

# Outcomes of twin-twin transfusion syndrome managed by a specialised twin clinic

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## ABSTRACT

**Introduction:** To determine the perinatal outcomes of monochorionic (MC) pregnancies complicated by the twin-twin transfusion syndrome (TTTS) that were managed in a specialised twin clinic at the KK Women's and Children's Hospital.

**Methods:** This was a 21-month retrospective study carried out from January 2002 to September 2003. MC pregnancies were followed up every two to three weeks with regular ultrasonographical and Doppler studies from the time monochorionicity was diagnosed. Standard criteria used for the diagnosis of TTTS are the presence of oligohydramnios/polyhydramnios sequence on ultrasonography. The severity of TTTS was staged according to Quintero's system.

**Results:** There were 77 sets of MC pregnancies in our database. 11 sets were diagnosed with TTTS, hence the incidence was 14.3 percent. The median gestation at diagnosis of TTTS was 17.4 (16.4 to 26) weeks. At first presentation, five were stage I, two were stage II, three were stage III and one was stage IV. Three pregnancies were terminated in the second trimester and one was lost to follow-up. Of the other seven, two were treated expectantly or delivered, four with amnioreduction/septostomy and one with cord occlusion. The median gestation at delivery is 30.8 (26.7 to 36.9) weeks. Four (57 percent) were delivered before 32 weeks and these same four pairs required neonatal intensive care. The overall perinatal survival was 78 percent (11/14) and the median diagnosis to delivery interval was 10.7 (3.1 to 17.5) weeks.

**Conclusion:** TTTS occurs in a significant proportion of MC pregnancies. The perinatal survival outcome of this group of patients managed in this clinic is comparable to that of other good centres.

**Keywords:** monochorionic pregnancy, perinatal outcomes, perinatal survival, twin-twin transfusion syndrome, ultrasonography

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## INTRODUCTION

Although multiple pregnancies account for only one percent of all pregnancies, they are responsible for nearly ten percent of all perinatal mortality<sup>(1)</sup>. The perinatal mortality rate in twins is five times higher than in singletons. Dizygotic twins arise from two fertilised eggs, whereas monozygotic twins arise from a single fertilised egg. One-third of all twins are monozygous. Monozygotic twinning rates are relatively constant at about four per 1,000 pregnancies with approximately 70% being monochorionic (MC)<sup>(2)</sup>. All MC twins are monozygotic. Not all dichorionic twins are dizygotic on the other hand, though all dizygotic twins are dichorionic. It is the chorionicity and not zygosity that determines the degree of perinatal risks and outcome<sup>(3)</sup>.

Chorionicity is usually determined between 10 to 14 weeks via ultrasonography with 100% accuracy<sup>(4)</sup>. Dichorionicity is confirmed by the presence of a twin peak sign (lambda sign) on ultrasonography whereas in MC twins, the twin peak sign is absent and in its place is the T sign (Fig. 1) which has a sensitivity of 100% and specificity of 98.2%<sup>(4)</sup>. MC twins have a higher rate of foetal loss before 24 weeks (12.2% vs 1.8%), as well as a perinatal mortality that is two times higher (2.8% vs 1.6%) when compared to dichorionic twins<sup>(3)</sup>. In MC twins, vascular circulatory communications occur along placental vascular anastomoses. These anastomoses may be bi-directional arterial-arterial or veno-veno, or unidirectional arteriovenous anastomoses. Haemodynamic imbalance is caused when the bi-directional anastomoses do not compensate for the unidirectional ones, resulting in the twin-twin transfusion syndrome (TTTS)<sup>(5)</sup>.

TTTS is a severe condition that complicates up to 15% of all MC twin pregnancies<sup>(6)</sup>. The cause and

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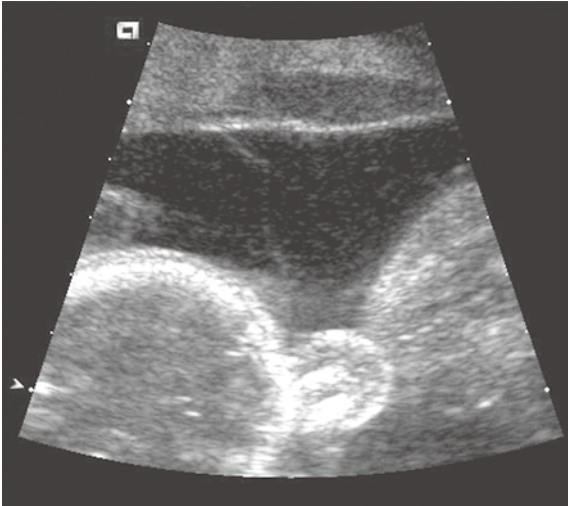


Fig. 1 Ultrasongraphical image shows the T sign in MC twins.

pathophysiology of TTTS remain poorly understood but placentas from MC pregnancies with TTTS have absent or significantly fewer artery-to-artery anastomoses than MC pregnancies without TTTS<sup>(7)</sup>. Hence, TTTS is attributed to unbalanced blood shifts from one twin (the donor) to the other twin (the recipient). Oligohydramnios develops in the donor twin who progressively becomes anaemic, growth restricted and oliguric, whereas polyhydramnios develops in the recipient who becomes plethoric, cardiomegalic and polyuric. The antenatal diagnosis of TTTS is the ultrasongraphical finding of severe discordance in amniotic fluid volumes, with polyhydramnios in the recipient's sac and oligohydramnios or anhydramnios in the donor's sac. Without treatment, a mortality rate of up to 80% can be expected<sup>(8)</sup>. Additionally, there is significant morbidity in surviving neonates due to premature birth as well as a result of acquired brain injury in-utero. Standard treatment options for TTTS include amnioreduction with or without septostomy, laser ablation of placental vascular anastomoses, and selective cord occlusion.

Unequal placental sharing in MC placentas contribute to intrauterine growth restriction, which occurs at an incidence of about 40% in MC twins. Acute transfusions can occur during labour or antenatally when a significant blood pressure difference occurs between the MC twins. This may result in the death of the donor twin, with concomitant damage or death of the co-twin. The estimated risk of death to the co-twin is 25%, with a further 25% risk of acquiring brain lesions in the event of the death of one twin<sup>(9)</sup>. In view of such high risks in MC twins, close surveillance for monochorionic twin pregnancies by specialised units was started for this group of high risk pregnancies.

The aim of our study was to determine the perinatal outcomes of MC pregnancies complicated by TTTS managed in a specialised twin clinic at the KK Women's and Children's Hospital (KKWCH), Singapore, a tertiary hospital with approximately 14,000 deliveries a year.

## METHODS

This was a retrospective study spanning a period of 21 months from January 2002 to September 2003. All MC twins followed-up at the KKWCH MC twin clinic were included in this study. These twins include all diagnosed in KKWCH and those referred from other hospitals. Monochorionicity was established by the absence of a twin peak sign on ultrasongraphy when scanned before 14 weeks gestation. In those referred after 14 weeks gestation, single placentation with a thin dividing membrane in concordant sex foetuses were used to identify probable MC twins. Once diagnosed as MC twins or probable MC twins, they underwent close surveillance every two to three weeks by ultrasongraphy for amniotic sac discordance, biometry and Doppler studies of the umbilical arteries. The standard diagnostic criteria for the diagnosis of chronic TTTS are the presence of oligohydramnios in one sac and polyhydramnios in the other sac on ultrasongraphy. The severity of TTTS at initial diagnosis is staged as per Quintero's classification<sup>(10)</sup>. In Stage I, there is amniotic fluid discordance. In Stage II, the donor's bladder becomes non-visible. In Stage III, Doppler flow studies become critically abnormal. In Stage IV, hydropic features are present in the foetuses.

When TTTS was diagnosed, surveillance frequency was increased to weekly at least. Amnioreduction/septostomy was offered to all patients when TTTS with severe polyhydramnios was diagnosed and when severe polyhydramnios recurred. Amnioreduction was performed by vacuum aspiration through an 18-gauge needle until it was technically difficult to continue and the deepest pool was less than 8 cm. Selective foetocide by cord occlusion was offered when preterminal TTTS was diagnosed. Preterminal TTTS is defined as a stage III TTTS with abnormal ductus venosus or umbilical venous Doppler changes, or a stage IV TTTS.

The primary outcome measure was perinatal survival defined as survival up to four weeks of life. Secondary outcome measures were: significant neonatal morbidity such as necrotising enterocolitis, respiratory distress syndrome, bronchopulmonary dysplasia, retinopathy of prematurity, cardiac defects, intraventricular haemorrhage, and neonatal jaundice.

**Table I. Antenatal characteristics.**

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G	Patient H	Patient I	Patient J	Patient K
Gestation at diagnosis (weeks)	26	26	17.3	19.4	16.4	20	17.3	16.7	18.7	17.4	17.0
Stage at diagnosis (Quintero)	I	I	I	I	I	II	II	III	III	III	IV
Worst stage (Quintero)	III	I	I	V	I	II	III	III	III	III	V
Therapeutic procedures	Delivery	No. Returned to home country for therapy	A, S	No	Declined. Opted for TOP	A, S	A, S	Declined. Opted for TOP	Declined. Opted for TOP	A, S	C (for twin 1)
Gestation at delivery (weeks)	26.7	NA	34.7	36.9	17	28.1	28.1	17	20.7	30.3	20.1
Mode of delivery	LSCS	–	LSCS	NVD, I stillbirth	–	NVD	LSCS	–	–	LSCS	NVD, (IUD of twin 2)

Therapeutic procedures: A – amnioreduction, S – septostomy, C – cord occlusion, TOP – termination of pregnancy; Mode of delivery: LSCS – lower segment caesarean section, NVD - normal vaginal delivery; NA – not applicable.

## RESULTS

There were a total of 25,074 deliveries at KKWCH from January 2002 to September 2003 and of these, 273 were twin pregnancies. A total of 77 MC twin pregnancies (52 MC and 25 probable MC) were seen during the study period. The racial composition was 43 Chinese, 17 Malays, 11 Indians, and six of other races. 11 patients were diagnosed with TTTS, giving an incidence of 14.3% in our cohort. Nine of the 11 sets (81.8%) were diagnosed as MC by the absence of the twin peak sign between 10 to 14 weeks gestation.

The median maternal age was 31 years (range 22 to 44 years). The median gestation at diagnosis of TTTS was 17.4 weeks (16.4 to 26 weeks). At first presentation, five cases were stage I, two were stage II, three were stage III and one was stage IV (Table I). One patient was lost to follow-up. This patient was diagnosed with stage I TTTS at 26 weeks gestation. She had returned to another country soon after diagnosis for antenatal care of her pregnancy. We had three patients who opted for elective termination of pregnancy (TOP), of which two (at 16.7 and 18.7 weeks gestation, respectively) were at stage III and one (at 16.4 weeks gestation) was at stage I.

Of the remaining seven patients, one was managed conservatively when the intrauterine death of one twin was diagnosed. One patient required urgent delivery for non-reassuring foetal status at diagnosis of TTTS at 26.7 weeks. We treated four patients with amnioreduction, with or without septostomy, and one patient with selective foetocide via cord occlusion. The cord occlusion

was accomplished by ultrasound-guided bipolar diathermy of the recipient in a pregnancy with stage IV TTTS after approval by the Ministry of Health and the Hospital Ethics Committee. In the immediate post-procedure period, the recipient foetus was well. Two weeks after the procedure, the recipient foetus was noted to be within both the donor and recipient sacs, with amniotic membrane around it, and with no cardiac activity.

The median gestation at delivery was 30.8 weeks (26.7 to 36.9 weeks). 85.7% (6/7 pregnancies) were delivered via abdominal route and 57.1% (8/14 babies) required intensive care. More than half of the pregnancies (57.1%) delivered before 32 weeks. The neonatal outcomes are illustrated in Table II. Excluding cases that were terminated electively, the overall neonatal survival beyond four weeks was 78.6% (11/14). Five pregnancies had two survivors, one pregnancy had one survivor and one pregnancy had none. The overall median diagnosis to delivery interval was 10.7 weeks (3.1 to 17.5 weeks) (Table III).

## DISCUSSION

The incidence of TTTS in our series (14.3%) is consistent with international figures<sup>(6)</sup>. TTTS is a severe complication occurring in MC twin pregnancies. If left untreated, the mortality is very high (80 to 100%) and foetuses will die in-utero or after birth in most cases<sup>(8)</sup>. Early diagnosis and treatment are essential for improving the poor prognosis of these pregnancies. This has led to the development of various interventional techniques

**Table II. Neonatal outcomes.**

	Patient A	Patient C	Patient D	Patient F	Patient G	Patient J	Patient K
Apgar at 5min (twin 1; twin 2)	9; 8	9; 9	9; nil (stillbirth)	9; 9	9; §	9; 9	0, 0
NICU admission	Both twins	No	No	Both twins	Both twins	Both twins	NA
Survival up to 28 days	Both twins	Both twins	One twin	Both twins	Both twins	Both twins	0
NICU stay (days) Twin 1	189	0	0	41	72	18	NA
NICU stay (days) Twin 2	63	0	NA	40	55	168	NA
Perinatal morbidity Twin 1	BPD NEC PDA IVH Hypothyroid (Died after 189 days of life)	Hyperglycaemia	NNJ CTEV	RDS ROP IVH	RDS PDA Pulm stenosis Ileal perforation with colostomy NNJ	RDS PDA Meconium plug syndrome Right germinal matrix haemorrhage NNJ	NA
Perinatal morbidity Twin 2	RDS PDA Hypothyroid	NNJ	NA	RDS ROP NNJ	ARPKD IVH RDS NNJ (Died after 55 days of life)	RDS VSD Meconium plug syndrome IUGR	NA

NICU: neonatal intensive care unit; Apgars at 5min: § – not scored; ARPKD: autosomal recessive polycystic kidney disease; NNJ: neonatal jaundice; RDS: respiratory distress syndrome; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; ROP: retinopathy of prematurity; VSD: ventricular septal defect; IVH: intraventricular haemorrhage; CTEV: congenital talipes equinovarus; NA: not applicable

**Table III. Impact of stage on delivery interval.**

	Gestation at diagnosis in weeks Median (range)	Gestation at delivery in weeks Median (range)	Diagnosis to delivery interval in weeks Median (range)
Stage I n=3	19.4 (17.3 -26)	34.7 (26.7 -36.9)	17.4 (0.7 -17.5)
Stage II n=2	18.7 (17.4 -20)	28.1 (28.1)	9.4 (8.1 - 10.7)
Stage III n=1	17.4	30.3	12.9
Stage IV n=1	17	20.1	3.1

over the last decade to improve the outcome of such pregnancies.

Aminoreduction is one of the key therapies used in the management of TTTS and serial reductions have been the mainstay of therapy for the past decade. Basically, excess amniotic fluid is removed from the recipient's sac by inserting a needle into the gestational sac under ultrasound guidance. Restoration of normal intra-amniotic fluid volume allows prolongation of pregnancy by reducing the risk of preterm labour and spontaneous rupture of membranes<sup>(11)</sup>. It also reduces maternal discomfort

and may improve fetal condition by increasing uteroplacental circulation<sup>(12)</sup>. Septostomy may also improve survival rates, and may reduce the number of amnioreductions necessary to relieve polyhydramnios, though its mechanism is unclear<sup>(13)</sup>.

A more recent development is foetoscopic laser surgery. Direct vision of the placenta is achieved through an endoscope, and the communicating vessels are identified and destroyed with a laser. Foetoscopic laser coagulation of placental anastomoses is the most logical treatment in that it interrupts blood flow through vascular

communications between the two fetuses<sup>(14,15)</sup>. In the Eurofoetus randomised controlled study comparing laser surgery versus serial amnioreductions, laser is shown to be a more effective first line treatment (76% versus 56% survival up to 28 days of life;  $p=0.009$ )<sup>(16)</sup>. However, it requires advanced equipment and is performed only in a few specialised centres around the world. Selective cord occlusion using bipolar diathermy under ultrasound guidance is used as a last resort for pre-terminal TTTS and has been shown to be effective in saving the co-twin<sup>(17,18)</sup>.

Despite being a small case series owing to the small population base in Singapore, the results from our study show that the overall perinatal survival rate at birth in pregnancies complicated by TTTS presenting before 28 weeks was 78.6%. This compares favourably with that of renowned centres around the world. The severity of TTTS and the gestation at delivery are the main factors in determining the perinatal outcome of such pregnancies<sup>(19)</sup>. Therefore, it is important to diagnose the condition as soon as possible in the second trimester and intervene when appropriate. It is important that all pregnancies have a routine early ultrasonographical scan for dating as twin pregnancies are often unexpected, and the determination of chorionicity is almost 100% accurate if scanned before 14-16 weeks. Since TTTS occurs in 10 to 15% of monochorionic twins<sup>(3)</sup>, the importance of such a scan cannot be overlooked if we are to reduce the morbidity and mortality associated with monochorionic twin pregnancies.

In most centres around the world, cases of TTTS upon diagnosis are referred to tertiary centres for further management. However, there are few centres with dedicated MC twin clinics. In Singapore, the MC twin clinic was started in January 2002 at the KKWCH with the aim to provide close surveillance for the detection of specific problems in MC twins such as TTTS and foetal growth restriction. Compared to an earlier series<sup>(13)</sup> in the same hospital, TTTS has been detected at earlier gestations and in earlier stages, and management had resulted in a longer diagnosis-delivery interval with a higher proportion delivering after 32 weeks (43% versus 0%). We attribute these good results to the set up of the MC twin clinic.

The idea for the set up of a specialised twin clinic was not without any evidence. O'Connor et al reported that intensive antepartum care in a twin clinic eliminated the need for antepartum hospitalisation<sup>(20)</sup>. Ellings et al reported that having a specialised multidisciplinary twin clinic improved

the perinatal outcome for twin gestations<sup>(21)</sup>. The improvements were attributed to intensive preterm birth prevention education, individualisation of prenatal care, as well as frequent maternal assessment by a consistent care provider. This approach reduced the rate of very early preterm delivery and its neonatal sequelae.

Papiernik et al developed a special program for multiple gestations in France that emphasises frequent patient visits, early work leave, cervical evaluation, and home visits by midwives. With this program, they were able to reduce the number of very low birth weight infants and perinatal deaths<sup>(22)</sup>. Vergani et al also reported lower incidence of delivery before 34 weeks and low birth weight infants when they developed a specific protocol for twin management<sup>(23)</sup>. However in these studies, monochorionic or dichorionic twin pregnancies were not differentiated.

Since the conclusion of this study, the twin clinic protocol was made more comprehensive. The patients are seen and counselled by the same maternal foetal specialist each visit. They would have two-weekly ultrasonographical scans from 16 weeks onwards for foetal biometry, amniotic fluid volume and Doppler flow studies. The Doppler detection of artery-to-artery anastomoses (AAA) would be performed for up to ten minutes after the completion of every basic ultrasonographical scan up to 26 weeks gestation (until one is found) as the presence of an AAA has been shown to be beneficial in terms of decreasing the risk of TTTS and in improving the survival, even if TTTS was diagnosed<sup>(24)</sup>. Transvaginal cervical length measurements would be made between 22 to 24 weeks, and weekly intramuscular depot medroxyprogesterone acetate offered if the cervical length was <2.5 mm. Uncomplicated MC twins are preferentially delivered between 36 to 37 weeks.

In conclusion, TTTS occurs in a significant proportion of MC twin pregnancies. Early detection by close surveillance may optimise the outcome of these pregnancies through the availability of modern intervention.

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