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Quantified discordant placental echogenicity in twin anemia–polycythemia sequence (TAPS) and middle cerebral artery peak systolic velocity

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KEYWORDS: middle cerebral artery Doppler; placental echogenicity; placental thickness; twin anemia–polycythemia sequence; twin–twin transfusion syndrome

ABSTRACT

Objective *To quantify sonographic placental echogenicity in twin anemia–polycythemia sequence (TAPS) and to correlate it with middle cerebral artery peak systolic velocity (MCA-PSV) measurements.*

Methods *We performed a retrospective search for consecutive TAPS cases between 16 and 36 weeks of gestation (MCA-PSV > 1.5 multiples of the median (MoM) in the anemic donor and < 1.0 MoM in the polycythemic recipient) in our database of monochorionic twin gestations from January 2007 until December 2016. In cases for which ultrasound images showing the donor's and the recipient's part of the placenta were available, echogenicity for both twins was quantified by image processing. MCA-PSV Doppler values of both fetuses were correlated to their respective placental echogenicity. Placental thickness of both twins was also measured.*

Results *Of 756 cases with MCA-PSV measurements identified from the database, 36 (4.8%) had TAPS; of these, 23 had TAPS combined with twin–twin transfusion syndrome and 13 showed isolated TAPS. Placental echogenicity could be quantified in 28 pregnancies. Mean ± SD placental echogenicity of donor twins was significantly higher than that of recipients (138.7 ± 22.8* vs *77.9 ± 37.0; P < 0.0001). Furthermore, a significant positive correlation was found between placental echogenicity and MCA-PSV MoM (R = 0.67, P < 0.0001). Mean placental thickness of donor twins (n = 20) was significantly higher than that of recipients (49.3 mm ± 13.4* vs *25.4 mm ± 10.1; P < 0.0001).*

Conclusions *Echogenicity of the placental share in recipient and donor twins with TAPS correlates with MCA-PSV values. Quantification of sonographic placental echogenicity may help to determine the severity of TAPS in monochorionic twins. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Twenty years ago, Frisch and coworkers[1] published the first description of a novel sonographic feature in a case of severe twin–twin transfusion syndrome (TTTS). Discordant placental echogenicity was described at 35 weeks of gestation, with a hyper- and hypoechogenic placental share for the donor and recipient twin, respectively. These two parts of the monochorionic placenta could be distinguished clearly. After birth, the twins showed a large hemoglobin concentration difference of 15 g/dL. This typical postnatal finding of anemia–polycythemia sequence (TAPS) was described in 2006 as a complication following laser treatment for TTTS by Robyr *et al.*[2]. The term TAPS was introduced by Lopriore *et al.*[3] in 2007, to define a chronic fetofetal net transfusion of erythrocytes that may occur spontaneously (in 5% of cases)[4] or following fetoscopic laser surgery for TTTS (in 3–16% of cases)[5]. The prenatal criteria of TAPS are an increased (> 1.5 multiples of the median (MoM)) middle cerebral artery peak systolic velocity (MCA-PSV) in the donor twin and a decreased MCA-PSV (< 1.0 MoM) in the recipient twin, without severe amniotic fluid imbalance. Recently, Tollenaar and colleagues[6] found a significant color-intensity difference on the maternal side of the placenta after birth, with a very pale placental area belonging to the anemic twin and an extremely dark placental share to the polycythemic twin.

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The aim of this study was to quantify sonographic placental echogenicity in TAPS and to correlate this with MCA-PSV Doppler findings in both twins.

METHODS

Our center is a tertiary referral center for fetal medicine. Ultrasound data from all pregnancies are entered prospectively into our computer database (ViewPoint 5.6.8.428: ViewPoint Bildverarbeitung GmbH, Wessling, Germany). We performed a retrospective search for consecutive cases diagnosed with TAPS between 16 and 36 weeks of gestation, with diagnosis made according to established prenatal criteria[3,7] (MCA-PSV > 1.5 MoM and < 1.0 MoM in the donor and recipient, respectively), in our database of monochorionic twin gestations from January 2007 until December 2016. We reviewed placental images of these cases and, if available, we retrieved those with placental shares of both the anemic donor and the polycythemic recipient twin documented on the same digital image (Figure 1). Alternatively, we used only images that were acquired with identical ultrasound machine presets and gain settings for both twins. If TAPS was combined with TTTS, data were stored before fetoscopic laser treatment. Furthermore, we also included post-laser TAPS cases.

The freely available ImageJ software (https://imagej.nih.gov/ij/) was used to quantify placental echogenicity. Representative and homogeneous placental shares of the donor and recipient twins, respectively, were traced separately. Intensity histograms were acquired in which the *x*-axis represented grayscale values and the *y*-axis the pixel number for each grayscale value (Figure 2). All single measurements were performed by C.B. and, for the purpose of assessing intraobserver variability, these were repeated after 1 month. One of the coauthors (A.D.), who was blinded to the previous results, performed the offline analysis and acquired placental echogenicity histograms. Additionally, placental echogenicity ratio was calculated by dividing placental histogram results of the donor by those of the recipient for each twin pair. In spontaneous isolated TAPS, as well as in post-laser cases, only the findings with the highest PSV in the MCA were analyzed. If longitudinal follow-up examinations were performed in TTTS cases, only the last finding before laser treatment was included. MCA-PSV was measured by pulsed-Doppler sonography using a Voluson E8 or E10 ultrasound machine (GE Healthcare Ultrasound, Milwaukee, WI, USA) with the angle of insonation kept as close as possible to 0°. Values were expressed in MoM according to reference ranges for monochorionic twins[8]. Furthermore, placental thicknesses of the donor and recipient twins were measured perpendicularly to the chorionic plate.

Statistical analysis

Results are presented as mean ± SD for data for which a normal distribution was confirmed using the Kolmogorov–Smirnov test. Simple linear regression analysis and Pearson's correlation were used to investigate the relationship between placental echogenicity and MCA-PSV. Intraclass correlation coefficient (ICC) (single measures, absolute-agreement, two-way mixed model) with 95% CI and the Bland–Altman method for assessing agreement, including calculation of the average discrepancy between measurements (bias), 95% limits of

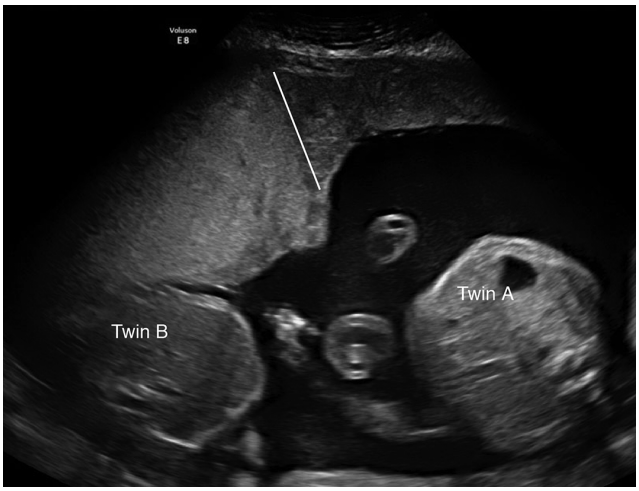

Figure 1 Transabdominal ultrasound image of pregnancy with twin anemia–polycythemia sequence, demonstrating discordant placental echogenicity and discrepancy in placental thickness (indicated by white line). Hypoechogenic thin area of anterior placenta belongs to polycythemic recipient Twin A and hyperechogenic thickened part belongs to anemic donor Twin B.

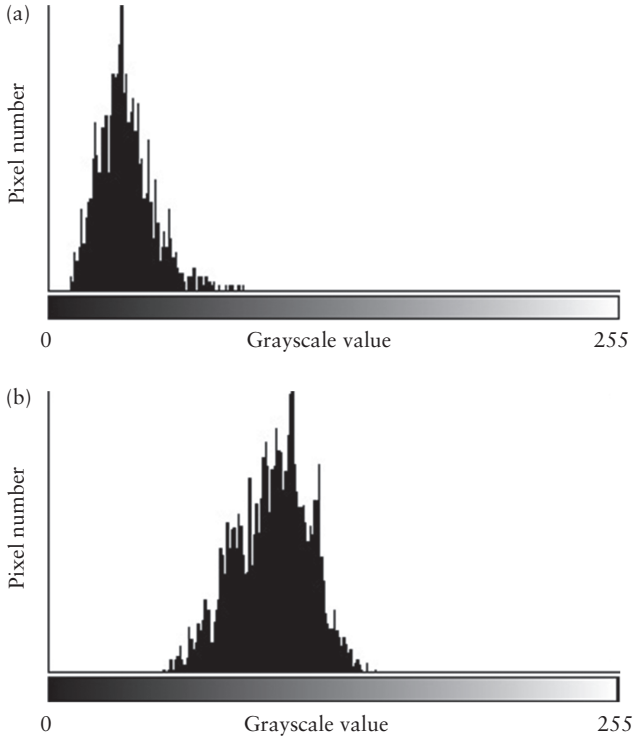

Figure 2 Intensity histograms showing the difference in placental echogenicity depicted in Figure 1, between recipient Twin A ((a); value 25) and donor Twin B ((b); value 110).

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agreement (LOA) and SD of bias, were generated to illustrate intraobserver and interobserver reliability. *A priori*, we considered placental echogenicity measurements to be of excellent reliability when ICC was > 0.9. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using the IBM SPSS Statistics package (Version 22, SPSS, Inc., Chicago, IL, USA) and GraphPad Prism (Version 5, La Jolla, CA, USA).

RESULTS

We identified 1362 monochorionic twin pregnancies in our database, of which 756 underwent MCA-PSV measurements between 16 and 36 weeks of gestation, and of these, 36 (4.8%) pregnancies fulfilled antenatal TAPS criteria. Of the 36 TAPS twin pairs, 32 were spontaneous cases and four developed after fetoscopic laser treatment. Twenty-three cases had TAPS combined with TTTS and 13 showed isolated TAPS (Figure 3). All pregnancies were diamniotic, except one previously published case with monoamnionicity[9]. Mean gestational age at presentation was 24.1 ± 4.8 weeks. Placentae were distributed equally on the anterior and posterior uterine wall. All women with TTTS were treated with fetoscopic laser ablation, however we did not perform any intrauterine blood transfusions.

Placental images of 28 participants were stored prenatally, and 25 of these showed placental shares of both twins on the same digital image. Mean placental echogenicity in donors was significantly higher than that in recipients (138.7 ± 22.8 *vs* 77.9 ± 37.0; $P < 0.0001$) (Figure 4). Mean placental echogenicity ratio was 2.1 ± 0.7.

ICCs for placental echogenicity of donors and recipients were 0.97 (95% CI, 0.96–0.98) and 0.96 (95% CI, 0.93–0.97) for intraobserver and interobserver reliability, respectively. Bland–Altman analysis showed mean differences of 3.1 ± 8.4 with 95% LOA of 19.6 to −13.4 for intraobserver, and 2.4 ± 8.4 with 95% LOA of 18.8 to −14.0 for interobserver reliability.

Furthermore, we found a positive correlation between placental echogenicity and MCA-PSV MoMs ($R = 0.67$, $P < 0.0001$) (Figure 5). In 20 twin pairs in which

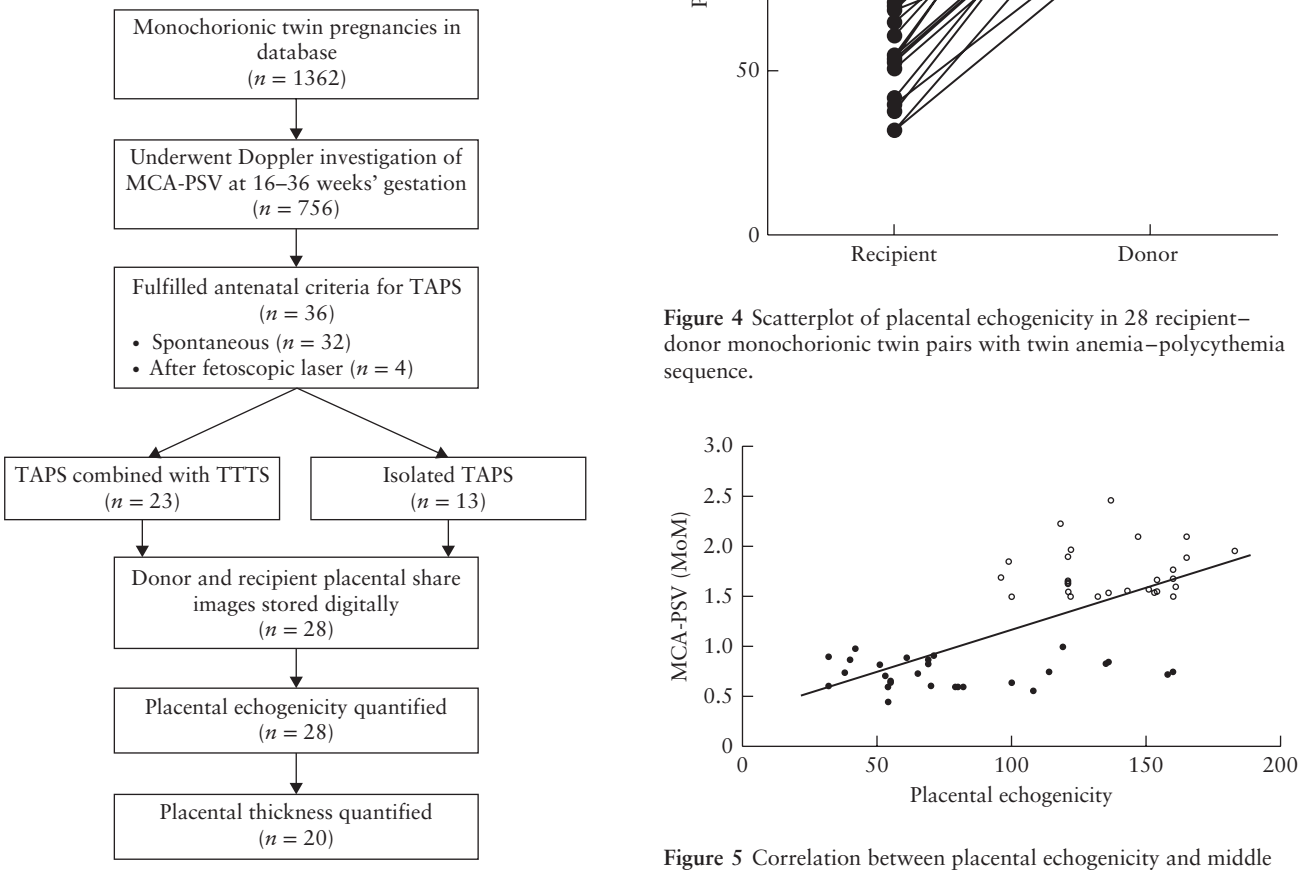

Figure 3 Flowchart showing inclusion, clinical characteristics and data availability of study participants.

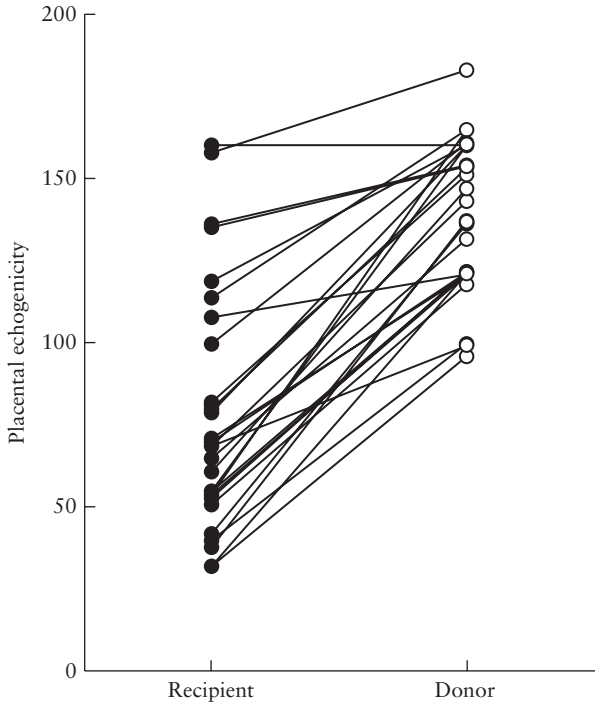

Figure 4 Scatterplot of placental echogenicity in 28 recipient–donor monochorionic twin pairs with twin anemia–polycythemia sequence.

Figure 5 Correlation between placental echogenicity and middle cerebral artery peak systolic velocity (MCA-PSV) multiples of the median (MoM) in 28 recipient (•) and donor (◦) monochorionic twin pairs with twin anemia–polycythemia sequence.

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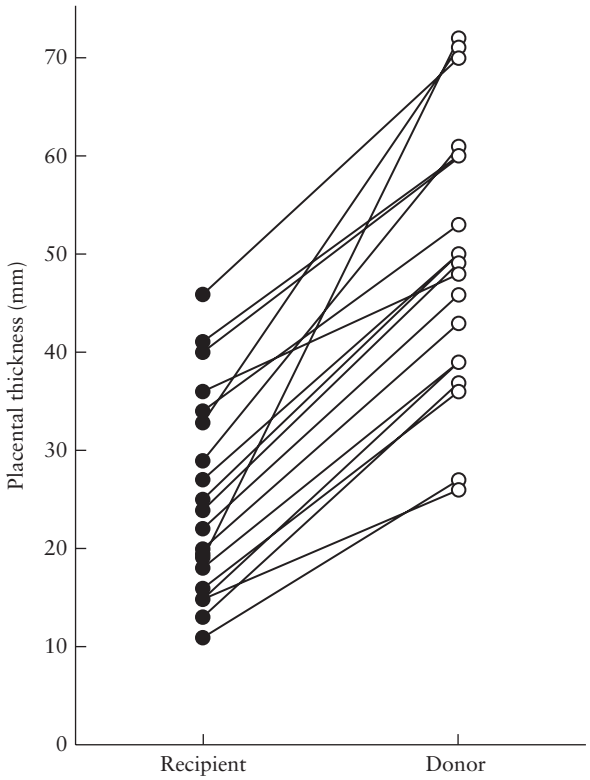

Figure 6 Scatterplot of placental thickness in 20 recipient–donor monochorionic twin pairs with twin anemia–polycythemia sequence.

placental thickness could be quantified, mean placental thickness of the donors was significantly higher than that of the recipients (49.3 mm ± 13.4 *vs* 25.4 mm ± 10.1; $P < 0.0001$) (Figure 6).

DISCUSSION

Our findings confirm that quantification of sonographic placental echogenicity is feasible, easy to perform and reflects disease severity in TAPS, regardless of whether or not it is combined with TTTS. Values for echogenicity differ significantly between the anemic and the polycythemic twins and correlate well with MCA-PSV.

Our results are in line with the findings of several case reports[9–12] which identified a striking difference in placental echogenicity between donor and recipient twins. They described a hydropic hyperechogenic placental share of the anemic twin and a relatively hypoechogenic or normal share of the polycythemic twin. Our data are also in agreement with the ISUOG Practice Guidelines on the role of ultrasound in twin pregnancy[13], albeit quantification of sonographic placental echogenicity is not considered in the guidelines. Furthermore, Kusanovic *et al.*[14] observed the histological characteristics of edematous or fibrotic immature villi and intervillous hemorrhage in the placental share of the donor, and de Laat and coworkers described the discrepancy in placental echogenicity and thickness between the twins as a first sign of TTTS[10].

Recently, van Winden and coworkers reviewed retrospectively 369 TTTS patients in USA who underwent fetoscopic laser treatment[15]. Before the procedure, 2.4% of pregnant women also met the criteria of TAPS in terms of MCA-PSV Doppler velocities. The authors concluded that the rarity of markedly discordant MCA-PSV values in TTTS patients may reflect the different patterns of anastomoses with a small degree of overlap between diagnoses. In contrast, Donepudi and coworkers observed a higher prevalence of TAPS, namely in 11 of 133 (8.3%) cases of TTTS, before laser treatment[16]. The prevalence of TAPS in all monochorionic twin pregnancies with MCA Doppler examinations in this study was 4.8%, which is in line with a previous report[4]. Unfortunately, none of the previously published articles reported any data on placental echogenicity. Despite the proven reproducibility of MCA-PSV Doppler examination[17], there are some circumstances in which this investigation may be difficult to perform in twin pregnancies; for instance at an advanced gestational age in the third trimester. To overcome the limitation of different gestational ages at examination, the MCA-PSV were transformed to MoM values.

A strength of this study is that it was performed in a single tertiary care center with vast experience in the management of monochorionic twins. However, a major limitation is its retrospective design, which does not allow reliable estimation of the incidence of TAPS with or without TTTS in a prospective manner. We had to restrict the application of ultrasound image processing to those cases that showed the placental share for both the recipient and donor twins, in order to compare intertwin measurements. However, the absolute values of placental echogenicity should be interpreted with caution, as gain settings were not standardized. We observed a wide range, from 32 to 160, of quantified placental share echogenicity in recipients; in contrast, most TAPS donor twins showed placental echogenicity above 100 and twice the median placental thickness as compared with recipients' placental site.

In conclusion, our study shows that discordant placental echogenicity and thickness and MCA-PSV measurements between monochorionic twins are objective ultrasound findings indicating TAPS. This is the first study describing the significant correlation between placental echogenicity and MCA-PSV in monochorionic twins. Prenatal quantification of placental echogenicity may help to determine the severity of TAPS, particularly in cases in which reliable MCA-PSV measurements are difficult to obtain in both twins.

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