What Should We Know About Twin to Twin Transfusion Syndrome: A Case Report

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Abstract
Background
Twin-to-twin transfusion syndrome (TTTS) is a condition that can occur as a complication of a monochorionic twin pregnancy that may develop at any stage of pregnancy and most cases are diagnosed in the second trimester of pregnancy. The syndrome is a placental vascular anomaly that can affect the two fetoplacental circulations which can result in hypotony, hypovolemia, anemia, and oliguria being developed in the donor, whereas the recipient fetus is at risk of hypertrophy, hypertension, hypervolemia, polycythemia, and polyhydramnios.

Case presentation
A 32-year-old multigravida woman (Gravida 5 Para 4 Abortion 0) with a gestational age of 26 weeks came to the Obstetrics and Gynecology Clinic of Unggul Karsa Medika Hospital with the results of the first ultrasound at 24 weeks of gestation which revealed monochorionic diamniotic intrauterine twins and anterior placenta with grade I maturity. Twin A Maturity of 23 weeks 2 days with a fetal weight of 578 grams, oligohydramnios, fetal kidney, and bladder are not visible, whereas Twin B Maturity of 26 weeks 6 days with a fetal weight of 1205 grams, polyhydramnios with a single 12 cm deepest pocket and normal fetal kidney with bladder distention. The diagnosis of twin-to-twin transfusion syndrome was made with twin A as donor twins and twin B as recipient twins.

Conclusion
TTTS can be diagnosed with routine prenatal ultrasound and can be deferred into 4 stages based on ultrasound and doppler results. There are multiple options for management including expectant management, amnioreduction, intentional septostomy, fetoscopic laser photocoagulation, selective reduction, and voluntary pregnancy termination.

Keywords: Fetus, Placenta, Pregnancy, Syndrome, Transfusion, Twins

Background
Twin-to-twin transfusion syndrome is a condition that can occur as a complication of a monochorionic twin pregnancy. The occurrence probability of TTTS is estimated at 10% to 15% of monochorionic diamniotic pregnancies. This syndrome can develop anytime of pregnancy. However, most cases are diagnosed in the second trimester of pregnancy.1

The basis of the syndrome is a placental vascular anomaly. Placental anastomoses linking the two fetoplacental circulations produce an uncompensated net transfusion of blood from the donor to the recipient twin. It is caused by net intertwin transfusion of blood from one fetus (donor) to the other fetus (recipient) through abnormal placental vascular communication. The overall incidence of perinatal mortality irrespective of gestational age is approximately 60%-70% and is almost 100% before 26 weeks. It is due to its poorly understood etiology and difficulty in diagnosing and treating.1

Hypotony, hypotrophy, hypovolemia, anemia, and oliguria are being developed in donor’s as a result. Whereas the second fetus is under the risk of hypertrophy, hypertension, hypervolemia, polycythemia, and polyhydramnios.
If no treatment is performed, fetal mortality occurs in 60-100% of cases. The aim of this case report is to remind the reader for early detection of this rare cases, so that the prognosis for the fetus in same cases is better in the future.

Case presentation
A 32-year-old multigravida woman (Gravid 5 Para 4 Abortion 0) with a gestational age of 26 weeks came to Unggul Karsa Medika Hospital Obstetrics and Gynecology Clinic with a request for a referral letter to a higher center. She got her first ultrasound done at 24 weeks which revealed monochorionic diamniotic intrauterine live twins. Placenta was anterior with grade I maturity.

Twin A
Maturity 23 weeks 2 days with fetal weight of 578 grams. It had oligohydramnios. Fetal kidneys and urinary bladder were not seen. As seen in figure 1.

Twin B
Maturity 26 weeks 6 days with a fetal weight of 1205 grams. It had marked polyhydramnios with a single deepest pocket of 12 cm. Fetal kidneys were normal with a distended urinary bladder. The diagnosis of twin-to-twin transfusion syndrome was made with twin A as the donor twin and twin B as the recipient twin. As seen in figure 2.

On general examination, we found pulse rate 102 times/minute, blood pressure 101/58 mmHg, respiration rate 20 times/minute, temperature 36.2°C, and the absence of pallor. Abdominal examina-

Discussion
Twin-Twin Transfusion Syndrome (TTTS) is a condition that affects twin gestations that share one placenta. This disorder highlights the importance of determining the chorionicity (number of placentas) and amnionic (number of amniotic sacs) for all twin gestations, which influence the therapeutic strategy. Four types of chorionicity and amnionic combinations of twin gestations are dichorionic diamniotic (DCDA, two placentas, and two amniotic sacs), monochorionic diamniotic (MCDA, one placenta, and two amniotic sacs), monochorionic monoamniotic (MCMA, one placenta, and one amniotic sac), and conjoined twins (one placenta, and one amniotic sac). In the most accepted model of monozygotic twinning, the number of placentas and amniotic sacs depends upon when the splitting of the zygote occurs. DCDA twins are resulted when splitting occurs between days 1 to 3, MCDA twins are resulted when splitting occurs between days 3 to 8, MCMA twins result when splitting occurs between days 8 to 13, and conjoined twins result when splitting occurs on or after day 13.

Etiology of TTTS is an increased number of arteriovenous anastomoses deep in the placenta. These arteriovenous anastomoses are capillary connections that forms in the cotyledon portion of the placenta. Unidirectional flow can happen in these AV anastomoses and result in the shunting of blood towards one twin and away from the other. Arterio-arterial (AA) anastomoses and veno-venous (VV) anastomoses can have bidirectional flow and are found more superficially on the placenta. AA anastomoses are protective against TTTS and decreased in twin gestations with TTTS.
MCMA twins have more AA anastomoses, which is the reason why frequency of TTTS is lower in these twins than in MCDA twins. Hypovolemic condition that experienced by one twin causes renal hypoperfusion, stimulating the renin-angiotensin-aldosterone system (RAAS) in affected twin. This leads to oliguria and oligohydramnios. The hypervolemia that occurred in the other twin causes cardiac stretch, increasing atrial natriuretic peptide and brain natriuretic peptide release in affected twin. This leads to oliguria and oligohydramnios. The condition inhibits the RAAS and leads to polyuria and polyhydramnios. atrioventricular valve insufficiency, diastolic dysfunction, and pulmonary stenosis or atresia can be found in the recipient. In contrast, vascular changes due to increased collagen synthesis and hypertrophy of the vascular media and smooth muscle layers can be seen in the donor.5

It is estimated that twin births account for about 2% to 4% of births worldwide. Based upon data from the National Vital Statistics System of the National Center for Health Statistics of the Centers for Disease Control and Prevention, the prevalence of twin births in the United States in 2018 was about 33 per 1000 live births or about 3% of live births. This is an increase in the rate of twinning from the rate of about 1.8% in the U.S. in 1980. Of twin gestations, an estimated 67% are dizygotic, and 33% are monozygotic. Among monozygotic twins, approximately 75% are MCDA. Twin-Twin Transfusion Syndrome occurs at a rate of about 8-10% of MCDA twin gestations, about 6% of MCMA twin gestations, and it is estimated that 1 to 3 per 10,000 births is affected by TTTS. TTTS can possibly occur in monozygotic twinning with in vitro fertilization. There are very few data regarding the prevalence of each stage of TTTS. Based upon data from referral centers, the Society for Maternal-Fetal Medicine (SMFM) estimates a prevalence of Stage I: 11% to 15%, Stage II: 20% to 40%, Stage III: 38% to 60%, Stage IV: 6% to 7%, and Stage V: 2%.2,6

Quintero Staging System is the staging system used for TTTS. It is based upon two-dimensional ultrasound and doppler study findings as follows:

- **Stage I**: oligohydramnios and polyhydramnios sequence, donor twin bladder is visible, doppler studies of umbilical artery/umbilical vein/ductus venosus are normal in both twins.
- **Stage II**: oligohydramnios and polyhydramnios sequence, donor twin bladder is not visible, doppler studies of umbilical artery/umbilical vein/ductus venosus are normal in both twins.
- **Stage III**: oligohydramnios and polyhydramnios sequence and abnormal Doppler study (only one of the following is required in either twin) [absent/reversed end-diastolic flow in umbilical artery, pulsatile flow in umbilical vein, or reversed a-wave flow in ductus venosus.]
- **Stage IV**: oligohydramnios and polyhydramnios sequence, and one or both fetuses have hydrops.
- **Stage V**: oligohydramnios and polyhydramnios sequence, and one or both fetuses have died.1

Twin-to-twin transfusion syndrome is a condition that can occur as a complication of a monochorionic twin pregnancy. The occurrence probability of TTTS is estimated at 10% to 15% of monochorionic diamniotic pregnancies. Although this syndrome can develop at any stage of pregnancy, most cases are diagnosed in the second trimester, with majority of cases are in stage III according to the Quintero scale. TTTS results from hemodynamic disorders that arise from intertwin vascular anastomoses in a common placenta. These anastomoses occur in every monochorionic placenta, however, TTTS does not develop in every single case of monochorionic gestation. It can distinguish several kinds of anastomoses: arterio-arterial (AA), veno-venous (VV), and arterio-venous (AV). AA and VV anastomoses located on the surface of the placenta, are more superficial and have the potential for bidirectional flow. AV anastomoses are named deep anastomoses settled via capillaries within the cotyledon deep in the placenta. Furthermore, they are more likely to cause a unidirectional blood flow between two fetuses. This condition can lead to hemodynamic unbalance between fetuses and the final development of TTTS. Moreover, this hemodynamic unbalance can be compensated by both VV and AA anastomoses, but TTTS placenta are reported to have more VV than AA anastomoses. This difference may result in the development of TTTS. The absence of arterio-arterial anastomoses is also related to higher mortality (42% vs 15%), but the presence of these connections does not always prevent the occurrence of TTTS. The first effect of unidirectional blood flow between the fetuses is the change in blood circulation volume in both twins. One of them is called a donor because it becomes hypovolemic and the other which becomes hypovolemic is the recipient. Disorders like this led to the progressive development of hypotonia, hypotrophy, anemia, and oliguria (caused by oligohydramnios) in the donor’s organism.
In contrast to the first one, in the second fetus organism, which is the recipient, hypertrophy, hypertension, hypervolemia, polycythemia and polyhydramnios are developing. Some of these characteristics are subsequently used in ultrasonography to determine the stage of TTTS using Quinte- ro scale.1,7,8

According to the SMFM Guideline on Twin-Twin Transfusion Syndrome, ultrasound is recommended for women with twin gestation at 10 to 13 weeks to evaluates viability, chorionicity, crown-rump length, and nuchal translucency. Crown-rump length and nuchal translucency abnormalities are associated with the development of TTTS. Other ultrasound findings that are associated with TTTS include velamentous umbilical cord insertion and intertwin membrane folding. Once MCDA twin gestation is diagnosed, it is recommended that the ultrasound scanning is repeated every two to four weeks to monitor for the development of TTTS, which usually develops in the second trimester and can be seen between 16 and 26 weeks. At 16 weeks, it is recommended to begin performing an ultrasound to assess maximal vertical pocket in each amniotic sac as well as fetal bladders with repeat scans every two weeks until delivery. This frequent scanning is recommended due to the varied progression of TTTS. Delivery timing differs depending upon individual characteristics of each pregnancy, including stage and intervention effects; thus, SMFM recommends delivery timing around 34 to 37 weeks if possible. To promote fetal lung maturation, SMFM also recommends considering steroids between the gestational ages of 24 to 34 weeks, especially due to the higher risk of preterm birth in this population. Doppler studies of the umbilical artery, umbilical vein, and ductus venosus in each twin is recommended to determine staging once TTTS is diagnosed. SMFM recommends fetal echocardiography in MCDA twin gestations due to the higher risk of congenital heart disease in this population, especially in gestations with TTTS, which affects the recipient twin’s heart. Cervix length evaluation is also recommended due to higher risk of preterm labor and miscarriage in both twin gestations and TTTS, and the prevalence of shortened cervix in about 6% to 7% of pregnancies complicated by TTTS. Counseling for the mother and her partner is recommended.4

Amnioreduction is usually done in order to correct the polyhydramnios to < 8 cm, can be done beyond 14 weeks, and can be performed once or serially. Selective reduction is not considered unless the TTTS has reached stage III or IV. Fetoscopic laser photocoagulation is done under ultrasound guidance between 15 to 26 weeks of gestation with the purpose of creating “two chorions”, each supplying one twin. The procedure can be done outside of this timeframe, but there is a greater risk of PPROM if it is done under 16 weeks. There is also a greater difficulty in coagulation due to the increased size of vessels if it is done over 25 weeks. In the past, selective coagulation of AV, AA, and VV anastomoses is recommended rather than non-selectively coagulate. However, there is concern that some anastomoses can be missed and resulting in a greater risk of recurrence of TTTS and twin anemia polycythemia sequence (TAPS).

These are management recommendations based on the stage of TTTS and gestational age and are:

a. Stage I: Expectant management is recommended due to similar outcomes compared to amnioreduction and fetoscopic laser photocoagulation. Weekly ultrasound checks can be considered. Additionally, only about 25% of Stage I TTTS progresses in stage, and with expectant management, the survival of at least one twin occurs in most pregnancies.

b. Stage II, III, IV: Fetoscopic laser photocoagulation is recommended at these stages at gestational age < 26 weeks.1,4 A multicenter RCT conducted by Senat et al.9 demonstrated better outcomes after fetoscopic laser coagulation than with serial amnioreduction, including increased survival rates of one or both twins, delivery at greater gestational ages, and superior neurological outcomes. It should be noted, this study did not include TTTS at Stage I, and thus, should not be applied to the management of that stage.

c. Stage V: No interventions have been evaluated at this stage.1,4

From the explanation above, there are several treatments that can be done as an effort to prevent morbidity and mortality in TTTS. However, due to limited equipment and medical personnel at the hospital, this examination and management could not be carried out. Patients are referred to high-level hospitals that have more complete facilities. Therefore, all we can do is provide mothers with adequate vitamins and nutrients.
Educations about the symptoms of TTTS, including contractions and a sudden increase in size, and advising patient to quickly report to their provider may help with earlier diagnosis of TTTS. Once diagnosed, patient education and counseling regarding the prognosis based upon the stage, management, and treatment options available along with their respective risks and benefits, and expected progression of the condition should be provided. Additionally, there should also be a discussion about the possibility of long-term complications after birth, including neurological complications.10

The death of one or both twins is a complication of TTTS, with the survival of one twin ranging from 15% to 70% and survival of both twins hovering around 50%. Cardiac complications often occur in both the recipient and donor; such as atrioventricular valve insufficiency, diastolic dysfunction, and pulmonary stenosis or atresia in the recipient, and vascular changes due to increased collagen synthesis and hypertrophy of the vascular media and smooth muscle layers in the donor. Twin gestations have increased risk of premature delivery, so thus premature delivery in TTTS. Neurological deficits including cerebral palsy and long-term neurodevelopmental impairment (NDI) are complications of TTTS and preterm delivery. However, expectant management also carries the complication risk of further stage progression; this risk of progression depends upon the stage at diagnosis as most (75%) of Stage I remain stable or regress without treatment. Potential complications of amnioreduction include the death of one or both twins (survival rates following this procedure range from 50 to 65%), need for serial amnioreduction, preterm premature rupture of membrane (PPROM), preterm labor, placental abruption, infection, and decreased success of potential future fetoscopic laser photocoagulation. Additionally, there is an increased risk of poor neurological outcomes, including cerebral injury, cerebral palsy, and NDI (Neurodevelopmental impairment) after amnioreduction compared to fetoscopic laser photocoagulation.10

Prognosis of TTTS depends on the stage, the severity of the disease, and gestational age at diagnosis. Younger gestational age and the higher stage at diagnosis are associated with poorer prognosis. Single twin survival is 15% to 70%, with 50% survival of both twins, even with treatment. Best prognosis is at Stage I with overall survival of 86%. Additionally, about 75% of Stage I remains stable or regresses. Less information was available for Stages II-IV, but perinatal death rate for Stage III and more is estimated to be 70% to 100%.

Regarding Stage V, following the demise of one twin, there is a 10% risk of death and a 10 to 30% risk of neurological complication in the other twin. Some studies showed an improved neurological outcome in the surviving twin if fetoscopic laser photocoagulation was performed earlier in gestation.11

We can suspect twin-to-twin transfusion syndrome based on the results of routine prenatal ultrasound. A fetomaternal consultant can confirm the diagnosis by conducting detailed testing to measure amniotic fluid volume, bladder filling, and blood flow in the recipient and donor twins.

If there is rapid increase of amniotic fluid volume, the uterine cavity will expand at an accelerated pace, thus making the mother at risk for preterm labor and shortening of the cervix. This may lead to preterm labor or preterm rupture of membranes. Therefore, maternal assessment of the cervical length and uterine activity is essential in all women with suspected TTTS.12

**Conclusion**

Twin-to-twin transfusion syndrome is a condition that can occur as a complication of a multiple monochorionic pregnancy. The etiology of TTTS is an increased number of arteriovenous anastomoses deep in the placenta. Of 2-4% twin births estimated around the world, 67% are dizygotic, while 33% are monozygotic with approximately 75% among them experiencing MCDA. TTTS might occur in 10-15% of monochorionic diamniotic twin pregnancies. TTTS can be diagnosed based on the results of routine prenatal ultrasound. A maternal-fetal medicine specialist can confirm the diagnosis by performing more detailed tests to measure amniotic fluid volume, bladder filling and blood flow in the recipient and donor twins. TTTS can be deferred into 4 stages based on ultrasound and doppler results. Multiple management options available once TTTS is diagnosed. These include expectant management, amnioreduction, intentional septostomy, fetoscopic laser photocoagulation, selective reduction, and voluntary pregnancy termination.
**List of abbreviations**

- TTTS - Twin-to-Twin Transfusion Syndrome
- DCDA - Dichorionic Diamniotic
- MCDA - Monochorionic Diamniotic
- MCMA - Monochorionic Monoamniotic
- AA - Arterio-arterial
- VV - Veno-venous
- AV - Arterio-venous
- TAPS - Twin Anemia Polycythemia Sequence
- NDI - Neurodevelopmental Impairment
- PPROM - Preterm Premature Rupture of Membranes
- SMFM - The Society for Maternal-Fetal Medicine
- RAAS - Renin-Angiotensin-Aldosterone System

**Declarations**

**Ethics approval and consent to participate**

Informed consent from the patient has been obtained before the study.

**Consent for publication**

Consent for publication regarding patient data has been obtained before the study. All the patient identity has been kept secret.

**Availability of data and materials**

Not Applicable

**Competing interests**

The authors declare that they have no competing interests.

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