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

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KEYWORDS: cardiomegaly; diagnosis; monochorionic twins; placental dichotomy; starry-sky liver; TAPS; twin anemia–polycythemia sequence

CONTRIBUTION

What are the novel findings of this work?
Placental dichotomy, fetal cardiomegaly and a 'starry-sky' liver are found commonly in pregnancy complicated by twin anemia–polycythemia sequence (TAPS).

What are the clinical implications of this work?
Investigating the presence of placental dichotomy, fetal cardiomegaly and/or starry-sky liver can be of additional help in improving the antenatal detection of TAPS in monochorionic twin pregnancy.

ABSTRACT

Objective *To investigate the prevalence of three additional ultrasound markers, placental dichotomy, cardiomegaly and 'starry-sky' liver, in monochorionic twin pregnancy with twin anemia–polycythemia sequence (TAPS).*

Methods *All monochorionic twin pregnancies, diagnosed antenatally with TAPS at our center between 2006 and 2019, were reviewed retrospectively for the presence of placental dichotomy, cardiomegaly in the donor twin and a starry-sky liver in the recipient twin. TAPS was diagnosed based on delta middle cerebral artery (MCA) peak systolic velocity (PSV) > 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. The secondary outcome was the prevalence of these ultrasound markers according to the antenatal stage of TAPS.*

Results *A total of 91 monochorionic twin pregnancies with TAPS were eligible for analysis. Placental dichotomy was observed in 44% (40/91) of TAPS cases. A total of 70% (64/91) of the TAPS donors developed cardiomegaly 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 and post-laser TAPS (69% (33/48)* vs *72% (31/43) and 64% (25/39)* vs *68% (28/41), respectively). Pregnancies with spontaneous TAPS showed a higher prevalence of placental dichotomy compared with post-laser TAPS (63% (30/48)* vs *23% (10/43)). At least one of the three ultrasound markers was detected in 86% (78/91) of TAPS cases, meaning that 14% (13/91) of cases presented solely with discordant MCA-PSV values. There was a trend towards increased prevalence of all three ultrasound markers with increasing antenatal TAPS stage.*

Conclusions *Placental dichotomy, fetal cardiomegaly and a starry-sky liver are commonly found in TAPS pregnancy. Investigating the presence of these ultrasound markers can be of additional help in improving antenatal detection of TAPS in monochorionic twin pregnancy.*

INTRODUCTION

Twin anemia–polycythemia sequence (TAPS) is a chronic form of unbalanced fetofetal transfusion through minuscule placental anastomoses, leading to anemia in the

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donor twin and polycythemia in the recipient twin[1]. In contrast to twin-to-twin transfusion syndrome (TTTS), TAPS occurs in the absence of amniotic fluid discordance. TAPS can develop spontaneously in 3–5% of monochorionic twin pregnancies or can occur iatrogenically in 2–15% of pregnancies treated with laser surgery for TTTS (post-laser TAPS), due to residual anastomoses[2–4]. Antenatal diagnosis of TAPS is based on discordant middle cerebral artery (MCA) peak systolic velocity (PSV) measurements (delta MCA-PSV > 0.5 multiples of the median (MoM)), with an increased MCA-PSV value in the donor twin suggestive of fetal anemia and a decreased MCA-PSV in the recipient twin suggestive of fetal polycythemia[5].

Although the identification of TAPS is primarily based on intertwin MCA-PSV discrepancy, other ultrasound markers suggestive of TAPS have also been reported. First, the placenta can show dichotomy, with a hyperechogenic placental share for the donor twin and hypoechogenic placental share for the recipient twin (Figure 1a)[6]. In some TAPS cases, this observation is accompanied by placental size discordance, with the hydropic thicker placental portion belonging to the donor and the thinner placental portion to the recipient[7]. Second, 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) (Figure 1c)[8]. Third, cardiomegaly can develop in anemic donor fetuses, because their hypoxic environment demands a higher cardiac output to continue to provide the body with adequate blood flow (Figure 1b)[9].

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

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

METHODS

In this retrospective study, all monochorionic twin pregnancies diagnosed with TAPS, at the Leiden University Medical Center (LUMC), Leiden, The Netherlands, between 2006 and 2019, were reviewed for the presence of placental dichotomy, cardiomegaly in the donor and a starry-sky liver in the recipient twin. The LUMC is the national referral center for fetal therapy and complicated monochorionic twin pregnancy in The Netherlands. Eligible for inclusion were TAPS cases, both spontaneous and post-laser, with available ultrasound records from the time of diagnosis until birth of the twins. TAPS cases with incomplete or missing ultrasound reports, or cases that were diagnosed only postnatally, were excluded from the study.

MCA-PSV assessment was performed in accordance with the technique of Mari *et al.*[11] described previously. TAPS was diagnosed in the presence of delta MCA-PSV > 0.5 MoM[5]. The following maternal, fetal and neonatal data were obtained retrospectively from digital medical records: maternal age; gravidity; parity; mode of delivery;

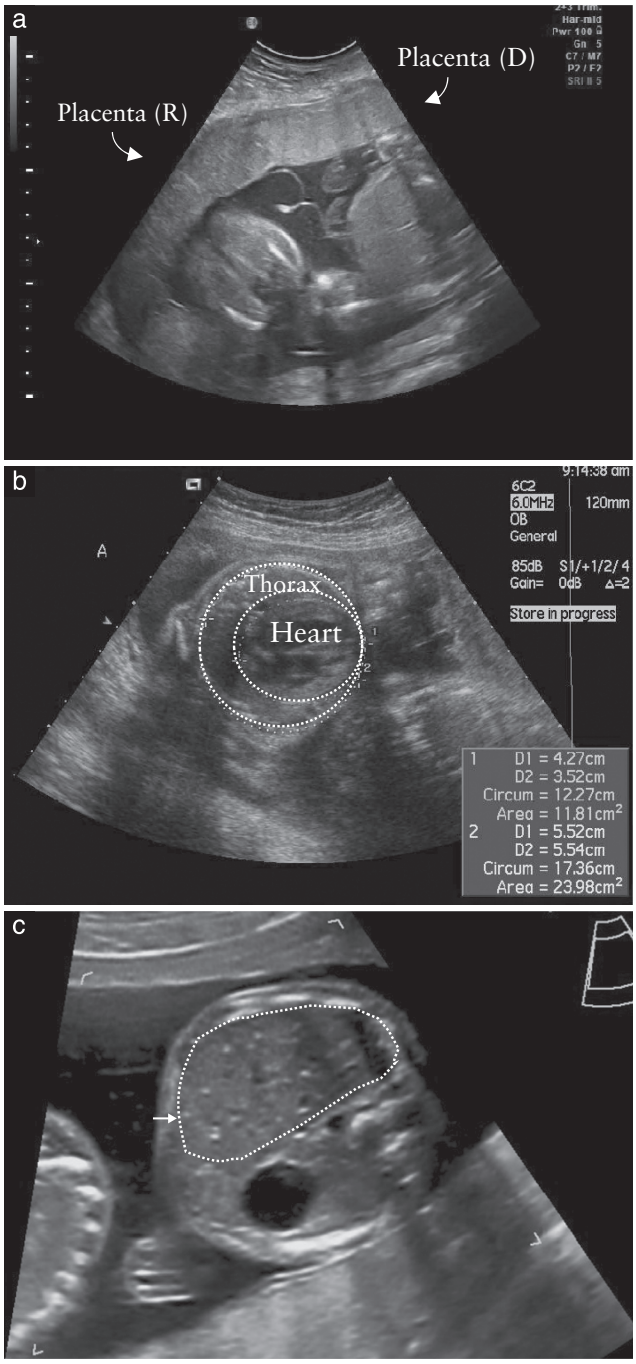

Figure 1 Ultrasound images showing placental dichotomy (a), cardiomegaly in donor twin (b) and starry-sky liver in recipient twin (c), in pregnancies with twin anemia–polycythemia sequence. D, donor; R, recipient.

antenatal TAPS stage; sex of twins; type of TAPS; gestational age at birth and 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.

The primary outcome was the prevalence of placental dichotomy, cardiomegaly in the donor twin or starry-sky liver in the recipient twin, and incidence of at least one of these findings in the total cohort and according to type of TAPS (spontaneous or post-laser). The secondary outcome was the prevalence of these ultrasound markers according to antenatal TAPS stage (Stages 1–5). The highest TAPS stage that was detected during pregnancy was recorded. All ultrasound examinations were carried out by experienced sonographers specialized in monochorionic twin pregnancy 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 (L.S.A.T. and F.S.) and any disagreements were resolved by a third observer (D.O.). Ultrasound images were eligible for assessment if there was a complete view of the placenta (allowing observation of placental dichotomy), a thoracic transverse section for the TAPS donor (allowing observation of the heart) and an abdominal transverse section for the TAPS recipient (allowing observation of the liver).

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were generated for all variables. Data are presented as median (interquartile range), *n* (%) or *n*/N (%), as appropriate.

RESULTS

Between 2006 and 2019, a total of 120 monochorionic twin pregnancies were diagnosed with TAPS at our center. Twenty-nine pregnancies were excluded, due to either a postnatal diagnosis ($n = 22$) or incomplete or missing ultrasound records ($n = 7$), leaving a total population of 91 TAPS pregnancies eligible for analysis. The presence of placental dichotomy and cardiomegaly could be evaluated in all eligible cases. The aspect of the liver was not described in any of the ultrasound reports of 11 TAPS recipients, and the corresponding ultrasound images of the liver were unavailable or inconclusive. Consequently, these cases were excluded from the prevalence estimation of starry-sky liver.

Baseline characteristics of the study population are presented in Table 1. The population consisted of 48 (53%) spontaneous TAPS and 43 (47%) post-laser TAPS pregnancies. Antenatal 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 1 Baseline characteristics of 91 pregnancies complicated by twin anemia–polycythemia sequence (TAPS), managed in Leiden University Medical Center, The Netherlands, between 2006 and 2019

Characteristic	*Value*
Maternal age (years)	32 (29–35)
Gravidity	2 (1–3)
Parity	1 (0–1)
Female fetal sex	50 (55)
Cesarean delivery	42 (46)
Delta MCA-PSV (MoM)	1.3 (0.9–1.7)
Spontaneous TAPS	48 (53)
Post-laser TAPS	43 (47)
Gestational age at birth (weeks)	32.4 (29.4–35.0)
Antenatal TAPS stage	
1	16 (18)
2	40 (44)
3	27 (30)
4	2 (2)
5	6 (7)
Antenatal management	
Expectant	40 (44)
Immediate delivery	1 (1)
IUT (with PET)	22 (24)
Laser surgery	18 (20)
Selective feticide	8 (9)
Termination of pregnancy	2 (2)

Data are presented as median (interquartile range) or *n* (%). IUT, intrauterine transfusion; MCA, middle cerebral artery; MoM, multiples of the median; PET, partial exchange transfusion; PSV, peak systolic velocity.

Table 2 presents the prevalence of the three ultrasound markers in the total TAPS population, and for spontaneous and post-laser TAPS separately. Placental dichotomy was observed in 44% (40/91) of TAPS pregnancies, 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 (69% (33/48) *vs* 72% (31/43) and 64% (25/39) *vs* 68% (28/41), respectively). Pregnancies with spontaneous TAPS showed a higher prevalence of placental dichotomy than post-laser TAPS twins (63% (30/48) *vs* 23% (10/43)). At least one of the three ultrasound markers was detected in 86% (78/91) of the TAPS cases, meaning that 14% (13/91) of cases presented solely discordant MCA-PSV values. Figure 2 depicts the prevalence of placental dichotomy, cardiomegaly, starry-sky liver and at least one of these ultrasound markers, according to TAPS stage. Overall, there was a trend towards increased prevalence of the ultrasound markers with increasing TAPS stage.

Table 2 Prevalence of placental dichotomy, cardiomegaly in donor twin, starry-sky liver in recipient twin and at least one of these ultrasound markers, in 91 pregnancies complicated by twin anemia–polycythemia sequence (TAPS), overall and according to type of TAPS

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

Data are presented as *n* (%) or *n*/*N* (%). *Eleven TAPS pregnancies (nine spontaneous and two post-laser) were excluded due to inconclusive description of starry-sky liver.

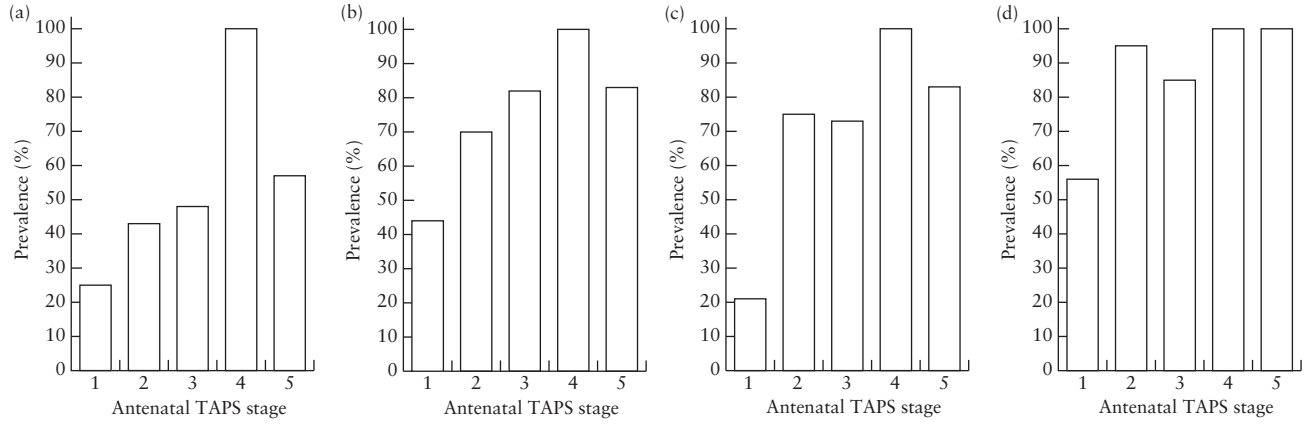

Figure 2 Prevalence of placental dichotomy (a), cardiomegaly in donor twin (b), starry-sky liver in recipient twin (c) and at least one of these ultrasound markers (d) in 91 pregnancies with twin anemia–polycythemia sequence (TAPS), according to antenatal TAPS stage. In total, 16 cases were Stage 1, 40 were Stage 2, 27 were Stage 3, two were Stage 4 and six were Stage 5.

DISCUSSION

In this study we assessed the prevalence of three ultrasound markers in TAPS pregnancies. We found that placental dichotomy was present in 44% of TAPS cases, cardiomegaly was detected in 70% of the TAPS donors and 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[12]. Unfortunately, there are still many clinics across the world in which MCA-PSV Doppler screening is not part of the standard care for monochorionic twin pregnancy. Consequently, diagnosis of TAPS is still missed frequently. Our study shows that searching for these three additional ultrasound markers could be of great value in centers that do not perform MCA-PSV Doppler regularly, since the majority of TAPS cases presented with at least one of these findings. However, a small subgroup of TAPS twins (14%) did not show any of these markers and presented solely with MCA-PSV discordance. Routine MCA-PSV examination therefore remains the cornerstone for 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, the majority being case reports. Stritzke *et al.*[6] described a TAPS case in which diagnosis was missed antenatally, because MCA-PSV Doppler measurements were not registered. However, a large difference in placental echogenicity was observed 4 weeks prior to delivery. Movva and Rijhsinghanni[13] reported on two TAPS cases in which the observation of placental dichotomy prompted sonographers to perform MCA-PSV Doppler measurements, which in turn revealed the diagnosis of TAPS. A starry-sky liver was described in two cases published by Soundararajan and Howe[8], in which it was seen as an early manifestation of severe TAPS.

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 and post-laser TAPS twins. Despite the fact that TAPS Stage 1 is usually regarded as a mild form of the disease, this study demonstrated that more than 40% of the donors in pregnancies with TAPS Stage 1 already showed signs of cardiac remodeling to the anemic environment. The exact role of the other two ultrasound markers in the pathophysiology of TAPS is not yet 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 of placental dichotomy increased with increasing TAPS stage, suggesting that it might be linked to the severity of the condition. Interestingly, Bamberg *et al.*[10] and a study from our own research group[14] underlined the association between the severity of TAPS and the degree of dichotomy in TAPS placentas, both on ultrasound and on postpartum macroscopic placental examination. Of note, placental dichotomy seemed far more prevalent in spontaneous than in post-laser TAPS twins, suggesting there might be a different response of the placenta to anemia following laser surgery.

A starry-sky liver might be the most difficult 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 does not have 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[15]. 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 several causes such as leukemic or neoplastic infiltration, infections or right-heart failure. However, none of these causes is present in TAPS recipients. Nonetheless, in line with placental dichotomy and cardiomegaly, the prevalence of starry-sky liver also seems to increase with increasing 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. It is possible that TAPS cases with additional ultrasound markers were detected more easily 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 that detection of these ultrasound markers was based on subjective impressions of individual specialized sonographers, and not on predefined standardized criteria, hindering the overall reproducibility of the results. Lastly, we were unable to assess the specificity and sensitivity of the markers. Future studies should focus on prospective identification of placental dichotomy, fetal cardiomegaly and starry-sky liver in the general population of monochorionic twins, in order to assess the exact clinical values of these (combined) ultrasound markers in the detection of TAPS. The most important strength of this study is the 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 present commonly in TAPS pregnancies. Looking for these ultrasound markers can be of additional help in improving the antenatal detection of TAPS in monochorionic twin pregnancy.

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