Part 2
Related syndromes
Chapter 6

Twin anemia-polycythemia sequence in two monochorionic twin pairs without oligo-polyhydramnios sequence

Enrico Lopriore MD
Johanna M Middeldorp MD
Dick Oepkes MD PhD
Humphrey HHH Kanhai MD PhD
Frans J Walther MD PhD
Frank PHA Vandenbussche MD PhD

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Abstract

Objective: To report an uncommon form of chronic inter-twin transfusion, referred to as twin anemia-polycythemia sequence (TAPS), with severe anemia in one twin and polycythemia in the other, without the characteristically associated twin oligo-polyhydramnios sequence (TOPS) seen in the classical twin-to-twin transfusion syndrome (TTTS).

Methods: Description of the clinical course and placental characteristics of two pairs of monochorionic twins with TAPS.

Results: The two pairs of monochorionic twins were born at 33 and 34 weeks’ gestation, respectively. Serial fetal ultrasound examinations revealed no signs of TOPS. At birth, both donor twins were severely anemic requiring blood transfusion and both recipients were polycythemic, one requiring partial volume exchange transfusions. Inter-twin difference in reticulocyte counts was extremely high, suggesting a chronic form of inter-twin blood transfusion. Placental injection studies revealed a preponderance of very small (< 1 mm) arterio-venous anastomoses in one direction.

Conclusions: Chronic inter-twin transfusion may lead to an uncommon form of inter-twin transfusion, named TAPS, not associated with TOPS, resulting in severe fetal or neonatal hematological complications. We hypothesize that TAPS is mediated through minuscule unidirectional anastomoses. TAPS can be diagnosed antenatally with Doppler studies and postnatally by hemoglobin and reticulocyte measurements.
Introduction

Twin-to-twin transfusion syndrome (TTTS) is a heterogeneous disease affecting monochorionic twin pregnancies and results from hemodynamic imbalance due to placental vascular anastomoses. Various forms of TTTS have been described: acute perimortem TTTS, acute perinatal TTTS and chronic TTTS. Acute perimortem TTTS occurs after intrauterine fetal demise of a co-twin and is due to acute exsanguination from the surviving twin into the low-pressure circulation of the demising co-twin. Acute perinatal TTTS may occur during birth due to acute inter-twin shifts of blood resulting from blood pressure differences associated with uterine contractions or changes in fetal position. Both acute forms of TTTS are mediated through superficial arterio-arterial and veno-venous anastomoses. The most common form of TTTS, referred to as chronic TTTS, occurs usually during the second trimester of pregnancy and affects 15% of monochorionic twin pregnancies. Chronic TTTS results from chronic inter-twin transfusion of blood mediated through arterio-venous anastomoses. Chronic TTTS itself is also a highly heterogeneous disease and may be staged using Quintero’s classification based on ultrasound criteria. Chronic TTTS is diagnosed when antenatal sonographic evidence of twin oligo-polyhydramnios sequence (TOPS) is found. TOPS is defined by deepest vertical pool of ≤ 2 cm and ≥ 8 cm in the donor’s and recipient’s amniotic sac, respectively. We report two cases of monochorionic twins with an unusual form of chronic TTTS. Both cases had hematological evidence of severe chronic inter-twin transfusion but no antenatal sonographic signs of TOPS. Placental injection studies revealed a preponderance of very small (< 1 mm) arterio-venous anastomoses in one direction.

Case presentation

Case 1

A 35-year-old gravida 2 para 1 was referred at 27 + 1 weeks’ gestation with a dichorionic-triamniotic triplet pregnancy after in vitro fertilization. Weekly ultrasound examination throughout pregnancy showed no signs...
of TTTS (last ultrasound examination was performed at 33 + 1 weeks’
gestation). Doppler measurement of the middle cerebral artery peak
systolic velocity (MCA-PSV) showed a mild increase (1.2 multiples of
median) in MCA-PSV in one of the monochorionic fetuses (maximum
velocity of 58 cm/sec at 33 + 1 weeks’ gestation). Labor was induced and
three girls were born vaginally at 34 + 0 weeks’ gestation. The last two
girls were the monochorionic twin pair. The second-born infant was pale
and weighed 1725 g (between 9th and 25th percentile for gestational age).
The third-born infant was plethoric and weighed 1695 g (9th percentile for
gestational age). Birth weight discordance was 2%. Apgar scores for the
second-born and third-born infant were 8/9/10 and 7/8/8, respectively.
Hemoglobin values for twin 2 and twin 3 were 7.6 g/dL (< 5th percentile for
gestational age) and 21.7 g/dL (> 95th percentile for gestational age) with
reticulocyte counts of 21% (absolute reticulocyte count 399 x 10^3/mm^3)
and 4% (absolute reticulocyte count 181 x 10^3/mm^3), respectively. The
anemic infant, who was also the fetus with increased MCA-PSV, required
a blood transfusion on day 1. No signs of acute hemorrhagic hypovolemic
shock at birth (heart rate 140 bpm, blood pressure 44/35 mmHg) were
present in the anemic infant. No evidence of placental abruption was found
and none of the infants were hypoxic at birth. Kleihauer-Betke test was not
done. The hematocrit value in the co-twin increased up to 69% on day 1,
but the infant remained asymptomatic and did not require a partial volume
exchange transfusion. Cranial ultrasound examination in both twins was
normal and further neonatal course was uneventful.
Macroscopic placental examination showed a velamentous insertion of the
umbilical cord of twin 3 and an injection study with colored dye revealed
five very small (< 1 mm) arterio-venous anastomoses (< 1 mm) from twin 2
to twin 3 (Figures 1 and 2).

Case 2
A 31-year-old gravida 5 para 3 was referred to our center at 16 weeks’
gestation with a twin pregnancy. The twin pregnancy had been diagnosed
as dichorionic in the referring hospital based on an ultrasound examination
at 10 weeks’ gestation. The course of the pregnancy was uneventful and no
signs suggestive of TTTS were found on monthly ultrasound examination.
FIGURE 1  Case 1. Triplet placenta after injection with colored dye. There is a monochorionic placenta (left-bottom side of the picture) and a fused dichorionic placenta (top-right) (blue for arteries and orange or yellow for veins). The five anastomoses from donor to recipient are in the white square that is enlarged in figure 2.

FIGURE 2  Case 1. The sky-blue arrows indicate five very small (< 1 mm) arterio-venous anastomoses from twin 2 (donor) to twin 3 (recipient).
MCA-PSV measurements were not done. One day after the last ultrasound examination at 33 + 3 weeks’ gestation, spontaneous rupture of membranes occurred and was followed by the birth of two boys. The first-born infant was pale and weighed 1880 g (between 9th and 25th percentile for gestational age). The second-born twin was extremely plethoric and weighed 1980 g (between 25th and 50th percentile for gestational age). Birth weight discordance was 5%. Apgar scores were 8/9/9 and 7/8/8 for the first-born and second-born infant, respectively. Hemoglobin values for twin 1 and twin 2 were 6.0 g/dL (< 5th percentile for gestational age) and 26.3 g/dL (> 95th percentile for gestational age) with reticulocyte counts of 30% (absolute reticulocyte count 525 x 10³/mm³) and 3% (absolute reticulocyte count 192 x 10³/mm³), respectively. The anemic infant had no signs of acute hemorrhagic hypovolemic shock at birth (heart rate 120 bpm; blood pressure 51/37 mmHg) but required a blood transfusion on day 1. No clinical or laboratory evidence of placental abruption was found. Kleihauer-Betke test was not performed. The second-born twin required oxygen administration and ventilatory support with CPAP due to cyanosis and respiratory failure. Severe hypoglycemia was corrected by intravenous glucose infusions. The hematocrit increased up to 90% on day 1 and two partial volume exchange transfusions were performed because of symptomatic polycythemia-hyperviscosity syndrome. Cranial ultrasound showed persistent bilateral periventricular echodensities in both twins. At macroscopic examination, the placenta was monochorionic-diamniotic. Colored-dye injection showed four very small (< 1 mm) arterio-venous anastomoses from twin 1 to twin 2 and one very small (< 1 mm) arterio-venous anastomosis from twin 2 to twin 1 (Figures 3 and 4). Microscopic examination showed that the dividing membrane was diamniotic.

Comment

In this study, we found evidence that monochorionic twin pregnancies without signs of TOPS can still be affected by chronic inter-twin transfusion resulting in severe fetal or neonatal hematological complications. We have named this condition twin anemia-polycythemia sequence (TAPS). Differential diagnosis in monochorionic twins with highly discordant
FIGURE 3  Case 2. Monochorionic placenta after injection with colored dye (blue or green for arteries and orange or yellow for veins). The five small arterio-venous anastomoses are only visible after enlargement. The four anastomoses from donor to recipient are in the white square that is enlarged in figure 4 (the single anastomosis from recipient to donor is not in the white square).

FIGURE 4  Case 2. The sky-blue arrows indicate four small arterio-venous anastomoses from twin 1 (donor) to twin 2 (recipient).
hemoglobin values at birth includes acute peripartum TTTS, chronic TTTS with TOPS and chronic TTTS with TAPS.

Other possible causes for isolated anemia or polycythemia should also be ruled out. Chronic anemia in newborns may result from partial placental abruption, infection or chronic feto-maternal hemorrhage. Unfortunately, Kleihauer-Betke test was not performed in our two cases, which is a limitation of our study. However, the associated combination with polycythemia in the co-twin clearly suggests a form of feto-fetal transfusion rather than feto-maternal transfusion. Common causes for polycythemia should also be excluded, such as chronic hypoxia associated with intrauterine growth retardation. Polycythemia due to chronic in utero hypoxia results from increased erythropoietin levels and reticulocytosis\textsuperscript{215,216}. Reticulocyte counts in the polycythemic infants in our reported cases were normal for gestational age, suggesting that polycythemia resulted from chronic inter-twin transfusion rather than from increased erythropoiesis secondary to chronic hypoxia.

A first possible diagnosis in both reported cases is that of acute peripartum TTTS. However, the anemic infant in acute peripartum TTTS has clinical signs of hemorrhagic hypovolemic shock such as pallor, tachycardia and hypotension\textsuperscript{47,186}. Also, reticulocyte counts after acute blood loss are typically not increased due to lack of time for compensatory hematopoiesis. Although it is difficult to completely rule out an acute peripartum TTTS event in our cases, acute peripartum TTTS should be disregarded for several reasons. First, no clinical signs of acute perinatal blood loss were found in the anemic infants. Second, very high reticulocyte counts were measured in both anemic infants, suggestive of chronic rather than acute blood loss. Finally, acute peripartum TTTS is mediated through (large) superficial anastomoses\textsuperscript{37,71}. Placental injection studies in both reported cases showed only minuscule arterio-venous anastomoses without superficial anastomoses. Small-caliber anastomoses have a high vascular resistance and theoretically do not allow large amounts of blood volume to be transfused acutely from one twin to the other (according to Poisseuille’s law of fluid dynamics).

A second possible diagnosis, that of the common form of chronic TTTS can be disregarded due to absence of the typical signs of TOPS. We suggest therefore that atypical forms of chronic TTTS without TOPS, but
associated with anemia in one twin and polycythemia in the other, be referred to as TAPS. TAPS differs significantly in terms of diagnosis and management from the typical form of chronic TTTS with the characteristic signs of TOPS. Therefore, a clear distinction between TAPS and TOPS is clinically more useful and reflects more accurately the heterogeneity of TTTS. TAPS may occur spontaneously (natural form) as reported in this study, but may also develop after laser surgery (iatrogenic form). Recent reports suggest that the iatrogenic form of TAPS may occur in up to 13% of cases after laser surgery\textsuperscript{213,214}. Interestingly, in iatrogenic TAPS, it is usually the former recipient who becomes anemic, whereas the former donor becomes polycythemic\textsuperscript{213,214}.

Most authors consider the presence of TOPS to be the major diagnostic criterion for chronic TTTS\textsuperscript{27,28,93,186}. Marked fetal growth discordances and inter-fetal hemoglobin differences may also be present but these features are not considered key elements in the diagnosis of chronic TTTS\textsuperscript{27,93,102}. Doppler studies are a standard requirement to determine Quintero staging once chronic TTTS is diagnosed\textsuperscript{27,28} and are also helpful in the diagnosis of fetal anemia after single intrauterine fetal death (acute perimortem TTTS)\textsuperscript{33}. Routine Doppler studies are also recommended after laser surgery to rule out fetal anemia\textsuperscript{213,214}.

We suggest that Doppler studies and MCA-PSV measurements also be performed during each follow-up visit in all uncomplicated monochorionic twin pregnancies, even in the absence of TOPS. Signs of fetal anemia in a monochorionic twin should then alert the perinatologist of the possibility of TAPS. Fetal anemia may affect cerebral oxygenation and result in hypoxic-ischemic cerebral injury, whereas polycythemia has been suggested to cause cerebral injury in TTTS by vascular sludging\textsuperscript{206}. Hypothetically, TAPS may also be responsible for some cases of unexplained fetal demise in monochorionic pregnancies without signs of chronic TTTS.

Whether TAPS is associated with increased mortality or morbidity is not known. If so, invasive procedures such as fetoscopic laser surgery, intrauterine blood transfusion or a combination of both, may improve outcome. At present, however, we think that invasive procedures are not indicated because the risk of procedure-related complications may outweigh the risk of mortality or morbidity.

There as several hypotheses on the origin of inter-twin amniotic fluid discordances in the common form of chronic TTTS with TOPS\textsuperscript{185}. It is
however not yet clear why there are no inter-twin amniotic fluid discordances in TAPS. One of the common denominators between the two reported cases is the preponderance of very small (< 1 mm), arterio-venous anastomoses in one direction. Vascular resistance in small-caliber vessels is higher than in larger vessels and reduces the volume of fluid passage (Poisseuille’s law). We hypothesize that if only a few very small placenta vascular anastomoses are present, inter-twin blood transfusion occurs very slowly and allows more time for hemodynamic compensatory mechanisms to take place. Activation or inactivation of the renin-angiotensin system may then induce the hypovolemic donor and the hypervolemic recipient to remain euvolemic, which in turn explains the absence of TOPS. However, compensatory hematopoiesis may not be sufficient to prevent severe anemia in the donor, despite the extremely high reticulocyte count. Another possible explanation is that the reported infants were born before TOPS had time to develop. Inter-twin hemoglobin discordance and amniotic fluid discordance varies with the state of progression of chronic TTTS. It is conceivable that some twins with chronic TTTS may first develop TAPS and then TOPS. As placental blood vessels enlarge throughout pregnancy, these vessels may eventually become just large enough to produce TAPS at a certain point in gestation, but not before this time. Regardless of the various hypotheses, our understanding of TAPS is clearly still incomplete.

In conclusion, perinatologists involved in the care of monochorionic twins should maintain a high index of suspicion, as antenatal ultrasound examination without Doppler studies does not rule out a chronic form of inter-twin transfusion. TAPS can occur in the absence of the characteristic inter-twin discordance in amniotic fluid volumes. TAPS should be diagnosed when large inter-twin discordance in fetal or neonatal hemoglobin levels and reticulocyte counts are found, in absence of TOPS. Placental injection studies may then reveal a preponderance of very small arterio-venous anastomoses in one direction.