Next steps towards improved care for twin anemia polycythemia sequence

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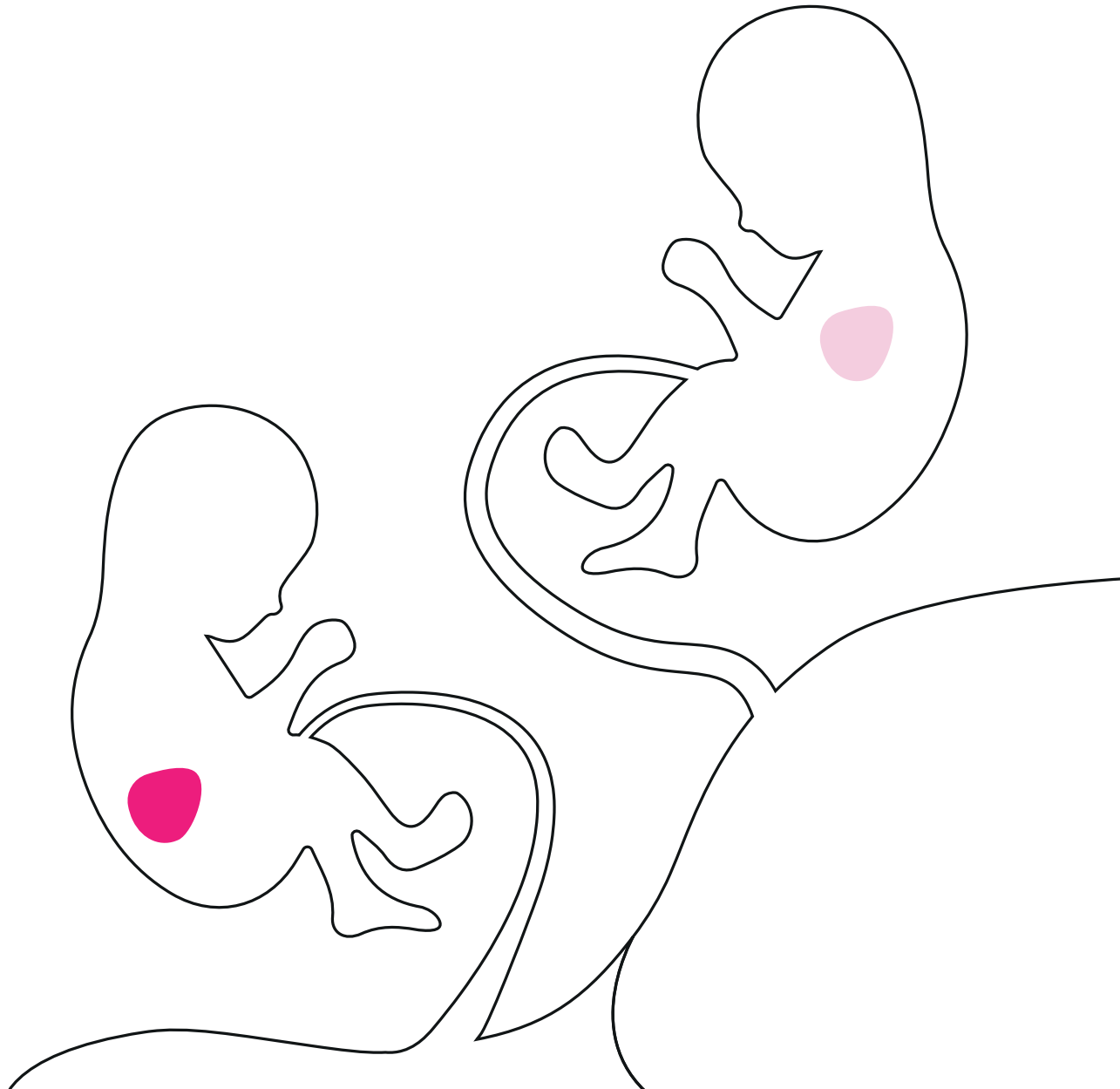
Chapter 4

The prevalence of fetal cardiomegaly, placental dichotomy and starry-sky liver in twin anemia polycythemia sequence



Abstract

Objective

To investigate the prevalence of additional ultrasound markers including placental dichotomy, cardiomegaly, and starry-sky liver in pregnancies with twin anemia polycythemia sequence (TAPS).

Methods

All monochorionic twins antenatally diagnosed with TAPS at our center between 2006-2019 were retrospectively reviewed for the presence of placental dichotomy, cardiomegaly in the donor and a starry-sky liver in the recipient. TAPS was diagnosed based on delta middle cerebral artery – peak systolic velocity > 0.5 multiples of the median. The primary outcome was the prevalence of placental dichotomy, cardiomegaly, starry-sky liver and at least one of these markers in both spontaneous and post-laser TAPS. Secondary outcome included the prevalence of these ultrasound markers per antenatal TAPS stage.

Results

Between 2006 and 2019, 91 monochorionic twins with TAPS were eligible for analysis. Placental dichotomy was observed in 44% (43/91) of TAPS cases. A total of 70% (64/91) of the TAPS donors developed cardiomegaly. A starry-sky liver was identified in 66% (53/80) of the TAPS recipients. The prevalence of cardiomegaly and starry-sky liver was roughly comparable between spontaneous TAPS and post-laser TAPS. Spontaneous TAPS showed a higher prevalence of placental dichotomy than post-laser TAPS twins, 63% (30/48) vs. 23% (10/43) respectively. In 86% (78/91) of the TAPS cases, at least one additional ultrasound finding was detected, meaning that 14% (13/91) of the cases presented solely with discordant MCA-PSV values. For all ultrasound markers, prevalence increased with incrementing antenatal TAPS stage.

Conclusion

Placental dichotomy, fetal cardiomegaly and a starry-sky liver are commonly found in TAPS pregnancies. Looking for these ultrasound markers can be of additional help in improving antenatal detection of TAPS in monochorionic twin pregnancies.

Introduction

Twin anemia polycythemia sequence is a chronic form of unbalanced feto-fetal transfusion through minuscule placental anastomoses leading to anemia in the donor and polycythemia in the recipient.[1] In contrast to twin-twin transfusion syndrome (TTTS), TAPS occurs in the absence of amniotic fluid discordances. TAPS can develop spontaneously in 3-5% of monochorionic twins or can occur iatrogenically in 2-15% of TTTS cases treated with laser, due to residual anastomoses.[2-4] Antenatal diagnosis is based on discordant middle cerebral artery peak systolic velocity (delta MCA-PSV > 0.5 MoM), with an increased MCA-PSV value in the donor, suggestive of anemia, and a decreased MCA-PSV level in the recipient, suggestive of polycythemia.[5]

Although identification of TAPS is primarily based on inter-twin MCA-PSV discrepancy, other ultrasound markers suggestive of TAPS have also been reported. Firstly, the placenta in TAPS can show dichotomy, with a hyperechogenic placental share for the donor and hypoechogenic placental share for the recipient (Figure 1).[6] In some TAPS cases, this observation is accompanied by placental size discordance, with a hydropic enlarged placental share for the donor and a flattened placental share for the recipient.[7] Secondly, polycythemic recipients can present with a starry-sky liver, a term that was coined for the sonographic pattern of the liver, characterized by clearly identified portal venules (stars) and diminished parenchymal echogenicity (sky).[8] Lastly, cardiomegaly can develop in anemic fetuses, because their hypoxic environment demands a higher cardiac output to continue to provide the body with adequate blood flow.[9]

The presence of these ultrasound markers has been described in a few case reports and case series.[6-8, 10] It is unknown whether these cases represent a small subgroup of TAPS, or that these sonographic findings are more ubiquitous in TAPS. Information on the true prevalence could contribute to enhanced understanding of the presentation of TAPS antenatally, and might lead to a timelier detection of the disease, especially in clinics where routine MCA-PSV Doppler measurements are not standard practice.

The aim of the current study was to investigate the prevalence of additional ultrasound markers including placental dichotomy, fetal cardiomegaly, and starry-sky liver in a large cohort of TAPS cases.

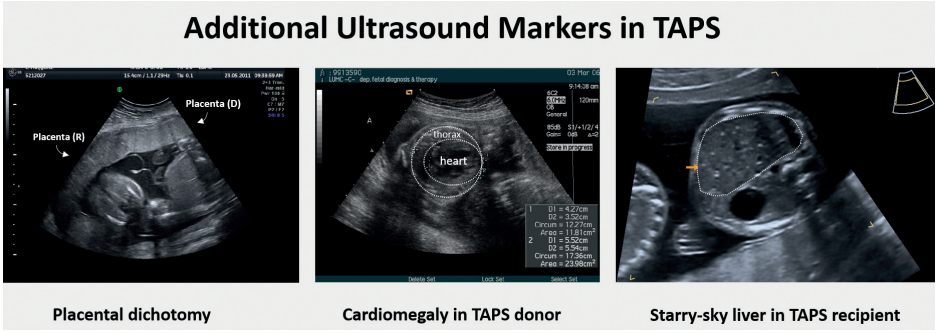


Figure 1. Ultrasound images of placental dichotomy, cardiomegaly in the donor, and starry-sky liver in the recipient in pregnancies with twin anemia polycythemia sequence (TAPS).

Methods

In this retrospective study, all monochorionic twins diagnosed with TAPS at the Leiden University Medical Center (LUMC) between 2006-2019 were reviewed for the presence of placental dichotomy, cardiomegaly in the donor and a starry-sky liver in the recipient. The LUMC is the national referral center for fetal therapy and complicated monochorionic twin pregnancies in The Netherlands. To be eligible for inclusion, TAPS cases needed to have ultrasound records from the moment of diagnosis to birth of the twins. TAPS cases with incomplete or lacking ultrasound reports, or cases that were only diagnosed postnatally were excluded from the study.

MCA-PSV assessment was performed in accordance with the previously described technique by Mari et al.[11] TAPS was diagnosed according to aforementioned antenatal criteria for TAPS (delta MCA-PSV > 0.5 MoM). [5] The following maternal, fetal and neonatal data were retrospectively obtained from digital medical records: maternal age, gravidity, parity, mode of delivery, antenatal TAPS stage, antenatal management (including expectant management, immediate delivery (within 7 days after diagnosis), intrauterine blood transfusion (IUT) with or without a partial exchange transfusion (PET), laser surgery, selective feticide and termination of pregnancy), sex of twins, and gestational age at birth.

The primary outcome was the prevalence of placental dichotomy, cardiomegaly in the donor, a starry-sky liver in the recipient and at least one of these findings, for the total group and per TAPS type (spontaneous and post-laser). The secondary outcome was the prevalence of these ultrasound markers

per antenatal TAPS stage (stage 1-5). For antenatal TAPS stage, the highest TAPS stage that was detected during pregnancy was recorded. All ultrasound examinations were carried out by experienced sonographers specialized in monochorionic twins at our center. For the current study, all available ultrasound reports were checked for the description of the aspect of the placenta (for placental dichotomy), heart of the donor (for cardiomegaly) and liver of the recipient (for starry-sky liver). In case of an inconclusive or absent description regarding any of the ultrasound markers, ultrasound images were reassessed by two of the authors (LSAT and FS). Any disagreements between LSAT and FS were resolved by a third observer (DO). Ultrasound images were eligible for assessment if there was a complete view of the placenta (allowing observation of placental dichotomy), an abdominal transverse section for the TAPS donor (allowing observation of the heart), and a thoracic abdominal section for the TAPS recipient (allowing observation of the liver).

Analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were generated for all variables. Data were presented as median with inter-quartile ranges (IQR) or n/N (%), where appropriate.

Results

Between 2006 and 2019, a total of 120 monochorionic twins were diagnosed with TAPS at our center. A total of 29 cases were excluded, either due to a postnatal diagnosis (n = 22) or incomplete or lacking ultrasound records (n = 7), yielding a total population of 91 TAPS twins eligible for analysis. The presence of placental dichotomy and cardiomegaly could be evaluated in all eligible cases. In 11 TAPS recipients, a description of the aspect of the liver was lacking in all ultrasound reports, and corresponding ultrasound images of the liver were unavailable or inconclusive. Consequently, these cases were left out of the prevalence estimation for starry-sky liver.

Table 1. Baseline characteristics for 91 TAPS pregnancies managed in the Leiden University Medical Center between 2006-2019

	TAPS cases (N = 91)
Maternal age (years)	32 (29-35)
Gravidity	2 (1-3)
Parity	1 (0-1)
Female – n/N (%)	50/91 (55)
Cesarean	42/91 (46)
Delta MCA-PSV (MoM)	1.3 (0.9-1.7)
Spontaneous TAPS	48/91 (47)
Post-laser TAPS	43/91 (53)
Gestational age at birth (weeks)	32.4 (29.4-35.0)
Antenatal TAPS stage	
I	16/91 (18)
II	40/91 (44)
III	27/91 (30)
IV	2/91 (2)
V	6/91 (7)
Antenatal treatment	
Expectant management	40/91 (44)
Immediate delivery	1/91 (1)
IUT (with PET)	22/91 (24)
Laser surgery	18/91 (23)
Selective feticide	8/91 (8)
Termination of pregnancy	2/91 (2)

Data are presented as n/N (%) or median (IQR)
TAPS, twin anemia polycythemia sequence; MCA-PSV, middle cerebral artery – peak systolic velocity; MoM, multiples of the median; IUT, intra-uterine transfusion; PET, partial exchange transfusion.

Baseline characteristics of the studied population are presented in Table 1. The population consisted of 48 (53%) spontaneous TAPS twins and 43 (47%) post-laser TAPS twins. Management included expectant management in 44% (40/91), IUT (with PET) in 24% (22/91), laser surgery in 20% (18/91) selective feticide in 9% (8/91), termination of pregnancy in 2% (2/91), and an immediate delivery in 1% (1/91) of cases.

Table 2. The prevalence of placental dichotomy, cardiomegaly in the TAPS donor, starry-sky liver in the TAPS recipient, and at least one of these ultrasound markers in TAPS twins.

	TAPS twins Total (N = 91)	**Spontaneous TAPS (N = 48)**	**Post-laser TAPS (N = 43)**
Placental dichotomy	40/91 (44)	30/48 (63)	10/43 (23)
Cardiomegaly in TAPS donor	64/91 (70)	33/48 (69)	31/43 (72)
Starry-sky liver in TAPS recipient[a]	53/80 (66)	25/39 (64)	28/41 (68)
At least one ultrasound marker	78/91 (86)	41/48 (85)	37/43 (86)

Data are presented as n/N (%).
[a]A total of 11 TAPS cases had inconclusive descriptions regarding a starry-sky liver and were therefore excluded from the prevalence estimation. The 11 cases consisted of nine spontaneous TAPS and two post-laser TAPS.
TAPS, twin anemia polycythemia sequence

Table 2 presents the prevalence of the three additional ultrasound markers for the total TAPS population, and for spontaneous and post-laser TAPS separately. Placental dichotomy was observed in 44% (40/91), cardiomegaly in 70% (64/91) of the TAPS donors, and a starry-sky liver was identified in 66% (53/80) of the TAPS recipients. The prevalence of cardiomegaly and starry-sky liver was roughly comparable between spontaneous TAPS and post-laser TAPS. Spontaneous TAPS twins showed a higher prevalence of placental dichotomy than post-laser TAPS twins, 63% (30/48) vs. 23% (10/43) respectively. In 86% (78/91) of the TAPS cases, at least one additional ultrasound finding was detected, meaning that 14% (13/91) of the cases presented solely with discordant MCA-PSV values. Figure 2 depicts the prevalence of placental dichotomy, cardiomegaly, starry sky liver, and at least one of these ultrasound markers, per TAPS stage. Overall, the prevalence of these ultrasound markers increased with incrementing TAPS stage.

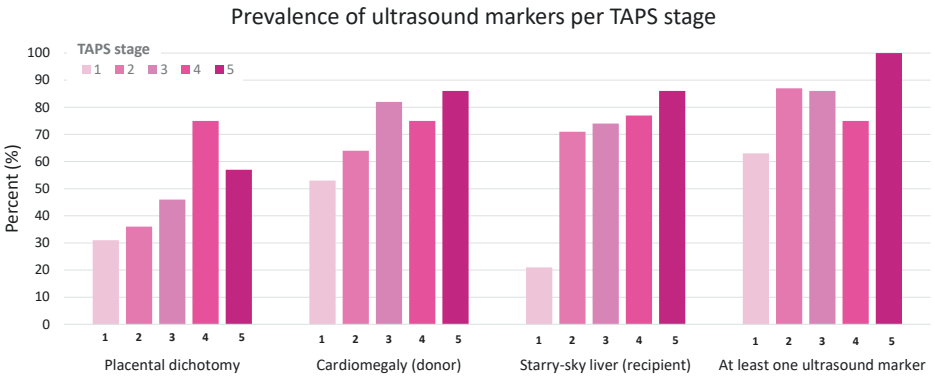


Figure 2. Prevalence (%) of placental dichotomy, cardiomegaly in the donor and starry sky liver in the recipient, per antenatal TAPS stage. In total, 16 TAPS cases were stage 1, 40 cases were stage 2, 27 cases were stage 3, two cases were stage 4 and six cases were stage 5.

Discussion

This study was aimed to assess the prevalence of three additional ultrasound markers in TAPS. We found that the prevalence of placental dichotomy was 44%, that cardiomegaly was detected in 70% of the TAPS donors and that 66% of the TAPS recipients presented with a starry-sky liver.

Since TAPS is characterized by a substantial risk for perinatal mortality and long-term neurodevelopmental impairment, timely antenatal detection is of utmost importance.[14] Unfortunately, there are still many clinics and guidelines across the world where MCA-PSV Doppler screening is not part of standard care for monochorionic twin pregnancies. Consequently, TAPS remains a frequently missed diagnosis. Our study shows that searching for these additional ultrasound markers could be of great value in centers that do not perform MCA-PSV measurements regularly, since the majority of TAPS cases present with at least one of these findings. However, a small subgroup of TAPS twins (14%) does not show any of these markers, and presents solely with MCA-PSV discordancy. Routine MCA-PSV examination therefore remains the cornerstone in the detection of TAPS antenatally.

This is the first study reporting on the prevalence of additional ultrasound findings in a large cohort of TAPS pregnancies. Until now, only a few small studies have been published with regard to this topic, and the majority concerned case reports. Stritzke et al. described a TAPS case that was missed

antenatally, because MCA-PSV Dopplers were not registered.[6] However, a large difference in placental echogenicity was observed four weeks prior to delivery. Movva et al. reported on two TAPS cases in which the observation of placental dichotomy prompted sonographers to perform MCA-PSV Dopplers, that in their turn revealed the diagnosis of TAPS.[15] A starry-sky liver was described in two cases published by Soundararajan et al., where it was seen as an early manifestation of severe TAPS.[8]

Although cardiomegaly in the donor has not been described as a typical marker for TAPS in the literature, our data show that it was the most frequently observed finding on ultrasound, both in spontaneous TAPS and in post-laser TAPS twins. Despite the fact that TAPS stage 1 is usually regarded as mild, this study demonstrated that more than half of the donors in this stage already showed signs of cardiac remodulation to the anemic environment. The exact role of the other two ultrasound markers in the pathophysiology of TAPS is not fully understood. Severe anemia can lead to fetal hydrops, a condition that is accompanied by excessive fluid accumulation in the fetal body. Since the placenta is an indispensable part of the fetal circulation, fluid accumulation in the placental tissue could be in line with the manifestation of the disease. However, our data show that placental dichotomy is detected before the fetus becomes hydropic. Whether placental dichotomy can be considered as a prehydropic sign that indicates a poorer prognosis is unclear. Notably, our results indicate that the prevalence seemed to increase with incrementing TAPS stage, suggesting it might be linked to the severity of the condition. Interestingly, Bamberg et al. and a study of or own research group underline the association between severity of TAPS and the degree of dichotomy in TAPS placentas, both on ultrasound and on post-partum macroscopic placental examination.[10, 16] Of note, placental dichotomy was more prevalent in spontaneous TAPS twins than in post-laser TAPS twins, suggesting there might be a different response of the placenta to anemia, once it has been lasered for TTTS.

A starry-sky liver might be the hardest of the three markers to identify on ultrasound, however, it is the only additional finding that can be detected for polycythemia. Whereas anemia can be accompanied by many signs of fetal decompensation, severe polycythemia in the recipient generally goes without additional fetal sequelae. Identification of a starry-sky liver as a reliable marker for polycythemia might therefore be of great value. Unfortunately, the exact

pathophysiological mechanism behind the development of starry-sky liver in fetal polycythemia remains to be unveiled. In general, the starry-sky pattern in the liver is thought to occur due to the edematous swelling of hepatocytes with a resultant decrease in the hepatic echogenicity.[17] The altered acoustic properties between the portal venules and hepatic lobules cause sonographic accentuation of the venule walls, creating a starry sky appearance. Hepatocyte swelling can arise from many causes including leukemic or neoplastic infiltration, infections, or right heart failure. However, none of them are present in TAPS recipients. Nonetheless, in line with placental dichotomy and cardiomegaly, the prevalence of starry-sky liver also seems to increase with incrementing TAPS stage, indicating an underlying mechanism for severe polycythemia and the development of this specific sonographic feature.

Due to the retrospective nature of the study, our results may be subject to selection bias. Possibly, TAPS cases with additional ultrasound markers were more easily detected and referred to our center than cases that progressed without any additional sonographic signs, resulting in an overestimation of the true prevalence. Another limitation is the fact that these ultrasound markers were based on subjective impressions of individual specialized sonographers and not on predefined standardized criteria, hampering overall reproducibility of the results. Lastly, we were unable to assess the specificity and sensitivity of the markers. Future studies should be aimed at prospective identification of placental dichotomy, fetal cardiomegaly and starry-sky liver in the general population of monochorionic twins, in order assess the exact clinical values of these (combined) ultrasound markers in the detection of TAPS. The most important strength of this study is high number of TAPS cases with ultrasound records and therefore this study is a valuable contribution to the knowledge of the presentation of TAPS prenatally.

In conclusion, this study shows that placental dichotomy, fetal cardiomegaly and a starry-sky liver are commonly found in TAPS pregnancies. Looking for these ultrasound markers can be of additional help in improving antenatal detection of TAPS in monochorionic twin pregnancies.

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