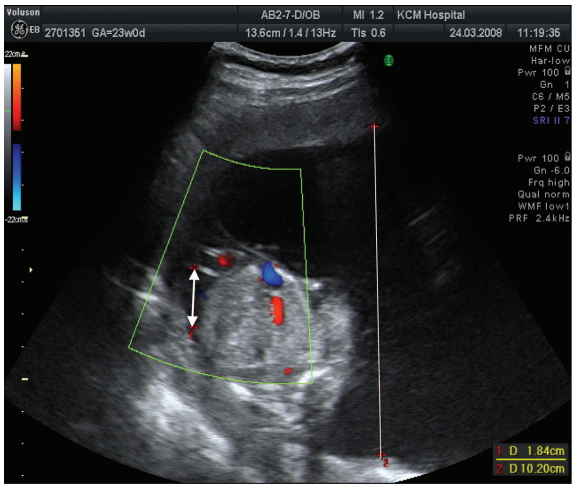

Fig. 1 Demonstration of DVP measurement of donor (double arrow line, left side of picture) and recipient (line, right side of picture)

Statistical analysis

Demographic and numerical data were presented as mean value and standard deviation or interquartile range of values. Categorical variables were presented as number of cases and percentage. Chi-squared and Fisher exact tests were used to determine the statistical significance of perinatal outcomes in each stage of TTTS and antenatal factors in predicting fetal outcomes. Prognostic factors on recipient and donor survival were presented as likelihood ratio. Confidence Interval Analysis (CIA) program was used to determine statistical significance of these prognostic factors.

Results

Twenty-seven cases of TTTS were found between January 2000 and November 2009. Twenty-two cases were retrospective study and five cases were prospective study. Two patients (both were stage I) delivered at other hospitals, therefore only 25 cases of TTTS were enrolled in the present study. Mean maternal age was 29.3 years, 18 of which (72%) were nulliparous. Mean gestation age at diagnosis was 22.9 weeks (interquartile range 15-32 weeks) (Table 1). All cases were categorized by Quintero staging system, 48% (12/25) of which were stage III. Mean gestational age at delivery was 31 weeks (interquartile range 20-40 weeks). The case that delivered at 40 weeks of gestation was TTTS stage III with donor demise at 23 weeks of gestation. After conservative treatment, the surviving fetus showed normal growth and Doppler study until spontaneous labor and vaginal delivery at 40 weeks of gestation. Seventeen pregnancies (68%) were delivered by cesarean section. Mean birth weight of recipients and donors were 2,179 g and 1,591 g, respectively. Twelve pregnancies (48%) were complicated by intrauterine fetal death (total 16 fetuses, six recipients, and 10 donors). Eight pregnancies had single fetal demise while both fetuses died in four pregnancies. Among the cases with single fetal demise, one of these was spontaneous abortion at GA 20 weeks of gestation, two selected termination of pregnancies, five pregnancies had single fetal survival. There was no neurological deficit of these surviving fetuses recorded during admission in the hospital.

Overall, perinatal survival was 58% (29/50), only one fetus (2%) was neonatal death. Perinatal survival in relation to severity of disease by Quintero staging system is demonstrated in Table 2. There were small numbers of cases in stage I (4 cases) and stage II (3 cases), therefore, the authors combined stage I and II and demonstrated them as the same group for perinatal survival. The perinatal survival in stage I-II

Table 1. Antenatal characteristics

Maternal age (yrs)*	29.3 $\pm$ 6.1
Nulliparity**	18 (72%)
Gestation at diagnosis (wks)***	22.9 (15-32)
Intervention**	
Amnioreduction	3 (12%)
Amniotic septostomy	1 (4%)
Amnioreduction and amniotic septostomy	10 (40%)
Selective feticide	1 (4%)
Termination of pregnancy	2 (8%)
Expectant	8 (32 %)
Antenatal corticosteroid**	15 (60%)
Gestation at delivery (wks)***	31 (20-40)
Diagnosis to delivery interval (wks)***	6.7 (0-20)
Last ultrasonography to delivery (days)***	2.4 (0-16)

* Present as mean $\pm$ standard deviation
** Present as number of cases (percentage of cases)
*** Present as mean (interquartile range)

Table 2. Impact of stage at diagnosis upon perinatal outcomes

Stage (no. of pregnancies)	No survivors n (%)	One survivor n (%)	Two survivors n (%)	At least one survivor n (%)	Recipient survivor N (%)	Donor survivor N (%)	Overall survival N (%)
I-II (7)	1 (14.2)	3 (42.9)	3 (42.9)	6 (85.8)	5 (71.4)	4 (57.1)	9/14 (64.3)
III (12)	5 (41.7)	3 (25.0)	4 (33.3)	7 (58.3)	6 (50.0)	5 (41.7)	11/24 (45.8)
IV (6)	1 (16.7)	1 (16.7)	4 (66.7)	5 (83.3)	5 (83.3)	4 (66.7)	9/12 (75.0)
Overall (25)	7 (28.0)	7 (28.0)	11 (44.0)	18 (72.0)	16 (64.0)	13 (52.0)	29/50 (58.0)

n = number of pregnancies cases
N = number of fetuses

was better than stage III (64.3% and 45.8%). However, the perinatal survival in stage IV was unexpectedly better than stage I-II (75% and 64.3%). There was no significant difference in perinatal survival with increasing in severity of disease (p = 0.19). Comparing between recipient and donor, overall recipient survivors were slightly more than donor (64% and 52%, p = 0.24).

The most common morbidity was neonatal hyperbilirubinemia, which occurred 58.8% in the recipient and in 53.8% in the donor. Respiratory distress syndrome (RDS) was the second most common morbidity that occurred in almost half of both recipient and donor survivors (47% and 46.2%). All of RDS neonates needed NICU and ventilator supports. Low Apgar scores at 1 and 5 minutes were found in both recipient and donor; median of the scores were 5, 7, and 6, 8, respectively. Other neonatal morbidities are shown in Table 3. The difference of these morbidities between recipient and donor did not reach statistical significance, except for cardiac failure (p = 0.02). There was no maternal mortality in the present study. The most common maternal morbidity was preeclampsia (6/25, 24%), most of which were mild preeclampsia (5/6). Only one case of stage I TTTS developed severe preeclampsia at 29 weeks of gestation and progressed to pulmonary edema. After treatment with dexamethasone to promote fetal lung maturity and magnesium sulfate to prevent eclampsia, the pregnancy was terminated by cesarean section. Both of her twins survived. Other maternal morbidity were gestational diabetes (12%), preterm labor (12%), PROM (12%). Eclampsia, postpartum hemorrhage, and puerperal infection were not found in the presented population.

The prognostic factors for prediction of perinatal outcomes are shown in Table 4 and 5. Progression of disease was the only significant prognostic factor for more chance of fetal death ($p < 0.001$). Neither recipient nor donor had specific prognostic factor for predicting their perinatal outcomes.

Discussion

The present study showed the outcomes of pregnancies complicated by TTTS, which mainly were treated by amnioreduction and/or amniotic septostomy (56% of cases). Overall perinatal survival rate was 58% which was higher than in the non-treatment population[2]. Two studies[7,8] had a large number of TTTS cases and were mainly treated by therapeutic amnioreduction (84.5% and 100% of cases). The overall perinatal survival rates in the first (112 cases) and second studies (223 cases) were 62.5% and 78%, respectively. The reason the presented overall perinatal survival rate was less than those of the two previous studies may be due to small number of cases and fewer cases of intervention. No statistical significance between the survival rate of recipients (64%) and donors (52%); p = 0.24. This outcome was similar to several previous studies[7-9].

Table 3. Neonatal outcomes

Outcomes	Recipient (n = 16)	Donor (n = 13)
Neonatal birth weight (g)*	2,179 ± (620.3)	1,591 ± (539.4)
Length of hospitalization (days)$^{\pi}$	32.6 (4-107)	40.4 (4-113)
Morbidity**		
1-min Apgar score < 7	6 (37.5%)	4 (30.8%)
5-min Apgar score < 7	2 (12.5%)	1 (7.7%)
NICU admission	8 (47.0%)	6 (46.2%)
Ventilator support	8 (47.0%)	6 (46.2%)
Respiratory distress	8 (47.0%)	6 (46.2%)
Hypoglycemia	4 (23.5%)	2 (15.4%)
Cardiac failure$^{\pi}$	6 (35.3%)	0 (0.0%)
NEC	1 (5.9%)	0 (0.0%)
Intraventricular hemorrhage	2 (11.8%)	2 (15.4%)
Patent Ductus Arteriosus	3 (17.6%)	3 (23.1%)
Sepsis	1 (5.9%)	2 (15.4%)

NEC = necrotizing enterocolitis; $^{\pi}$ = $p < 0.05$

* Present as mean ± standard deviation

** Present as number of cases (percentage of cases)

Table 4. Prognostic factors on perinatal outcomes

Prognostic factors (cases)	Number of survivors			p-value
	0	1	2	
Gestational age at diagnosis ≤ 20 weeks (10)	4	2	4	0.52
Weight Discordance ≥ 30% (14)	5	4	5	0.56
AEDF or REDF of UA in Donor (14)	6	3	5	0.17
Reverse a wave of DV or pulsatile of UV in recipient (7)	2	1	4	0.60
Progression of disease (14)	6	7	1	<0.001
Hydrops fetalis (8)	1	2	5	0.37
EFW of donor < 5th centile (13)	4	5	4	0.33

* AEDF = absent end diastolic flow; REDF = reversed end diastolic flow; UA = umbilical artery; DV = ductus venosus; UV = umbilical vein; EFW = estimated fetal weight

Table 5. Prognostic factors on recipient and donor survival chances

Prognostic factors	Recipient survival		Donor survival	
	LR (95% CI)	Survival chance (%)	LR (95% CI)	Survival chance (%)
Gestational age atdiagnosis ≤ 20 weeks	0.84 (0.32, 2.22)	60	0.92 (0.35, 2.41)	50
Weight discordance ≥ 30%	1.01 (0.40, 2.09)	64.3	0.51 (0.24, 1.10)	35.7
AEDF or REDF of donor	0.56 (0.29, 1.08)	50	0.69 (0.34, 1.41)	42.9
Reverse a wave of DV or pulsatile of UV in recipient	1.41 (0.34, 5.83)	71.4	1.23 (0.34, 4.40)	57.1
Progression of disease	0.42 (0.22, 0.83)	42.9	0.25 (0.09, 0.69)	21.4
Hydrops fetalis	1.69 (0.43, 6.68)	75	2.77 (0.69, 11.17)	75
EFW of donor < 5 centile	0.66 (0.32, 1.35)	53.8	0.79 (0.37, 1.69)	46.2

Neonatal morbidities in the study also showed no statistical significance between donors and recipients except neonatal cardiac failure which were found only in recipients (6 cases). This finding strongly represented the prenatal abnormal volume overload and caused cardiac dysfunction in recipients. Overall intraventricular hemorrhage (IVH) (13.3%) was less than an earlier study of Duncombe GJ et al, which were 27.9% in recipients, 9.8% in donors, and 19.4% overall[10]. This may reflect the benefit from antenatal usage of corticosteroid for promotion of fetal lung maturity[11].

Interestingly, perinatal survival rate in the present study was not correlated with the severity of the disease at first diagnosis. TTTS stage IV in the present study showed better outcomes than stage III and even in stage I-II. There have been many studies regarding validation of the Quintero staging system for indicating the prognosis and severity of disease. Taylor MJO et al reported no significant influence of stage at presentation on survival. They proposed that Quintero staging system did not indicate the outcome but might be more useful in monitoring disease progression[12]. Luks FI et al also concluded in their study that Quintero staging system might not be helpful in predicting the direction, degree or speed of progression of disease[13]. On the contrary, Duncombe GJ et al studied the perinatal characteristics and outcomes of 69 cases of TTTS and found direct relation between perinatal outcomes and Quintero staging of disease and gestation at delivery[10]. However, the case number in the present study was too small, so the conclusion that the prognosis of the conservatively treated TTTS was unrelated to the staging cannot be made.

Multiple gestations are at increased risk of adverse maternal outcome such as postpartum hemorrhage, pregnancy related hypertension, and a

higher cesarean section rate[14,15]. Preeclampsia was the most common maternal morbidity in the presented population. Agudelo AC et al[15] found that multiple gestation had adjusted RRs of 3.0 (95% CI, 2.9-3.3) for eclampsia, 2.2 (95% CI, 1.9-2.5) for preeclampsia, and 2.0 (95% CI, 1.9- 2.0) for postpartum hemorrhage. Sibai BM and colleagues[16] reported the rate of hypertensive disorder were significantly higher among twin gestations than among those with singleton gestations. They found the RR was 2.04 (95% CI, 1.6- 2.59) for gestational hypertension and 2.62 (95% CI, 2.03- 3.38) for preeclampsia. Maternal outcomes and morbidities in TTTS have not ever been the main objective of study and reported before. It might be due to the hypothesis that there was no difference in maternal outcome between TTTS and overall multiple gestation. However, due to the small number, the authors could not draw conclusion regarding outcomes of TTTS from the present study.

Until now, there are no strong prognostic factors for prediction of the fetal survival rate in TTTS. The prognostic factors the authors selected to study for chance for number of survivors came from the previous studies[8,17] and the authors reckoned most general obstetricians could examine these factors by themselves. Taylor MJO et al[17] studied the antenatal factors at diagnosis for prediction outcome of TTTS and found three factors that could independently predict poor survival outcomes. Those were AEDF or REDF of umbilical artery in the donor, abnormal pulsatility of the venous system in the recipient, and absence of an arterioarterial anastomosis. Another study[8] showed the survival rate was significantly related to gestational age at diagnosis, presence of AEDF in umbilical artery velocity waveforms, presence of hydrops, mean volume of amniotic fluid removed per week, large birth weight and gestational age at delivery. In the present study, the significant prognostic factors in previous studies such as AEDF or REDF of umbilical artery in donor, reversed a wave of DV in recipient and presence of hydrops were not statistically associated with perinatal outcomes. Progression of disease was the only significant prognostic factor that could predict perinatal outcome, which supported the previous study[12] that Quintero staging system had a role in monitoring disease.

An important limitation of the present study was the small number of the population. The main reasons were 1) the rarity of TTTS itself and 2) the study design of single center-based. At present, most studies about TTTS are designed as multicenter studies in order to collect larger number of cases. Therefore, further study as a multicenter trial is encouraged for more useful impact. Since laser therapy has proved to be the treatment of choice for severe TTTS, further multi-centered study including laser surgery should be performed.

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การศึกษาผลลัพธ์การคลอด ในครรภ์แฝดที่มีภาวะการถ่ายเทเลือดไม่สมดุลระหว่างทารกทั้งสอง ในโรงพยาบาลจุฬาลงกรณ์

สุขสันต์ กอแพร่พงศ์, สมชาย ธนวัฒนาเจริญ

วัตถุประสงค์: *เพื่อศึกษาผลลัพธ์การคลอดของหญิงตั้งครรภ์แฝดที่มีภาวะการถ่ายเทเลือดไม่สมดุล ระหว่างทารกทั้งสอง (TTTS) ซึ่งได้รับการดูแลรักษาที่โรงพยาบาลจุฬาลงกรณ์ รวมทั้งผลต่อมารดาจากการตั้งครรภ์ดังกล่าว*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงพรรณนาในหญิงตั้งครรภ์แฝดที่ได้รับการวินิจฉัย TTTS และคลอดบุตรที่โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่เดือน มกราคม พ.ศ. 2543 ถึง พฤศจิกายน พ.ศ. 2552 โดยเป็นการศึกษาย้อนหลังในผู้ป่วยที่ได้รับการวินิจฉัยก่อนเดือน สิงหาคม พ.ศ. 2551 อัตราการรอดชีวิตของทารก, ภาวะแทรกซ้อนของทารกหลังคลอดและมารดา ถูกบันทึกผลและนำมาวิเคราะห์ นอกจากนี้ผลการตรวจโดยอัลตราซาวด์ก่อนคลอด ถูกนำมาวิเคราะห์เพื่อหาปัจจัยเสี่ยงที่มีต่อผลลัพธ์การคลอด*

ผลการศึกษา: *มีผู้ป่วย TTTS ที่ศึกษาทั้งหมด 25 ราย อัตราการรอดชีวิตของทารกโดยรวมเท่ากับ ร้อยละ 58 (29 ใน 50 ราย) โดยไม่พบความสัมพันธ์ระหว่างอัตราการรอดชีวิตกับระดับความรุนแรงของโรค ($p = 0.19$) อัตราการรอดชีวิตในระยะที่ 1-2, ระยะที่ 3 และระยะที่ 4 คือร้อยละ 64.3, 45.8, 75 ตามลำดับ ไม่พบการเสียชีวิตของมารดาจากการศึกษานี้ ภาวะแทรกซ้อนของมารดาที่พบมากที่สุดคือ ภาวะครรภ์เป็นพิษ พบร้อยละ 24 (6 ใน 25 ราย) การเปลี่ยนระดับความรุนแรงที่มากขึ้นขณะตั้งครรภ์เป็นปัจจัยเดียวที่มีผลต่อการเสียชีวิต ของทารกอย่างมีนัยสำคัญทางสถิติ ($p < 0.001$)*

สรุป: *พบอัตราการเสียชีวิตของทารกในผู้ป่วย TTTS ที่ทำการศึกษานี้ สูงถึงร้อยละ 42 เนื่องจากประชากรที่ทำการศึกษามีจำนวนน้อย ดังนั้นไม่สามารถสรุปได้ว่า ระดับความรุนแรงของโรคไม่เกี่ยวข้องกับการพยากรณ์โรค การเปลี่ยนระดับความรุนแรงที่มากขึ้นขณะตั้งครรภ์เป็นปัจจัยที่มีผลต่อการเสียชีวิตของทารก*