Twin-twin transfusion syndrome and twin anemia polycythemia sequence: Screening, prevalence, pathophysiology, and diagnosis

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INTRODUCTION

Twin-twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS) are serious complications of monochorionic (MC) twin gestations. Only MC twins have these complications because, in contrast to dichorionic twins, the circulatory systems of almost all MC twins have arteriovenous (AV) anastomoses in the placenta, thus forming a vascular connection between them.

- **TTTS** – TTTS is characterized by relative hypovolemia of one twin and hypervolemia of the other as a result of many or large AV anastomoses deep in the placenta. The cardinal prenatal finding is MC placentation with discordant amniotic fluid volumes (maximum vertical pocket <2 cm in one amniotic sac and >8 cm in the other amniotic sac). (See 'Twin-twin transfusion syndrome' below.)

- **TAPS** – TAPS is an atypical chronic form of TTTS caused by slow transfusion of red blood cells through a few very small (<1 mm diameter) placental AV anastomoses [1], resulting in anemia of one twin and polycythemia of the co-twin. Amniotic fluid volumes are normal. The cardinal prenatal finding is MC placentation with middle cerebral artery-peak systolic velocity greater than 1.5 multiples of median (MoM) in one twin and less than 0.8 MoM in the other twin. (See 'Twin anemia polycythemia sequence' below.)

These descriptions reflect the characteristics of each disorder in its classic, pure form. However, diagnosis can be challenging because TAPS, TTTS, and a third disorder, selective intrauterine growth restriction (sIUGR), are not necessarily mutually exclusive of each other and can present together in any combination.

This topic will review screening, prevalence, pathophysiology, and diagnosis of TTTS and TAPS. Management and outcome of patients with TTTS and TAPS, including neurodevelopmental outcomes, are discussed separately. (See "Twin-twin transfusion syndrome: Management and outcome".)

MONITORING MONOCHORIONIC PREGNANCIES FOR DEVELOPMENT OF TTTS AND TAPS

Twin pregnancies are often first diagnosed when a pregnant woman undergoes a first-trimester ultrasound examination for pregnancy dating, evaluation of vaginal bleeding, or measurement of nuchal translucency as a component of screening for Down syndrome (trisomy 21). Upon diagnosis of twins, determination of chorioamnionicity is essential to guide follow-up, which is different for monochorionic (MC) versus dichorionic (DC) twins. (See "Twin pregnancy: Prenatal issues", section on 'Assessment of chorionicity and amnionicity' and "Twin pregnancy: Prenatal issues", section on 'Chorionicity- and amnionicity-based follow-up'.)

In MC twin pregnancies, serial fetal ultrasound examinations are necessary to monitor for development of TTTS and TAPS, as well as selective intrauterine growth restriction (sIUGR) because these disorders collectively affect 15 to 20 percent of MC gestations, have high morbidity and mortality, and are amenable to interventions that can reduce morbidity and mortality. Their clinical findings overlap, so identifying the differences among them will help in

differential diagnosis (table 1). We suggest referring all MC twin pregnancies to a maternal-fetal medicine specialist for consultation and/or comanagement.

We have developed an ultrasound screening protocol for MC twins, as depicted in the table (table 2), to detect TTTS, TAPS, and sIUGR. This protocol is based on data from case series and our clinical experience and modified from guidelines published by the Society for Maternal-Fetal Medicine and the International Society for Ultrasound in Obstetrics and Gynecology [2-4].

In the first trimester, we determine chorionicity and measure nuchal translucency and crown-rump length in both twins as part of routine obstetric ultrasound assessment. In meta-analyses, nuchal translucency discrepancy >20 percent, nuchal translucency >95th percentile in one or both fetuses, crown-rump length discrepancy ≥10 percent, and abnormal ductus venosus (DV) flow at the first-trimester ultrasound scan were each associated with development of TTTS but with low sensitivity [5,6]. Nuchal translucency discrepancy and abnormal DV flow had the highest sensitivities at 53 and 50 percent, respectively [5]. We do not perform DV Doppler in the first trimester for predicting TTTS because Doppler in early pregnancy exposes the twins to the highest ultrasound power without clear benefit in predicting or reducing complications from TTTS.

We typically begin monitoring for TTTS in the second trimester, at 16 weeks of gestation, and continue through 36 weeks (table 2). The onset of TTTS is usually gradual and during the second trimester at or after 16 weeks, but can occur suddenly and later in gestation [2,7]. TAPS, as well as sIUGR, typically develops in the late second or the third trimester [7].

TWIN-TWIN TRANSFUSION SYNDROME

Prevalence — Our best estimate of the prevalence of TTTS is 9 to 15 percent of monochorionic (MC) diamniotic (DA) twin pregnancies [8,9] and 6 percent of monoamniotic twin pregnancies [10]. These figures may underestimate the true prevalence because they are largely based on data from live borns and sonograms in the second half of pregnancy, which miss early fetal losses that may have been related to TTTS [8].

Pathophysiology

Antepartum TTTS — Post-delivery placental injection studies in MC twins have identified three types of vascular connections: arterioarterial (AA), venovenous (VV), and arteriovenous (AV). The three major factors in the pathogenesis of TTTS are unbalanced AV anastomoses, release of vasoactive mediators, and lack of AA anastomoses.

- **AV anastomoses** occur deep in the placenta when chorionic plate surface arterial vessels from one twin and chorionic plate surface venous vessels from the other twin descend into the placental parenchyma and connect in the underlying cotyledon to form a capillary network (ie, the cotyledon is supplied by an artery of one twin and blood is drained through a vein of the co-twin).

  AV anastomoses are unidirectional: If there are more or larger AV anastomoses in one direction than in the other direction (ie, unbalanced anastomoses), then uncompensated hydrostatic and osmotic forces will lead to net transfer of fluid from one twin to the other, resulting in the TTTS phenotype. If the number and size of AV anastomoses and thus blood flow going in one direction is the same as the number and size and thus blood flow going in the opposite direction (ie, balanced anastomoses), then TTTS does not develop.

  The initial developmental process that leads to formation of the unbalanced vascular system and subsequent TTTS phenotype in some MC twin pregnancies but not in others has not been determined. Dichorionic (DC) twins do not develop TTTS (with rare exceptions [11]) because they each have their own placenta without any intertwin anastomoses, even when the placenta has a fused appearance.

- **Vasoactive mediators** are released in response to changes in intravascular volume and affect the cardiovascular and renal function of both twins.

  Hypoperfusion of the kidneys of the chronically hypovolemic twin (called the donor twin) results in activation of the renin-angiotensin-aldosterone system (RAAS) and release of angiotensin II, renin, aldosterone, and vasopressin in an ongoing attempt to restore its intravascular volume and maintain its blood pressure [12,13]. This leads to oliguria, with anhydramnios and the "stuck twin" phenotype in severe cases.

  Chronic hypervolemia in the recipient twin causes its cardiac atria to stretch and release atrial natriuretic peptide; ventricular stretch results in release of brain natriuretic peptide [14]. These hormones promote vasodilation, natriuresis, and inhibition of the RAAS, leading to polyuria and polyhydramnios. Over time, however, the recipient can develop hypertensive cardiomyopathy as a result of ongoing volume overload, elevated levels of endothelin I, and elevated levels of RAAS mediators that it acquires from the donor through the AV anastomoses, even though its own RAAS system is down-regulated [15-17]. Venous hypertension is a late stage of the process and results in movement of intravascular fluid into the interstitial spaces and functional lymphatic obstruction, leading to hydrops fetalis [18].

- **AA anastomoses** are thought to be protective against development of TTTS by correcting intertwin volume imbalance caused by the unbalanced AV anastomoses [19,20]. The observation that AA anastomoses are rare to nonexistent in TTTS supports this theory.

AA and VV anastomoses are very different from AV anastomoses as they occur exclusively on the placental surface (not deep), are end-to-end (not capillary) anastomoses, and allow bidirectional (not unidirectional) blood flow. Thus, they do not cause the TTTS phenotype.

Intrapartum TTTS — In a minority of cases, acute intrapartum TTTS occurs during delivery from a rapid and large intertwin blood transfusion from donor to recipient [21,22]. This leads to acute anemia and possibly hypovolemic shock in the donor and acute polycythemia in the recipient twin. The reported incidence is 1.5 to 2.5 percent of all MC twins, irrespective of the mode of delivery [23].

The acute transfusion is thought to occur through both AV and AA anastomoses, but it is not clear why a balanced situation acutely becomes unbalanced [24]. Hypotheses include changes/maturation of the placenta late in gestation, hemodynamic changes that occur after the birth of one twin and before the birth of the second twin, and timing of cord clamping.

Prenatal (fetal) diagnosis — TTTS is typically diagnosed on an ultrasound examination performed in the early-to-mid second trimester.

Diagnostic criteria — The prenatal diagnosis of TTTS is based upon ultrasonographic evidence of a single MC placenta with twin oligohydramnios/polyhydramnios sequence, after exclusion of other disorders of discordant amniotic fluid volume (see 'Differential diagnosis' below). The maximum vertical amniotic fluid pockets for oligohydramnios and polyhydramnios are usually defined as <2 cm and >8 cm, respectively. Alternatively, some providers use gestational age-based criteria for defining polyhydramnios (≥6 cm at 15 to 17 weeks, ≥8 cm at 18 to 20 weeks, and >10 cm at ≥20 weeks) [25].

When severe, oligohydramnios in the donor's sac leads to a "stuck twin" appearance: The fetus appears stuck to the uterine wall because there is no or minimal fluid in its sac and its amniotic membrane lies against its body (image 1A-B). By contrast, the recipient twin is freely mobile within a large volume of amniotic fluid (image 2A-E), which also compresses the donor twin's sac.

These criteria reflect the characteristics of the disorder in its classic, pure form. However, diagnosis can be challenging because TAPS, TTTS, and selective intrauterine growth restriction (sIUGR) are not necessarily mutually exclusive of each other and can present together in any combination.

Postdiagnostic fetal evaluation and potential findings — After a presumptive diagnosis of TTTS is made based on identification of amniotic fluid discordancy, we perform the following assessments of both twins to exclude other disorders in the differential diagnosis (see 'Differential diagnosis' below); look for other findings potentially associated with TTTS; and assign the stage (see 'Classic staging' below), on which twin follow-up and pregnancy management are based (see "Twin-twin transfusion syndrome: Management and outcome"). TTTS is not associated with an increased risk for chromosomal abnormalities or genetic syndromes, so fetal genetic studies are not offered unless there is another reason for these studies.

At 16 to 18 weeks:

- **Doppler studies** of the umbilical artery (UA), umbilical vein (UV), and ductus venosus (DV) are needed for classification of disease severity (see 'Classic staging' below), and middle cerebral artery-peak systolic flow velocity (MCA-PSV) is needed to evaluate for TAPS (defined by MCA-PSV greater than 1.5 multiples of median [MoM] in one twin and less than 0.8 MoM in the other twin), which sometimes coexists with TTTS. (See 'Diagnostic criteria' below.)

- **Comprehensive anatomic survey** – Twins are at increased risk for congenital anomalies, and MC twins are at increased risk compared with DC twins. Anomalies that could lead to growth disturbance or oligohydramnios are of particular importance since they may affect the differential diagnosis of TTTS versus sIUGR versus upper or lower urinary tract anomalies resulting in amniotic fluid discordance. (See 'Differential diagnosis' below.)

- **Assessment for hydrops fetalis** – One or both fetuses may show signs of hydrops (combination of ascites, pleural or pericardial effusions, and skin edema). If one twin is hydropic, it is usually the recipient twin. Hydrops is a factor in classification of disease severity. (See 'Classic staging' below and "Nonimmune hydrops fetalis", section on 'Diagnosis'.)

- **Assessment of bladder size** – The donor's bladder size may be normal or decreased. The recipient's bladder size may be normal or increased. Bladder size is a factor in classification of disease severity. (See 'Classic staging' below.)

- **Biometry** – Growth restriction is a potential complication of TTTS, developing in upwards of 50 percent of donor twins [26], and also a key component of sIUGR. (See 'Differential diagnosis' below.)

- **Echocardiogram**

  - **Recipient twin** – Right ventricular outflow tract abnormalities, including functional or anatomic pulmonary atresia/stenosis, have been observed in approximately 10 percent of recipient twins [27-30]. Hypertrophy can develop in one or both fetal cardiac ventricles. (Hypertrophy is measured with ultrasound and defined as ventricular wall or intraventricular septal thickness greater than two standard deviations [SD] for gestational age).

    Right-sided myocardial dysfunction is two- to threefold more common than left-sided dysfunction, although echocardiographic studies have revealed that, in the early stages of TTTS, left ventricular filling pressures can rise and systolic function can decrease before right ventricular function becomes abnormal [31]. Right-side dysfunction is not surprising since the right ventricle is the dominant ventricle in the fetal heart. Depressed myocardial contractility and severe tricuspid regurgitation can be identified in addition to a reversed a-wave on Doppler interrogation of the DV. Functional obstruction of the pulmonary artery is signified by reverse filling of the ductus arteriosus from the aortic arch [16].

  - **Donor twin** – The donor twin generally has a normal echocardiogram. In advanced stages, the donor may have low output cardiac failure.

Differential diagnosis

- A pre-TTTS state should be considered when findings do not meet diagnostic criteria. Second-trimester MC pregnancies with polyhydramnios of one sac and normal amniotic fluid volume in the other sac or amniotic fluid volume discordance not fulfilling the diagnostic criteria for TTTS are at increased risk of progressing to TTTS, especially if one twin is growth restricted [32,33]. In contrast to our routine screening protocol (table 2), we perform weekly ultrasound examinations in these cases to determine the maximum vertical amniotic fluid pocket until the presence or absence of TTTS becomes clear. We would also perform a prompt ultrasound examination in women with polyhydramnios in one sac who become acutely symptomatic. (See 'Maternal clinical manifestations' below.)

- Prelabor preterm rupture of membranes (PPROM) of one sac can cause amniotic fluid discordancy. PPROM is readily diagnosed or excluded by testing for amniotic fluid in the vagina. (See "Preterm prelabor rupture of membranes: Clinical manifestations and diagnosis", section on 'Diagnostic evaluation and diagnosis'.)

- Congenital anomalies can result in amniotic fluid discordance (eg, renal agenesis in the suspected donor twin can cause oligohydramnios, upper gastrointestinal tract obstruction in the suspected recipient can cause polyhydramnios). Renal anomalies causing amniotic fluid discordance can usually be readily diagnosed or excluded by a fetal anatomic survey, but gastrointestinal anomalies, such as esophageal atresia, are more challenging. (See "Prenatal sonographic diagnosis of cystic renal disease" and "Prenatal diagnosis of esophageal, gastrointestinal, and anorectal atresia".)

- Congenital fetal infection may be sufficiently severe to cause growth restriction with or without amniotic fluid abnormalities. We do not test for infection when we suspect TTTS, except when fetal findings associated with infection are present, such as cerebral calcifications, cerebral ventriculomegaly, echogenic fetal bowel, hepatosplenomegaly, and/or hepatic calcifications.

- The term "selective intrauterine growth restriction" is used in the scenario where the discordance in estimated fetal weight between twins is >25 percent and the small twin's estimated weight is <10th percentile, with or without reduced amniotic fluid volume. The larger twin has normal amniotic fluid volume. Amniotic fluid discordance (when present) raises the possibility of TTTS. In a series of 324 cases referred to a specialty center because TTTS was suspected, the diagnosis was confirmed in 77 percent (n = 249), and the remaining patients had either discordant amniotic fluid volume that did not meet criteria for TTTS (56 percent) or sIUGR (44 percent) [34].

  Distinguishing TTTS complicated by IUGR in the donor twin from sIUGR can be difficult since in both situations the IUGR fetus may have oligohydramnios (table 1). The key to distinguishing between the two entities is based on the ultrasound findings in the normal sized co-twin: In pregnancies with sIUGR, the co-twin will be appropriately grown and have normal amniotic fluid volume (defined as maximum vertical pocket >2 cm and <8 cm), whereas when IUGR is part of TTTS, the appropriately grown co-twin usually has polyhydramnios (maximum vertical pocket >8 cm) since it is the recipient.

  Determining the true diagnosis, TTTS versus sIUGR, is paramount in deciding on therapeutic options. Laser photocoagulation of placental anastomoses is the treatment of choice for TTTS with or without concomitant IUGR (see "Twin-twin transfusion syndrome: Management and outcome"). Treatment for isolated sIUGR is based on expert opinion, variable (expectant management with fetal monitoring, early delivery), and depends on the gestational age (eg, selective reduction at previable gestational ages). (See "Selective intrauterine growth restriction in monochorionic twin pregnancies".)

Classification of TTTS — Classification systems have been created to provide a standardized means of describing increasing severity of TTTS. The use of different systems must be taken into consideration when comparing reported pregnancy outcomes.

Classic staging — The five classic stages of disease are based on findings from two-dimensional ultrasound and Doppler velocimetry of the UA, UV, and DV [35]:

- Stage I
  - Oligohydramnios and polyhydramnios sequence
  - The bladder of the donor twin is visible
  - Doppler indices (UA, UV, DV) in both twins are normal
- Stage II
  - Oligohydramnios and polyhydramnios sequence
  - Bladder of the donor is not visualized
  - Doppler indices (UA, UV, DV) in both twins are normal
- Stage III
  - Oligohydramnios and polyhydramnios sequence
  - Abnormal Doppler indices: At least one of the following is present in either twin: absent or reversed end-diastolic velocity in the UA, reversed flow in a-wave of the DV, or pulsatile flow in the UV
- Stage IV
  - Oligohydramnios and polyhydramnios sequence
  - One or both fetuses show signs of hydrops
- Stage V
  - Oligohydramnios and polyhydramnios sequence
  - One or both fetuses are dead

Although this classic staging represents one method of standardization, there are several important limitations. Atypical presentations can occur; as an example, the donor twin may have both a persistent bladder and abnormal umbilical Doppler flow. In addition, although higher stages are generally associated with a worsening perinatal prognosis, the clinical presentation of a particular case does not always follow an orderly progression of stages. As an example, a stage I case may progress rapidly in several days to stage III, but regression of disease can occur in as many as 15 percent of stage I cases and 60 percent of stage II disease [36].

Other classification systems — Given the limitation of classic staging for predicting progression of disease, some experts have proposed using fetal echocardiographic assessment (cardiovascular score), mainly of the recipient twin, to provide the information needed to distinguish between pregnancies that are evolving to severe TTTS versus those that have stable early TTTS that can be managed expectantly. We do not use any of these systems, but they are routinely used in some other centers.

- **Cardiovascular Profile Score (CVPS)** – This score was originally developed for use in hydropic fetuses to predict congestive heart failure and fetal outcome. It incorporates heart size, cardiac function, and Doppler blood flow studies of the UA, UV, and DV into the scoring profile. For each category, 2 points are assigned for normal findings and either 1 or 0 points for abnormal findings, depending on severity [37].

  In one study of CVPS to assess cardiac status and outcome in 62 recipient twins following intervention, the overall neonatal survival rate was 61 percent (76/124), and recipient survival rates were better with higher CVPS (74 percent [25/34] for CVPS of 10 versus 31 percent [5/16] for CVPS <9) [38]. Classic staging was not predictive of recipient survival. The authors concluded that cardiac assessment by CVPS may improve clinical decision making and timing of fetal interventions. However, the results are difficult to interpret since the initial treatment for TTTS was a therapy that is no longer used (amnioreduction) in 51 percent (32/62) of cases, with over one-third at Quintero stage III.

- **CHOP score** – The Children's Hospital of Philadelphia (CHOP score) has developed a cardiovascular scoring system based on echocardiographic and peripheral Doppler findings in a study of 150 donor and recipient

fetuses [39]. When four grades of progressively worsening cardiovascular abnormalities were compared with classic staging, marked differences were noted. As an example, when fetuses classified as stage II were reclassified by cardiovascular score, the spread of cardiovascular score grades from least to most severe was grade 1 (35 percent), grade 2 (30 percent), grade 3 (25 percent), and grade 4 (10 percent). However, a subsequent prospective evaluation of 158 cases of TTTS prior to laser therapy at another center failed to find an association between an increasing CHOP score and perinatal survival [40].

- **The Cincinnati modification** of the classic staging system is another cardiovascular scoring system [41]. This system divides stage III into A, B, and C classifications based on progressively worsening echocardiographic findings of three parameters in the recipient fetus (presence and severity of atrioventricular valvular incompetence, ventricular wall thickening, and ventricular function as assessed by the myocardial performance index [MPI]). Cases are upstaged from the classic stage based on the presence of these fetal echocardiographic findings.

Although assessment of the cardiovascular system has provided further insight into the pathophysiology and severity of TTTS, available profiling schemes do not appear to be predictive of progression of disease or perinatal outcome following laser photocoagulation. Determining the role of fetal echocardiography in the diagnosis and management of TTTS will require coordinated research in a multicentered collaborative setting, which is underway through the Fetal Heart Society. Risk stratification in advanced TTTS is being assessed, specifically focusing on the association of mitral regurgitation with perinatal mortality in stage III to IV TTTS [42].

Many of the proposed components of fetal echocardiographic assessment are technically difficult to perform (such as the MPI, which is used to assess global ventricular function). This raises concern regarding the feasibility and effectiveness of cardiovascular scoring systems as potential screening tests in widespread clinical populations.

Maternal clinical manifestations — TTTS is usually first suspected because of characteristic fetal findings on ultrasound examination, as discussed above [43]. The mother is usually asymptomatic, but symptoms related to excessive uterine distention may occur, including discomfort when lying supine, insomnia, early satiety, lower abdominal pain, orthopnea, and pelvic pressure (in patients with advanced cervical change) [2]. Mirror syndrome (ie, generalized maternal edema usually associated with hypertension) has been reported in cases with a hydropic fetus [44-46]. (See "Nonimmune hydrops fetalis", section on 'Mirror syndrome'.)

Premature cervical shortening (image 3) occurs in some patients, although cervical length in TTTS is normally distributed, with a mean±SD of 38±10 mm at 16 to 24 weeks of gestation [47]. The pathogenesis of cervical shortening is unclear. Although excessive uterine distention is the presumed etiology, we have not found an association between intraamniotic pressure and pretreatment cervical length or gestational age at delivery [48]. Pretreatment cervical length <28 mm in patients with TTTS in this gestational age range has been associated with an increased risk for preterm birth, but the optimum management of these patients is unclear, given the lack of data from randomized trials. We consider use of either progesterone 200 mg vaginally daily or a pessary (eg, Arabin cervical pessary or any incontinence pessary) reasonable approaches but do not place a cerclage. In the largest cohort study, cervical cerclage did not prolong pregnancy or improve perinatal survival [49]. However, practice patterns vary widely both in terms of defining the cervical length warranting treatment (eg, <10, 20, or 28 mm) and the intervention offered (vaginal progesterone, pessary, or cerclage). (See "Twin pregnancy: Prenatal issues", section on 'Potential interventions'.)

Follow-up and management — After the diagnosis of TTTS has been made, follow-up and management depend on the stage and are discussed in detail separately. (See "Twin-twin transfusion syndrome: Management and outcome".)

TWIN ANEMIA POLYCYTHEMIA SEQUENCE

Types of TAPS and prevalence — TAPS is a complication of monochorionic (MC) twins characterized by a severe intertwin hemoglobin difference and, in contrast to TTTS, no oligohydramnios or polyhydramnios in its classic, pure

form [50-52].

It may occur as a consequence of treatment of TTTS by laser ablation or may occur spontaneously.

- **Post-laser TAPS** – TAPS occurs in 2 to 13 percent of TTTS pregnancies treated with laser ablation [53,54]. (See "Twin-twin transfusion syndrome: Management and outcome", section on 'Twin anemia polycythemia sequence'.)

- **Spontaneous TAPS** – On rare occasions, TAPS may precede development of TTTS. More commonly, spontaneous TAPS in the absence of other clinical signs of TTTS can be considered an atypical, chronic form of TTTS, usually first diagnosed in the late second or third trimester (in contrast to TTTS, which is typically diagnosed in the early-to-mid second trimester) [55]. It has been reported in 3 to 6 percent of previously uncomplicated third-trimester MC diamniotic twins [56,57].

Pathophysiology

- **Post-laser TAPS** – Placental injection studies from TTTS pregnancies treated with laser ablation have demonstrated the presence of residual anastomoses in those pregnancies that later developed TAPS. In the majority of cases, the residual anastomoses were very small (<1 mm), unidirectional arteriovenous (AV) anastomoses without accompanying arterioarterial (AA) anastomoses.

  The small residual anastomoses allow slow passage of red cells usually from the former recipient twin to the former donor twin, gradually leading to highly discordant hemoglobin levels [53]. The former recipient twin now becomes anemic, while the former donor twin now becomes polycythemic (a reversal of the previous net blood flow during TTTS) [58]. Severe polycythemia can lead to fetal and placental thrombosis, while severe anemia can lead to hydrops fetalis [59].

  The slowness of this process allows for hemodynamic compensation, which is hypothesized to be the reason for absence of the amniotic fluid volume discordancy seen in TTTS [20].

- **Spontaneous TAPS** – Spontaneous isolated TAPS occurs when few very small AV anastomoses allow the slow unidirectional flow of blood from a donor twin to a recipient twin. The resulting pathophysiology (anemia/polycythemia with normal amniotic fluid volumes) is the same as described above for post-laser TAPS. The placentas in cases of spontaneous TAPS have on average three to four very small (<1 mm) AV anastomoses, with AA anastomoses in only 10 to 20 percent of cases [51]. By comparison, the placentas of patients with TTTS have more or larger AV anastomoses and no or minimal AA anastomoses. (See 'Pathophysiology' above.)

Diagnosis

Diagnostic criteria

- **Prenatal** – Prenatal diagnosis is based on findings on ultrasound examination. TAPS is diagnosed when the middle cerebral artery-peak systolic velocity (MCA-PSV) is >1.5 multiples of median (MoM) in one twin and <0.8 MoM in the other twin [53,59-61]; however, criteria are not uniform across studies (some authors use MCA-PSV <1.0 MoM [57]). Intertwin MCA-PSV differences >0.5 MoMs [62] and >0.37 MoMs [63] have also been proposed. Although they appear to have better diagnostic accuracy, validation studies are needed.

  Placental discordance echogenicity is a common but nonspecific finding that supports the diagnosis: The anemic donor's region of the placenta is thickened and hyperechoic, while the plethoric recipient twin's region of the placenta has a normal appearance, with clear demarcation between the donor and recipient territories (image 4).

  These criteria reflect the characteristics of the disorder in its classic, pure form. However, as discussed above, diagnosis can be challenging because TAPS, TTTS, and selective intrauterine growth restriction are not necessarily mutually exclusive of each other and can present together in any combination.

- **Postnatal** – At delivery, a striking color difference on the maternal side of the placenta suggests the diagnosis: one side (donor) is pale or pinkish, and the other side (recipient) is dark (picture 1) [64].

  Postnatal diagnosis is based on an intertwin hemoglobin difference ≥8.0 g/dL in conjunction with an intertwin reticulocyte ratio >1.7 (reticulocyte count of the donor twin divided by the reticulocyte count of the recipient twin) and a placental injection examination showing few very small (1 mm) AV anastomoses with flow in a single direction [57].

Postdiagnostic evaluation and potential fetal findings — After a diagnosis of TAPS is established by MCA-PSV, Doppler blood flow studies of the umbilical artery (UA), umbilical vein (UV), and ductus venosus (DV) are needed for classification of disease severity, which is the basis for further follow-up and management. (See 'Staging of TAPS' below and "Twin-twin transfusion syndrome: Management and outcome", section on 'Twin anemia polycythemia sequence'.)

The anemic fetus may have a dilated heart, tricuspid regurgitation, and ascites. The liver of the polycythemic fetus has a starry sky pattern due to diminished echogenicity of the liver parenchyma and an increased brightness of the portal venule walls.

TAPS is not associated with an increased risk for chromosomal or structural abnormalities or genetic syndromes, so fetal genetic studies are not offered unless there is another reason for these studies.

Differential diagnosis — Although there is some overlap between the findings for TAPS and TTTS (table 1), MCA-PSV discordance is diagnostic of TAPS and not present in pure TTTS, while amniotic fluid discordance (oligohydramnios and polyhydramnios sequence) is suggestive of pure TTTS and not present in TAPS. Fetal growth discordancy may develop in TAPS or TTTS but is not a characteristic of either disorder [7].

Intrauterine infection with Parvovirus B19 can cause fetal anemia; however, both fetuses will be anemic [65]. (See "Parvovirus B19 infection during pregnancy" and "Parvovirus B19 infection during pregnancy", section on 'Maternal-fetal effects'.)

Staging of TAPS — Severity of TAPS can be staged prenatally and postnatally, as follows [57].

Prenatal classification:

- Stage 1 – MCA-PSV >1.5 MoM in the donor and <1.0 MoM in the recipient, without other signs of fetal compromise
- Stage 2 – MCA-PSV >1.7 MoM in the donor and <0.8 MoM in the recipient, without other signs of fetal compromise
- Stage 3 – Stage 1 or 2 plus cardiac compromise of donor by any of the following:
  - Absent or reversed end-diastolic velocity in the UA
  - Pulsatile flow in the UV
  - Increased pulsatility index
  - Reversed flow in the DV
- Stage 4 – Stage 1 or 2 plus hydrops of donor
- Stage 5 – Demise of one or both fetuses preceded by TAPS

Postnatal classification is based on the degree of hemoglobin difference (g/dL) between twins:

- Stage 1 – >8
- Stage 2 – >11
- Stage 3 – >14
- Stage 4 – >17

- Stage 5 – >20

Follow-up and management — After the diagnosis of TAPS has been made, follow-up and management depend on the type (post-laser or spontaneous) and stage and are discussed in detail separately. (See "Twin-twin transfusion syndrome: Management and outcome", section on 'Twin anemia polycythemia sequence'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Multiple gestation".)

SUMMARY AND RECOMMENDATIONS

- Monochorionic (MC) twin pregnancies should be monitored with serial ultrasound examinations for development of twin-twin transfusion syndrome (TTTS), twin anemia polycythemia sequence (TAPS), and selective intrauterine growth restriction (sIUGR) (table 2). The diagnostic criteria for the classic, pure form of each disorder are shown in the table (table 3). However, diagnosis can be challenging because TAPS, TTTS, and sIUGR have overlapping findings and can present together in any combination. (See 'Introduction' above and 'Monitoring monochorionic pregnancies for development of TTTS and TAPS' above.)

TTTS

- The prenatal diagnosis of TTTS is based upon ultrasonographic evidence of a single MC placenta with polyhydramnios/oligohydramnios sequence. The maximum vertical amniotic fluid pockets for oligohydramnios and polyhydramnios are usually defined as <2 cm and >8 cm, respectively. Severe oligohydramnios results in the "stuck twin" appearance. (See 'Diagnostic criteria' above.)

- The TTTS phenotype results from unbalanced placental intertwin arteriovenous (AV) anastomoses that lead to hypovolemia in one twin (donor twin) and hypervolemia in the other (recipient twin). It is typically first detected on ultrasound examinations performed in the early-to-mid second trimester. Uncommonly, acute intrapartum TTTS results in acute anemia and possibly hypovolemic shock in the donor twin and acute polycythemia in the recipient twin at delivery. (See 'Pathophysiology' above.)

- The five classic stages of TTTS are based on findings from two-dimensional ultrasound and Doppler velocimetry of the umbilical artery, umbilical vein, and ductus venosus. Higher stages, which are characterized by abnormal Dopplers with or without hydrops, are generally associated with a worsening perinatal prognosis, but the clinical presentation of a particular case does not always follow an orderly progression of stages. (See 'Classic staging' above.)

TAPS

- TAPS may occur spontaneously or after laser treatment of TTTS. It results when a few, very small AV anastomoses allow the slow unidirectional flow of blood from a donor twin to a recipient twin. This causes anemia in the donor and polycythemia in the recipient twin, but (in contrast to TTTS) amniotic fluid volumes in both gestational sacs remain normal because the slow process allows hemodynamic compensation. (See 'Pathophysiology' above.)

- Prenatally, TAPS is diagnosed when the middle cerebral artery-peak systolic velocity is >1.5 multiples of median (MoM) in one twin and <0.8 MoM in the other twin, although criteria are not uniform across studies. (See 'Diagnostic criteria' above.)

  Discordance in placental echogenicity on prenatal ultrasound supports the diagnosis: The anemic donor has a thickened hyperechoic placenta, and the plethoric recipient has a normal placental region, with clear

demarcation between the donor and recipient territories (image 4).

- Postnatal diagnosis of TAPS is based on an intertwin hemoglobin difference ≥8.0 g/dL in conjunction with an intertwin reticulocyte ratio >1.7 (reticulocyte count of the donor twin divided by the reticulocyte count of the recipient twin) and a placental injection examination showing very small superficial AV anastomoses. (See 'Diagnostic criteria' above.)

- Severity of TAPS can be staged; staging criteria are different for prenatal versus postnatal cases. (See 'Staging of TAPS' above.)

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Topic 6789 Version 34.0

GRAPHICS

Similarities and differences among TTTS, TAPS, and sIUGR on ultrasound examination of both twins

Ultrasound finding	TTTS	TAPS	Selective intrauterine growth restriction
Fluid discordance	+++++ Oligohydramnios in one sac and polyhydramnios in the other sac	–	++ Oligohydramnios in the sac of the intrauterine growth restricted twin, normal amniotic fluid volume in the AGA twin
Growth discordance (>25% difference between twins)	++ 50% will have estimated fetal weight <10th percentile	+	+++++ 100% will have estimated fetal weight <10th percentile
MCA Doppler discordance (>1.5 MoM in donor/anemic AND <0.8 MoM in recipient/plethoric)	++	+++++	+
Fetal bladder discordance	Small donor bladder and/or enlarged recipient bladder	–	–
Ductus venosus abnormalities	+++++	++	++
Fetal hydrops	+++++	+	–
Placental appearance: Donor side hyperechoic and thickened, recipient side normal	++	+++++	-

"+" signifies the prominence of the ultrasound finding. "–" signifies that the ultrasound finding is not associated with the diagnosis.

TTTS: twin-twin transfusion syndrome; TAPS: twin anemia polycythemia sequence; AGA: appropriate for gestational age; MCA: middle cerebral artery; MoM: multiples of the median.

Graphic 110205 Version 6.0

Ultrasound screening protocol for monitoring monochorionic multifetal pregnancies

Gestational age	Purpose of ultrasound examination and frequency
11 to 14 weeks	▪ One examination for: • Assessment of gestational age and estimated date of delivery • Assessment of chorioamnionicity • Measurement of nuchal translucency*
16 AND 18 weeks	▪ Fetal size ▪ Early fetal anatomic survey, including presence and size of fetal bladders ▪ MVP of amniotic fluid ▪ Doppler measurement of MCA-PSV ▪ Doppler measurement of end-diastolic velocity in the UA ▪ Assessment for PDE
20 weeks	▪ Fetal size ▪ Detailed fetal anatomic survey, including presence and size of fetal bladders ▪ MVP ▪ Fetal echocardiogram ▪ Doppler measurement of MCA-PSV ▪ Doppler measurement of UA end-diastolic flow velocity ▪ PDE
20 to 22 weeks	▪ Transvaginal ultrasound measurement of cervical length
22 to 32 weeks	▪ Serial examinations of fetal growth every 4 weeks ▪ Serial examinations of the following every 2 weeks: • MVP • Presence and size of fetal bladders • Doppler measurement of MCA-PSV • Doppler measurement of UA end-diastolic flow velocity • PDE
32 to 36 weeks	▪ Continue serial examinations of fetal growth every 4 weeks ▪ Weekly examinations: • Biophysical profile score • Doppler measurement of MCA-PSV • Doppler measurement of UA end-diastolic flow velocity • PDE

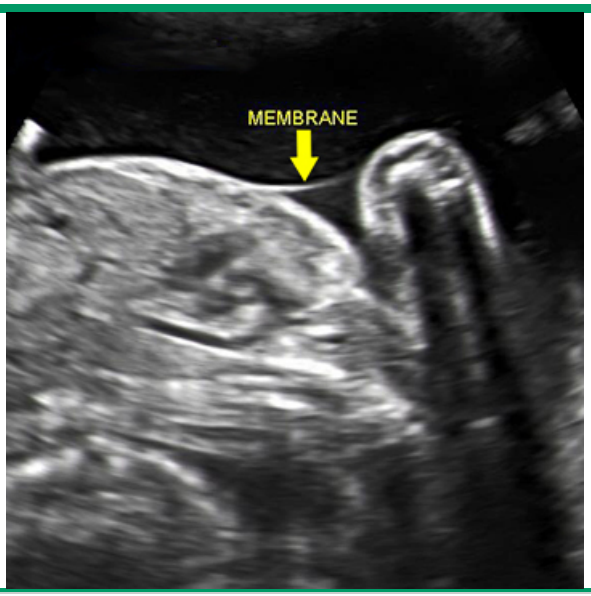
MVP: maximum vertical pocket; MCA: middle cerebral artery; PSV: peak systolic velocity; UA: umbilical artery; PDE: placental discordance echogenicity.
* Increased nuchal translucency has been associated with trisomy 21, a variety of congenital anomalies, developmental and genetic syndromes, and twin-twin transfusion syndrome. Refer to UpToDate content on cystic hygroma and increased nuchal translucency.

Modified from:

1. *Khalil A, Rodgers M, Baschat A, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol 2016; 47:247.*
2. *Society for Maternal-Fetal Medicine, Simpson LL. Twin-twin transfusion syndrome. Am J Obstet Gynecol 2013; 208:3.*
3. *Sueters M, Middeldorp JM, Lopriore E, et al. Timely diagnosis of twin-to-twin transfusion syndrome in monochorionic twin pregnancies by biweekly sonography combined with patient instruction to report onset of symptoms. Ultrasound Obstet Gynecol 2006; 28:659.*

Graphic 118804 Version 3.0

Donor twin with marked oligohydramnios

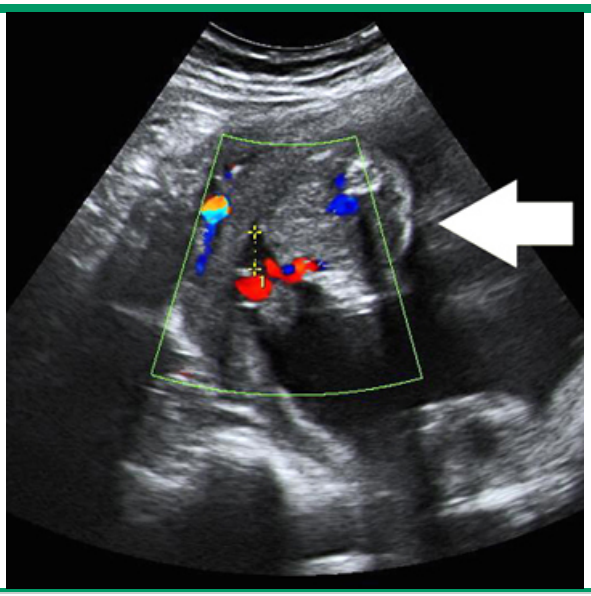


Donor twin with marked oligohydramnios at 24+2 weeks of gestation. Arrow denotes the membrane, which can be seen extending between the lower fetal abdomen and the fetal thigh of the donor twin. The difficulty in finding this membrane can often lead to the erroneous diagnosis of monoamniotic twins. The sac of the recipient twin has polyhydramnios.

Courtesy of Kenneth J Moise, Jr, MD, and Anthony Johnson, DO.

Graphic 63614 Version 6.0

Color Doppler of donor twin with oligohydramnios

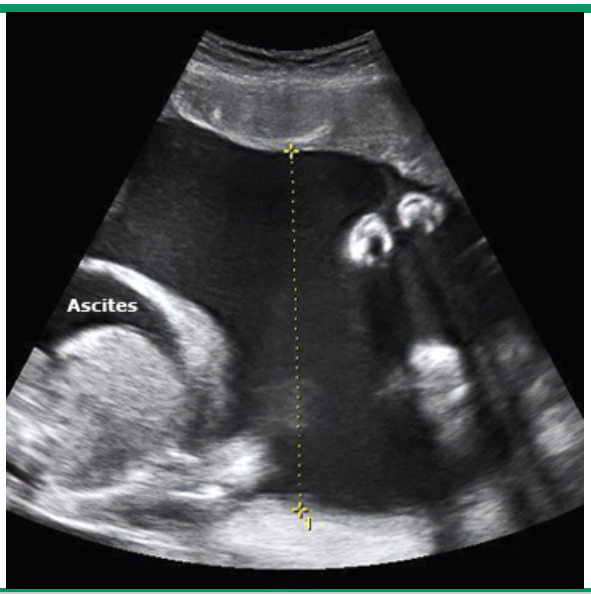


Stuck donor twin at 21 weeks of gestation. Arrow denotes the donor twin against the left upper quadrant of the uterine cavity. Note that the calipers indicate a maximum vertical amniotic pocket of only 1 cm. The cord can be seen with color Doppler adjacent to the abdomen of the donor twin.

Courtesy of Kenneth J Moise, Jr, MD & Anthony Johnson, DO.

Graphic 66239 Version 4.0

Recipient twin with polyhydramnios and ascites

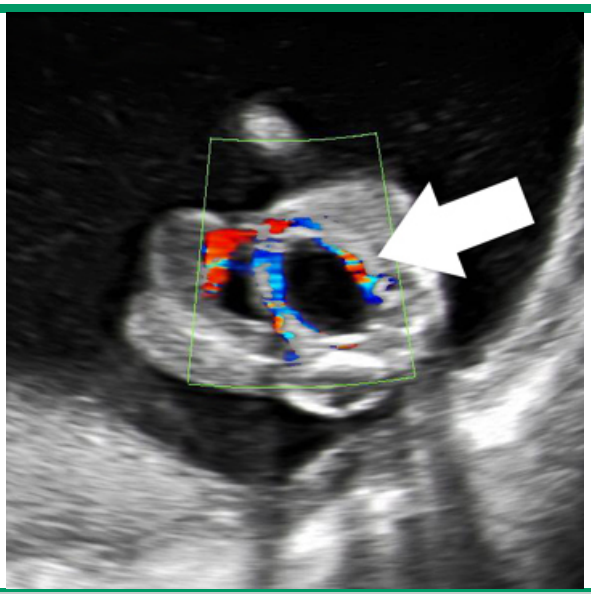


Recipient fetus at 22 weeks of gestation on left with polyhydramnios; the deepest vertical pocket is approximately 13 cm. The recipient also has a wide rim of ascites.

Courtesy of Kenneth J Moise, Jr, MD & Anthony Johnson, DO.

Graphic 76957 Version 6.0

Color Doppler of distended fetal bladder in recipient twin

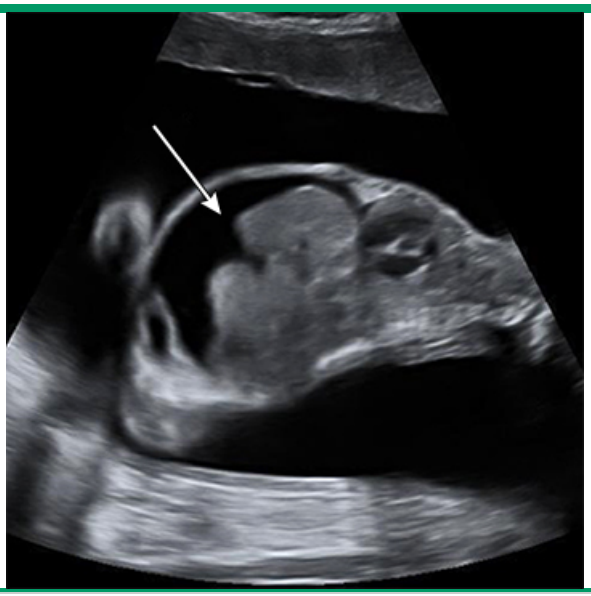


Distended fetal bladder in the recipient fetus is noted at approximately 21.5 weeks of gestation.

Courtesy of Kenneth J Moise, Jr, MD & Anthony Johnson, DO.

Graphic 52874 Version 4.0

Hydropic recipient twin



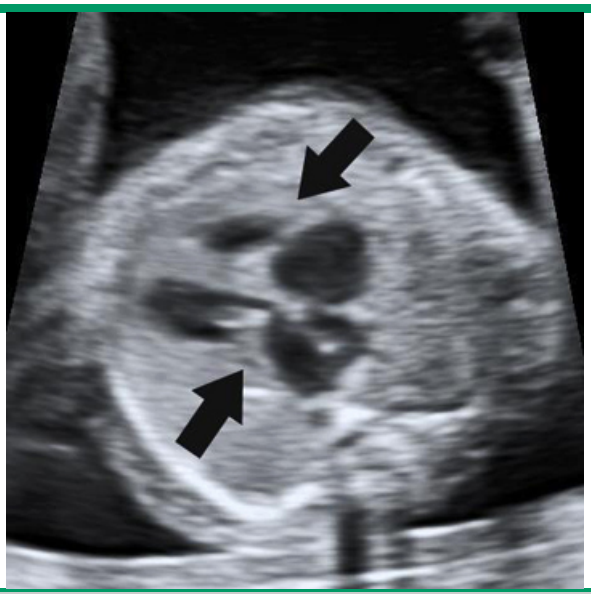
Sagittal view of the recipient twin at approximately 25 weeks of gestation. The fetal head (not in image) is to the right, and the fetal buttocks are to the left. Arrow points into area of ascites. A small pleural effusion is also present; thus, the fetus meets criteria for hydrops (Quintero Stage IV TTTS).

TTTS: twin-twin transfusion syndrome.

Courtesy of Kenneth J Moise, Jr, MD, and Anthony Johnson, DO.

Graphic 76546 Version 6.0

Cardiac abnormalities of recipient twin

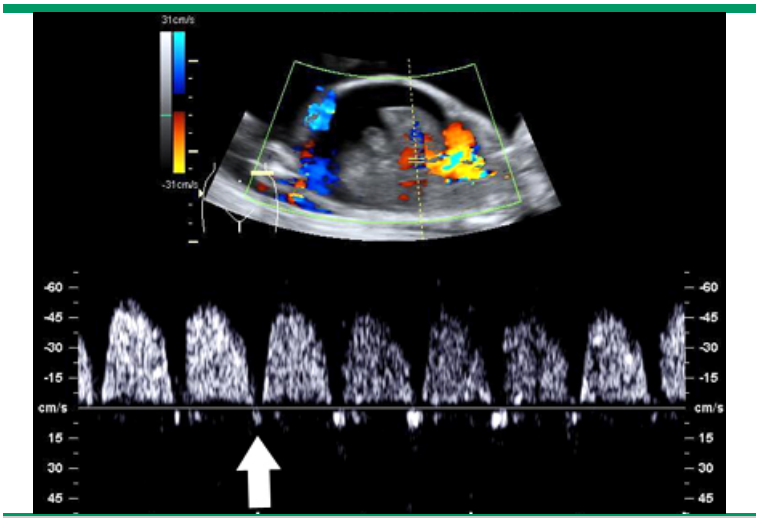


Cross section of the fetal chest and heart of the recipient fetus at approximately 25 weeks of gestation. Arrows point to the thickened myocardial walls of the fetal heart. The interventricular septum is also thickened.

Courtesy of Kenneth J Moise, Jr, MD & Anthony Johnson, DO.

Graphic 54479 Version 4.0

Doppler of ductus venosus in recipient twin

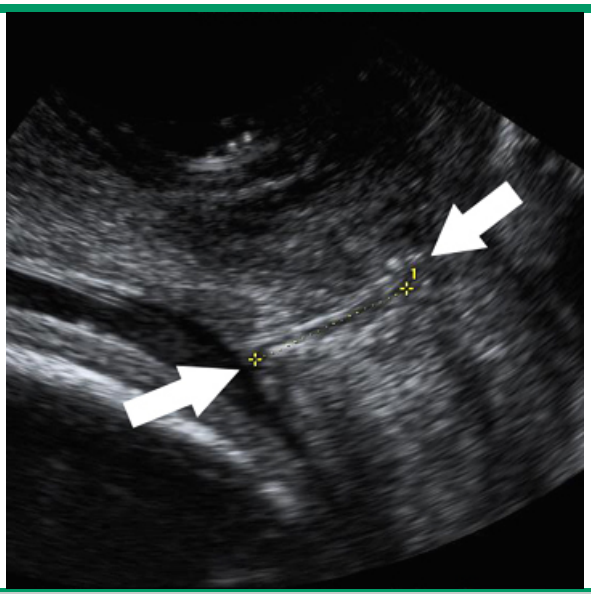


Doppler study of the fetal ductus venosus in this recipient twin at approximately 25 weeks of gestation. Fetal ascites can be noted in the top image. In the bottom image, the arrow points to the reversed "a" wave of the ductus venosus that occurs during diastole.

Courtesy of Kenneth J Moise, Jr, MD & Anthony Johnson, DO.

Graphic 67334 Version 5.0

Short cervix in patient with pregnancy complicated by TTTS

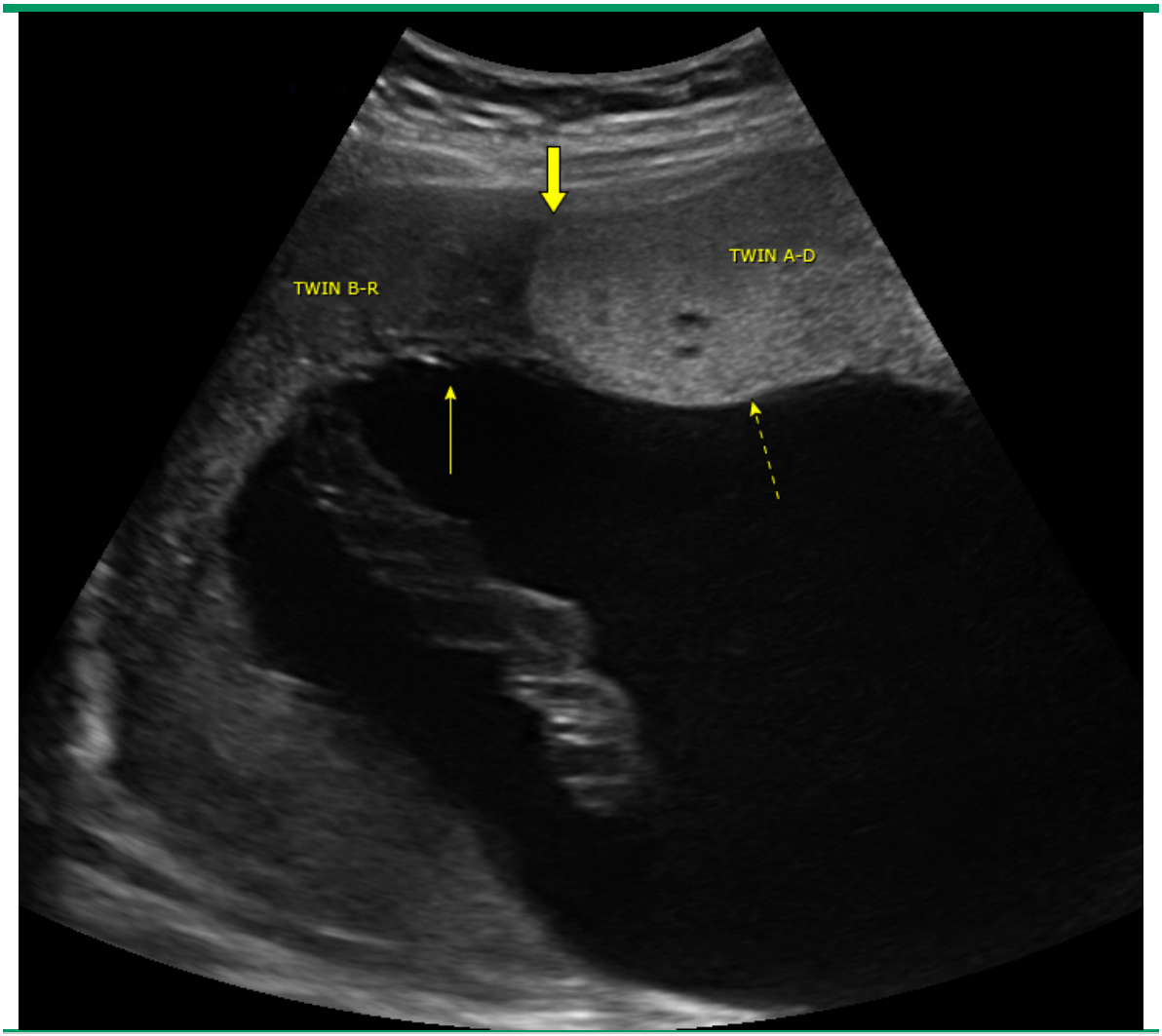


Transvaginal cervical length indicating a short cervix of 1.15 cm due to extreme polyhydramnios at approximately 21.5 weeks of gestation.

Courtesy of Kenneth J Moise, Jr, MD & Anthony Johnson, DO.

Graphic 78079 Version 4.0

Prenatal ultrasound image of the placenta in twin anemia-polycythemia sequence

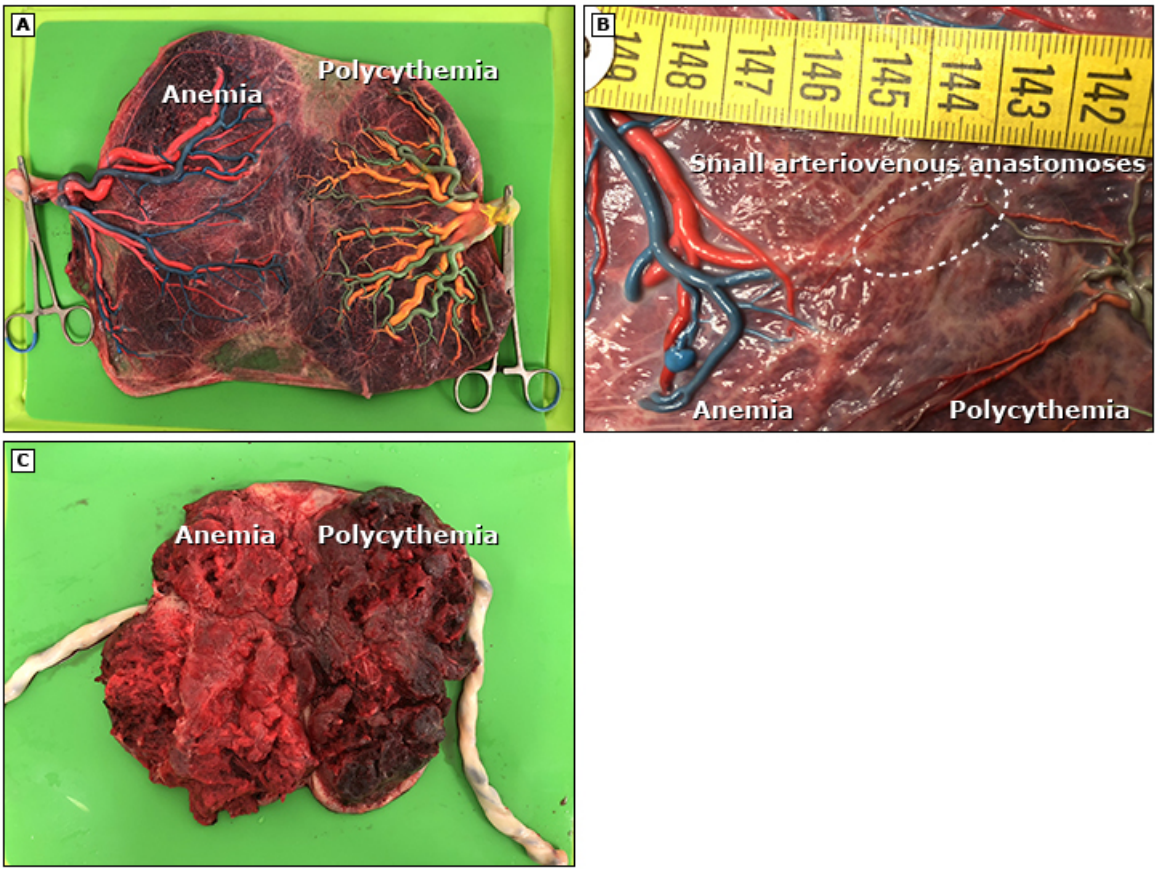


Ultrasound image of the placenta in TAPS. The donor placenta (TWIN A-D) appears thickened and hyperechogenic (dashed arrow), and the recipient placenta (TWIN B-R) appears thinner and hypoechoic (thin arrow). The demarcation between the two placental territories is easily seen (thick arrow).

TAPS: twin anemia polycythemia sequence.

Graphic 110197 Version 2.0

Postnatal placenta in TTTS/TAPS



Images show the fetal and maternal surface of a TAPS placenta showing the difference in color and tiny surface single arterial-venous vessel.

TTTS: twin-twin transfusion syndrome; TAPS: twin anemia polycythemia sequence.

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Graphic 122092 Version 1.0

Diagnostic thresholds for distinguishing complicated disorders that occur in monochorionic multifetal pregnancies

Disorder	Diagnostic criteria
Twin-twin transfusion syndrome	Amniotic fluid volume discordance: ▪ Donor MVP <2 cm ▪ Recipient MVP >8 cm
Twin anemia polycythemia sequence	MCA-PSV discordance: ▪ Donor <1.0 MoM with recipient >1.5 MoM Placental findings on ultrasound: ▪ Donor (anemic) region: Hyperechoic and thickened ▪ Recipient (plethoric) region: Normal appearance
Selective fetal growth restriction	Estimated fetal weight discordance >25% with small twin <10th percentile Type based on UA Doppler velocimetry: ▪ Type I: Normal flow ▪ Type II: Absent or reversed end-diastolic flow ▪ Type III: Intermittent absent or reversed end-diastolic flow

MVP: maximum vertical pocket; MCA: middle cerebral artery; PSV: peak systolic velocity; MoM: multiples of median; UA: umbilical artery.

Modified from:

1. Khalil A, Rodgers M, Baschat A, et al. ISUOG Practice Guidelines: role of ultrasound in twin pregnancy. Ultrasound Obstet Gynecol 2016; 47:247.
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Graphic 118803 Version 3.0

Contributor Disclosures

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