Twin-to-Twin Transfusion Syndrome: Part 1. Types and Pathogenesis
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*Neoreviews* 2008;9:e370
DOI: 10.1542/neo.9-9-e370

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Twin-to-Twin Transfusion Syndrome: Part 1. Types and Pathogenesis

Ona M. Faye-Petersen, MD,* Timothy M. Crombleholme, MD†

Objectives After completing this article, readers should be able to:
1. Differentiate acute and chronic twin-to-twin transfusion syndrome (TTTS).
2. Describe the role of placental anastomoses in TTTS.
3. List the primary factors contributing to the development of TTTS.
4. Describe characteristics of the placenta in the presence of TTTS.
5. Characterize fetal adaptations to TTTS.

Abstract Twin-to-twin transfusion syndrome (TTTS) may be acute or chronic, but chronic TTTS complicates 10% to 20% of monochorionic twin gestations and has an 80% to 100% mortality rate if severe and left untreated. Both types are due to the presence of placental anastomoses between the two twins, but the mechanisms involved in the development of chronic TTTS are particularly complex and incompletely understood. Many of the apparent pathogenic mechanisms have implications for the appearances and cardiovascular and physiologic disturbances of neonates born following this intrauterine condition and their response to treatment. We present an update in the pathogenesis of TTTS that includes an overview of the placental features, fetal adaptive and maladaptive responses, and molecular mechanisms involved in the development of TTTS.

Introduction Twin-to-twin transfusion syndrome (TTTS) is a gestational condition in which the circulation of one twin and the other communicate via placental anastomoses. It is almost exclusively restricted to monochorionic (monozygotic) twins with diamniotic monochorionic (DiMo) placentations and clinically presents as two types, acute and chronic. Rarely, TTTS can occur in dichorionic gestations but only if there is a vascular connection between the two circulations.

Acute, clinically relevant TTTS is rare and usually occurs during delivery from a sudden hemodynamic incident, such as cord compression or vascular rupture with vasa praevia that affects only one of the twins. (1)(2) In these instances, the twins are of similar birthweight, but due to peripartum acute shift(s) of blood through large, chorionic plate anastomoses, (3) most commonly large venovenous anastomoses, (4) one twin is pale and the other is plethoric. Initially, both twins may have similar hematocrit and hemoglobin values or the plethoric twin has an increased erythrocyte count and hemoglobin. However, the pale twin becomes notably anemic within hours of birth, as intravascular volume is reconstituted. (3)(5) Acute transfusion syndrome also may occur with delivery of the first twin, with the first twin draining blood into the second prior to clamping of the first twin’s cord. Alternatively, following delivery and clamping of the cord of the first twin, blood may flow rapidly from the second twin across placental anastomoses into the monochorionic placenta due to the sudden drop in blood pressure within the placental angioarchitecture perfused by the first twin. A similar scenario of acute transfusion can occur with intrauter-
ine fetal death of one twin; the placenta of the dead twin becomes a low-resistance vascular tree, and the viable twin may partially or quickly exsanguinate into the placenta. The sudden hypotension may result in the demise of the second twin or significant ischemic brain injury if the co-twin survives the hypotensive episode. Finally, an acute event can complicate chronic TTTS suddenly and reverse the prior donor-recipient relationship. Thus, although rare, acute TTTS may explain otherwise confusing or paradoxical findings on antenatal ultrasonography or at delivery. (1)(5) Careful examination of the placenta in these clinical settings, with assessment of the presence and types of vascular communications, can play a role in determining the cause of unexpected neonatal hemoglobin values or newborn morbidities or sudden mortality.

Chronic TTTS, hereafter designated simply as TTTS, is a condition of a sustained, net imbalance of blood volume transfused between twins of a DiMo placentation. Purportedly due to inter-twin vascular anastomoses in the placenta, one twin becomes the net donor and the co-twin becomes the effective recipient. TTTS generally is stated to complicate 10% to 20% of all monochorionic twin gestations, but inclusive review has revealed an incidence of 4% to 35% in the United States. (6) The relatively broad incidence range of TTTS likely reflects differences in clinical criteria used to make the diagnosis. (3) Severe TTTS is reported to occur in 5.5% to 17.5% of cases. (7)

TTTS is detected ultrasonographically as fetal growth discordance and differences in amniotic sac size, the so-called “poly-oli” or twin oligohydramnios polyhydramnios syndrome picture. In severe TTTS, the donor twin becomes progressively hypovolemic and develops oliguria and oligohydramnios due to decreased renal perfusion as well as abnormal umbilical artery Doppler velocimetry. The oligo-/anhydramnios of the donor twin may become so severe as to inhibit fetal movement. As the fetus becomes more closely enwrapped in its amnion, it appears “stuck” to the uterine sidewall or its placenta (ie, “stuck twin” syndrome.) The recipient twin becomes hypervolemic and hypertensive, which leads to polyuria and polyhydramnios. The recipient is characteristically larger, with cardiomegaly/visceromegaly (Fig. 1), and may exhibit abnormal venous Doppler study results due to progressive ventricular hypertrophy and worsening diastolic compliance. Both twins are affected adversely in TTTS. Hydrops fetalis may develop in either twin, but congestive failure is seen most commonly in the recipient. Left untreated, severe TTTS has an 80% to 100% mortality rate, particularly if it is detected before 20 weeks of gestation. (8)(9)

Prior to ultrasonography, the criteria for diagnosing TTTS were derived from neonatal experience with the condition in which a greater than 5.0-g/dL (50.0-g/L) difference in neonatal hemoglobin value and greater than 20% growth discordance was seen between the twins. However, these classic discrepancies between weight and hemoglobin values now are appreciated to occur in 25% or fewer of cases detected by ultrasonography. (9)(10) For example, hemoglobin discrepancy frequently is not observed at midgestation, and severe TTTS may exist prior to observing a 20% or greater fetal weight discordance. (9) As described previously, cases of intrauterine death of the donor twin may result in acute net blood flow reversal, with the smaller, deceased twin suddenly becoming plethoric and the former recipient becoming pale and anemic. (11) The severity of TTTS has been described via a number of systems, notably the clinical stages proffered by Quintero and associates (12) and later modified by Harkness and Crombleholme. (9)

Pathogenesis of TTTS
Ultrasonographic, ex vivo and in vivo placental, mathematically derived vascular models and fetal and neonatal blood sample studies have revealed TTTS to be a complex and dynamic pathologic condition. In addition to the inter-twin vascular connections, fetal biochemical, humoral, and functional adaptations also appear to be determinants of TTTS onset and progression. (1)(8)(9)(10)

Placental Structure
TTTS is believed to develop because all DiMo twins initially share the chorion, the extraembryonic mesen-
chyme. This layer differentiates into connective tissue stromal plugs that develop vascular cores through vasculogenesis, which successively branch, via angiogenesis, to form the chorionic villous tree. Thus, although each twin has its own umbilical cord vessels and acquires its own connections to and exerts its own influences on the developing vascular territories within the placenta, DiMo twins theoretically have numerous “opportunities” for vascular connections (chorangiopagus vessels) to form and persist as sites of “third” circulation. Indeed, several ex vivo injection studies have demonstrated such anastomoses, and studies using erythrocytes, pancuronium, and microbubble contrast agents as markers, as well as color Doppler studies, have provided in vivo evidence. At least 85%, if not essentially all DiMo twins, have shared circulation. The shared villous tree has been shown to consist of direct, superficial anastomoses between the twins’ umbilical cord branch vessels on the chorionic plate surface and “deep” sites, wherein the arterial ramifications from one twin’s cord pierce the chorionic plate to supply a portion(s) of the villous tree that is drained by an unpaired vein from the co-twin (Fig. 2). (Chorionic plate arterial and venous vessels are normally paired, but in a region of shared villous tree in a DiMo placenta, the afferent artery from the donor is unpaired, as is the efferent vein of the recipient.) The unidirectional “deep” arteriovenous (A-V) anastomoses within the placental cotyledons and occurring at the villous capillary level have been implicated as the major determinants of the imbalanced shunting of blood occurring in TTTS. The reader is referred to a collective discussion among major investigators of TTTS, but at least 80% of cases of TTTS have been attributed to imbalances in the number, size, and direction of deep A-V anastomoses.

Because of the putative major role of inter-twin anastomoses, most investigations of TTTS have been directed toward study of the DiMo placental vasculature. Studies generally have identified a paucity of anastomoses as a prominent risk factor in the development of TTTS. Paucity, especially of deep anastomoses, leads to fewer chances for volumetric balance in cross-circulation between the twins. Larger numbers of superficial chorionic anastomoses, particularly arterio-arterial (A-A) connections, appear to confer relative protection against the development, early onset, or severity of TTTS. However, the “protective effect” of these A-A anastomoses remains somewhat controversial. Venovenous (V-V) connections comprise a lower percentage of anastomotic types found in DiMo gestations and have been associated with poorer perinatal outcome. V-V anastomoses are seen in 20% of DiMo placentas, A-A in 75%, and A-V in 70% by clinical and pathologic studies, but fetoscopic studies have shown that 95% of anastomoses are A-V. However, some investigators have proposed that V-V anastomoses may provide compensatory reversal of blood flow in some situations. Presumably, as the recipient’s central venous pressure rises with hypervolemia and ensuing congestive failure, the V-V anastomoses may be “protective” to both twins by helping to alleviate right ventricular failure in the recipient and theoretically shunting blood back to the venous system of the donor. The relatively fewer numbers of V-V connections, in addition to their anatomy and lower pressure differential, may be determinants of how effectively they contribute to balancing inter-twin blood flow.

Some researchers’ observations that the average numbers of superficial vascular connections are not significantly different between gestations involving severe 

*Figure 2. Diagram of the anastomoses in a DiMo placenta. The right umbilical cord is from the donor twin (II) and the left umbilical cord from the recipient (I). The chorionic plate shows arterioarterial (A-A) and venovenous (V-V) superficial anastomoses. Normally, each arterial branch of the chorionic plate is paired with a venous vessel. However, in the so-called “deep anastomosis,” an unpaired artery (blue for relatively low oxygenated blood) from one twin (II in the diagram) supplies a portion of the chorionic villous tree that is drained by an unpaired vein from the co-twin (I in the diagram) (red to signify better oxygenated blood.)*
TTTS and those that do not (14) and the fact that 80% to 90% of DiMo twins do not develop TTTS has led other investigators to propose that more than numerical differences in anastomoses is involved in the pathogenesis of TTTS. Recent evidence suggests that vascular diameter and resistance and the pattern of chorionic plate vascular branching are important factors. Umur and associates, (17)(20) using a complex mathematical computer model, determined that, for a given radius, an A-A anastomosis has lower resistance than the equally sized afferent artery of an A-V anastomosis, which might explain the apparent protective effect of A-A anastomoses noted in most studies of TTTS. By their calculations, blood flow could be balanced more efficaciously through an A-A anastomosis than through oppositely directed A-V anastomoses, even though the pressure gradient in the A-V anastomoses was greater.

De Paepe and colleagues (16) studied the chorionic plate branching pattern in DiMo placentas from gestations without TTTS and those affected by severe TTTS. They found that gestations involving severe TTTS were more likely to exhibit chorionic magistral or a mixed magistral and diffuse pattern than unaffected gestations (60% versus 44%). The presence of a magistral pattern (a chorionic vascular pattern composed of relatively large-caliber, sparsely branching vessels that extended from the cord insertion site to the placental periphery without significant diminution in diameter), even when mixed with the more favorable disperse pattern (characterized by progressive and relatively uniform, dichotomous, fine branching of vessels from the cord insertion site, with the smaller and smaller subdivisions extending to the placental periphery), also was associated with higher incidences of other placental anatomic features implicated in the development of TTTS, such as unequal distribution of vascular territory and marginal or velamentous cord insertions. In addition, donor twins were more than twice as likely to have the magistral or mixed pattern as recipients, and when one or both twins had the magistral or mixed pattern, the average number of intertwin anastomoses was fewer. These investigators suggested that the predominance of magistral and mixed patterns in the donor twins’ placentas may be related to the observations that magistral patterns in singleton placentas are associated with absent end-diastolic blood flow (AEDF) in the umbilical arteries (UAs). AEDF has been attributed to the effects of a smaller peripheral vascular tree that results in increased vascular resistance to forward flow from the UAs. The low end-diastolic flow in the donor’s UAs combined with the magistral/mixed pattern might result in preferential routing of blood flow through anastomoses to the recipient twin. Thus, evidence supplied by the various placental structural studies of TTTS indicates vascular resistance, cross-sectional area, and other hemodynamic factors are contributing elements in the development, timing of clinical onset, and severity of TTTS. (8)

Unequal sharing of the placental disc is an additional risk factor for the development of TTTS. (1)(18) However, when and how disk inequality develops is unclear. The early developing chorionic villous tree may connect preferentially to the vasculature of the umbilical cord of one twin over that of the other. With unequal division of the inner cell mass, one embryo may develop a larger heart and, thereby, greater stroke volume and cardiac output, such that its perfusion of the developing villous tree initially is more robust. (1) However, others have proposed that unequal sharing may reflect abnormalities of placentation. Not all twin pairs that have TTTS exhibit significant growth discordance, and there is evidence that abnormalities of placentation may be relatively more responsible for the growth discordance in TTTS than imbalances in inter-twin transfusion. (21) Approximately 20% of cases of TTTS have concomitant evidence of placental insufficiency that usually, but not always, affects the donor twin. (22) The combination of placentation anomalies, flow inequalities, and fetal response may determine whether the donor’s placental territory appears grossly pale and bulky (Fig. 3) (with edematous large villi containing increased Hofbauer [chorionic villous macrophage] cells and nucleated fetal erythrocytes characteristic of fetal anemia) or whether it is pale and atrophic-appearing, with small villi. (3)(11)(23) Conversely, the recipient’s parenchymal territory usually is deep red-brown and firm due to villous congestion, but it also may show microscopic villous edema if the fetus is in congestive failure.

Marginal or velamentous cord insertions or single umbilical artery are associated with increased risks of the development and severity of TTTS. (1)(11)(16)(24) Of note, although DiMo twins comprise 20% of twin gestations, they have significantly increased rates of cord anomalies over diamniotic dichorionic twins, with more than 50% of marginal cord insertions, more than 40% of velamentous cord insertions, and nearly 50% of all single umbilical artery cases occurring in DiMo twins. (25) DiMo twins, therefore, are at constitutively increased risks for the underlying morbidity and mortality associated with cord compression, cord accident with thrombosis, and vessel rupture. Such cord events could compound any underlying risks of chorangangiopagus, especially
Figure 3. A DiMo placenta from clinically diagnosed case of "stuck twin syndrome" wherein Twin 1 (single cord clamp) was clinically designated as the donor Twin and Twin 2 (two cord clamps) as the recipient. A. The chorionic plate, with the donor twin side (D) on right showing a thin cord and the recipient side (R) on left having a thick, edematous cord segment. Note the large vessels that course under the transparent dividing membrane. B. The chorionic plate in 3A after the amnion and dividing membrane have been peeled from its surface to expose the vessels. The donor, Twin 2 (D), has an unpaired arterial vessel that courses to a shared lobule (arrow) that is drained by a vein from the recipient (R), when the vessel is traced back proximally toward the cord insertion site of Twin 1. Further examination revealed several other deep anastomoses of smaller caliber that had the "expected" donor-to-recipient arteriovenous (A-V) arrangement as well as some small "reversed" recipient-to-donor A-V-directed connections and some arterioarterial (A-A) anastomoses. C. An A-A anastomosis (white arrow) between a donor artery (yellow arrow) and a recipient artery (blue arrow). Images 3A–C underscore the importance of a thorough pathologic examination in TTTS cases because the net imbalance of the shunts ultimately contributes to the donor-recipient relationship. D. The maternal surface of a "classic" TTTS case shows a congested recipient (R) and pale edematous donor side (D). E. The formalin-fixed sections of the placenta in 3D (maternal surface on left aspect of sections) shows the difference in the donor’s pale tissue and the recipient’s congested tissue. However, the demarcation, although fairly distinct, is not a consistently transmural division, as might be suggested from the appearance of the maternal surface. Figures 3A–D are modified from Faye-Petersen, et al (23) and are used with permission.
for the donor twin. Donor twins are more likely to have velamentous cord insertion than are recipients. (26)

**Fetal Adaptive/Maladaptive and Placental Responses**

The asymmetric, bidirectional inter-twin exchange of blood and its biochemical components results in hemodynamic, osmotic, and physiologic changes in the fetuses. (1)(8)(9)(10) Hypovolemia and decreased renal blood flow in the donor may cause a number of renal structural and functional aberrations, especially in severe TTTS, including renal tubular degeneration and cellular apoptosis, loss of glomeruli or reduction in tubular number, and maldevelopmental progression to renal dysgenesis. (27)(28) Renal hypoperfusion also has been linked to activation of the renin-angiotensin system (RAS) (27)(29)(30) and elevated antidiuretic hormone concentrations (31) in the donor. Donors have hyperplasia of juxtaglomerular apparatuses, with increased numbers of renin-secreting cells (27) and upregulation of renin synthesis, (29) which are presumed to represent adaptive responses to restore euvolemia. However, in severe TTTS, activation of the RAS and associated elevations in angiotensin II (AT II) likely result in AT II-mediated fetal vasoconstriction that further compromises renal blood flow, leading to worsening oliguria and oligohydramnios. Increased fetal adrenal production of aldosterone may play a contributing role. (27)(29)(30)(31) Bajoria and colleagues (31) recently found that donors’ plasma and amniotic fluid concentrations of vasopressin were threefold higher than those of their co-twin recipients. (DiMo twins that did not have TTTS had higher concentrations than the recipients in TTTS, but they were not discrepant or as elevated as those in TTTS.) Thus, good evidence suggests that the oligohydramnios of the donor twin is a consequence of poor renal perfusion due to net hypovolemia, but it is exacerbated by vasoconstriction, mediated by AT II/vasopressin. Fetal vasoconstriction also may reduce placental blood flow to the villous tree, which may contribute to growth restriction in the donor. (27)(29)(30)

In severe cases of TTTS, hypervolemic recipients have renomegaly and glomerulomegaly consistent with increased renal blood flow, and immunohistochemical studies have revealed they have downregulation of the RAS, with markedly reduced numbers of renin-secreting cells and renin synthesis. (27)(29)(30) However, they have paradoxically high concentrations of renin and aldosterone, and the cardiomegaly, cardiomypathy, hypertension, and nephrosclerosis seen in recipients in TTTS are insufficiently explained by hypervolemia alone. Such observations are supportive evidence for transfer of these and possibly other vasoactive effectors from the donor to the recipient across placental anastomoses. The hemorrhagic necrosis and microangiopathic lesions seen in kidneys from recipients in severe TTTS also may be related to transanastomotic passage of hormones from the donor. (30)(32) Low concentrations of antidiuretic hormone in the recipient, together with elevated renin concentrations secreted by the donor, are likely responsible for worsening hypervolemia and polyuria/polyhydramnios in recipients. Maternal sequelae of fetal elevations in vasoactive substances have been appreciated recently. Elevated fetal renin-AT II values have been associated with maternal pseudoprimary hyperaldosteronism, (33) and it is possible that these contribute to changes in maternal perfusion of the placental bed.

In addition to anastomotic transfer of vasoactive mediators, increased cardiac synthesis and secretion of natriuretic peptides (NPs) have been linked to the progression of TTTS. NPs are a family of biochemical mediators that normally regulate blood pressure and body fluid homeostasis through their diuretic, natriuretic, and vasodilatory effects as well exerting antiproliferative effects on cardiovascular/mesenchymal tissue. Exploration of their role in the pathogenesis of adult cardiac hypertrophy and cardiomyopathy has led to greater appreciation of their importance in normal embryofetal development and their role in cardiomyopathy in the recipient twin in TTTS. In the fetus, in contrast to the adult, both atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormones are normally at high circulating concentrations and are expressed at high concentrations in the ventricles (in the normal adult, they are in expressed at low concentrations in cardiac atria and ventricles, respectively.) Their release is stimulated primarily by increased myocardial stretch and volume overload, hyperpermolality, and hypoxia, and vasoconstrictors, such as AT II, vasopressin, and endothelin-1 (ET-1), have been shown to result in their increased expression and secretion. ANPs and BNPs appear to be integral to embryonic fetal salt and water and blood pressure regulation, and the peptide system is likely functional by midgestation. ANP and BNP also appear to be important mediators of cardiogenesis because of their inhibitory effects on myocardial and fibroblast cell proliferation. Their effects on fetal aldosterone concentrations are unknown, but they suppress aldosterone synthesis in the adult. A third NP, c-type natriuretic peptide (CNP), which is found in adult genitourinary, pituitary, and brain tissues, is not produced in any significant quantity in the fetal or adult
heart, although it is secreted by the placenta. Placental production of NPs (ANP, BNP, CNP) affect vasorelaxation in the fetoplacental vasculature and likely help regulate blood supply to and within the fetus.

ANP and BNP both bind to natriuretic receptor NPR-A, a guanyl cyclase-linked receptor, which leads to generation of cytosine-GMP and the cascade that results in their physiologic effects. (34)

Bajoria and colleagues (35)(36) demonstrated that recipient twins in TTTS have higher concentrations of ANP, BNP, and ET-1 than their co-twin donors or DiMo twins without TTTS and that high concentrations of BNP and ET-1 are particularly correlated with cardiac dysfunction in the recipient. They suggested that these compounds might be used as early markers of cardiac compromise. It is plausible that the immaturity of the fetal kidney and its inability to concentrate urine may be exacerbated by the vasodilatory and diuretic effects of BNP and ANP released due to hypervolemia and contribute to polyuria/polycydrhnamnios or be compounded by BNP stimulation due to AT II transferred from the donor. Increased ANP concentrations in blood and amniotic fluid have been detected in recipients in TTTS, greater than donor twin’s and uncomplicated DiMo twin pair’s values. Increases in ANP also are related directly to increases in amniotic fluid volumes, and markedly increased immunostaining for ANP localizes predominantly to the heart and cytoplasm of the distal convoluted tubules of the kidneys of recipients when compared with measurements for donor twins. These data are supportive evidence that polyhydramnios in the recipient twin occurs as a consequence of ANP-mediated increases in fetal urine output due to ANP expression in both cardiac and renal tissues. (37)

Cardiac hypertrophy with cardiac dilatation is seen in recipients in TTTS and likely is due to the increased cardiac preload and increased afterload pressures due to hypertension. (30)(38) Of note, ventricular hypertrophy predominates and dilatation is comparatively “mild,” with right ventricular compromise preceding and generally exceeding that of the left ventricle. (9) Although the right ventricle is the primary “workhorse” of the fetal heart, and fetal myocardium can proliferate, other developmental factors likely contribute to the myocardial mural thickening detected by ultrasonography. Fetal myocardium is “stiffer” than the adult heart. The fetal myocardium has a greater percentage of noncontractile elements (60% versus 30% in the mature heart) and relatively delayed removal of calcium from troponin C, and the ventricles have a shorter phase of early passive diastolic filling and a greater reliance on atrial contraction. Fetal lamb studies have shown that after 4 to 5 mm Hg, further atrial preload does not result in increased stoke volume. Thus, the fetal heart is inherently and mechanically less efficient, is less able to increase stroke volume, and displays impaired relaxation. (39) These effects may represent, in part, disruption of the NP system, which has been shown to be NP receptor-dependent in murine models. NP receptor-deficient, Npr1+/− knockout mice develop hypertension, cardiac hypertrophy, and fibrosis. The absence of the receptor effectively inhibits vasorelaxation despite elevated concentrations of BNP and ANP. Moreover, cardiac hypertrophy can result independently of the presence of hypertension because the lack of receptor does not permit inhibition of myocardial proliferation/enlargement and fibroplasia.

The murine studies also may help to explain why cardiac anomalies are more common in recipient than donor survivors. Recipient twins are at increased risk for right ventricular outflow tract obstruction and pulmonary valvar stenosis/atresia with intact ventricular septum. (9) The progressive hypertrophy, reduced systolic function, and tricuspid valvar insufficiency lead to progressive decline in flow across the pulmonary valve. In a case in which the infant underwent surgical repair, the trileaflet semilunar valvar anatomy was identified as normal except for adhesions of the coapted leaflets. Thus, the pulmonary valvar stenosis/atresia in recipient twins seems to represent a unique form of “acquired congenital heart disease” and not a primary malformation. (9) ANP/BNP signaling interruption may play a significant role in the generation of cardiac hypertrophy and dysfunction. (34) The right and left ventricular myocardium have embryologic differences, and the number of NP receptors in the right ventricle may be inherently lower; once proliferation and hypertrophy ensue, the right ventricle may become progressively more vulnerable to the effects of preload, afterload, and pressors.

Although cardiac dysfunction is more common and more dramatic in recipients, decreased cardiac performance and injury also may occur in donor twins in TTTS. (8)(9) Protracted increase in cardiac demands and energy expenditure, due to continued transfusion of the co-twin, and hypoxemia and acidemia, due to the anemia and probable shrinking efficiency of placental function, contribute to decreased cardiac function and growth restriction in the donor. (8) Umbilical arterial end-diastolic forward blood flow diminishes to become absent (AEDF). (8)(10)(21)(38)(40) Hydrops from high-output cardiac failure can ensue in the donor due to loss of oncotic pressure from chronic transfusion (8) and
hypoproteinemia due to passive hepatic congestion and reduced hepatic synthesis that reflects reduced blood delivery to the liver (due to splanchnic vasoconstriction and relative preservation of blood shunting through the ductus venosus with effective bypass of the liver) and placental insufficiency with reduced nutritional supply.

Other Molecular Mechanisms Implicated in TTTS

Myriad other factors have been identified as determinants in normal and abnormal placental development in singleton gestations, and it is likely that aberrations in expression, timing of onset, and duration of expression of these angiogenic and trophophelic factors potentially are involved in the pathogenesis of TTTS. Several appear to have implications for the asymmetric placental and chorionic vascular branch pattern development, placentation, and fetal growth restriction in the donor twin. Detailed discussion of these complex factors is beyond the scope of this review, but chorionic vascular proliferation, branching, and lengthening are affected by oxygen tension and hormonal factors that exist in the maternal space, (1)(5)(41)(42) relative values of promoters of angiogenesis (ie, vascular endothelial growth factor A and placent growth factor), (43)(44)(45) populations and distributions of receptors to these growth factors, relative concentrations of trophoblast-produced and milieus-associated antiangiogenic determinants, (44)(45)(46) and effects of local mediators such as nitric oxide. (16)(47) The roles of insulin-like growth factors and receptors, (48)(49)(50) fetally produced hormones such as leptin, (48)(50)(51)(52) and placental inflammatory mediators such as interleukin-6, -8, and -10 (5)(49) likely will be determined to have a role in the pathogenesis of abnormalities associated with the vasculature, placentation, and growth of the placenta and fetal twin pair.

Summary

TTTS is a complex condition that results from circulatory imbalances due to placental anastomoses between DiMo twins. Its date of onset, rate of progression, and severity are multifactorial and reflect numbers and types of anastomoses, unequal sharing of the placenta, transusion of vasoactive mediators from the donor, abnormal expression of hormones that affect cardiac function in the recipient, and the effects of fetoplacental vascular resistance. Many of the deleterious effects of TTTS have implications for the necessity for and responsiveness to medical therapies for neonates born of these complicated gestations. The intrauterine environment of TTTS, with its circulating mediators and shifts in blood shunted between the twins, ultimately can affect cardiac, renal, and hepatic function of the twins. Greater understanding of the pathogenesis of TTTS can help neonatologists explain the sometime confusing findings in the donor and recipient twins.

References

NeoReviews QUIZ

1. Chronic twin-to-twin transfusion syndrome (TTTS) is a condition characterized by a sustained imbalance of blood volume transfused between twins, with one twin becoming a donor and the other twin becoming a recipient of the transfusion. Of the following, the most accurate statement regarding chronic TTTS is that:

A. Arterioarterial anastomoses in the placenta are associated with poorer perinatal outcome than arteriovenous anastomoses.
B. Chronic TTTS is almost exclusively restricted to twins with diamniotic monochorionic placentations.
C. Marginal or velamentous umbilical cord insertions or a single umbilical artery lessen the severity of TTTS.
D. Recipient twins are more likely than donor twins to have a chorionic magistral blood vessel pattern.
E. Recipient twins are more susceptible than donor twins to fetal entrapment in the amnion ("stuck twin syndrome").

2. In chronic TTTS, the asymmetric inter-twin exchange of blood and its biochemical components results in hemodynamic, osmotic, and pathophysiologic changes in the fetuses. Of the following, the hormone most likely to be upregulated in the recipient twin in chronic TTTS is:

A. Aldosterone.
B. Angiotensin II.
C. Arginine-vasopressin.
D. Atrial natriuretic peptide.
E. Renin.
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DOI: 10.1542/neo.9-9-e370

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