Next steps towards improved care for twin anemia polycythemia sequence

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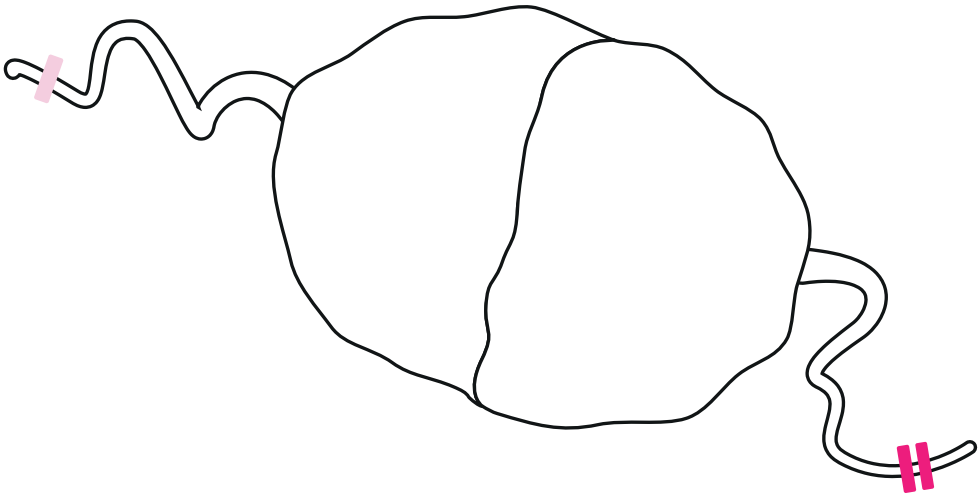
Chapter 8

Can color difference on the maternal side of the placenta distinguish between acute peripartum twin-twin transfusion syndrome and twin anemia polycythemia sequence?



Abstract

Objective

To investigate the color difference between two placental shares in monochorionic placentas with acute peripartum twin–twin transfusion syndrome (TTTS) and twin anemia polycythemia sequence (TAPS).

Methods

We evaluated all digital pictures of TAPS, acute peripartum TTTS and a control group of uncomplicated monochorionic placentas examined at our center. We determined the color intensity of the individual placental share on the maternal side of each monochorionic placenta using an image–processing program and calculated the color difference ratio (CDR).

Results

Digital pictures of 5 acute peripartum TTTS, 25 TAPS and 54 control group placentas were included in this study. The median CDR in acute peripartum TTTS was significantly lower compared to TAPS placentas, 1.20 (inter-quartile range (IQR) 1.05–1.20) and 2.50 (IQR 1.85–3.34), respectively ($p < 0.01$), and was comparable to the control group (CDR 1.11, IQR 1.05-1.22).

Conclusion

TAPS placentas have a higher CDR compared to acute peripartum TTTS placentas. Examining color difference on the maternal side of the placenta might help distinguish between acute peripartum TTTS and TAPS.

Introduction

Monochorionic twins share a single placenta and are connected to each other through vascular anastomoses, allowing inter-twin blood transfusion. Unbalanced net inter-twin blood transfusion can lead to various disorders, including chronic twin–twin transfusion syndrome (TTTS), acute peripartum TTTS and twin anemia polycythemia sequence (TAPS).

Chronic TTTS, the most well-known form of TTTS, is characterized by the development of oligohydramnios in the donor and polyhydramnios in the recipient. This chronic form of TTTS occurs in 10% of monochorionic twin pregnancies and is most often diagnosed during the second trimester.[1] Acute peripartum TTTS results from a rapid and large inter-twin blood transfusion from donor to recipient through large anastomoses during delivery,[2, 3] and complicates 2.5% of the monochorionic twin pregnancies.[4]

In contrast to acute peripartum TTTS, TAPS is characterized by a chronic and slow blood transfusion from donor to recipient through miniscule vascular anastomoses during the course of pregnancy, causing the donor to become anemic and the recipient to become polycythemic, without discordances in amniotic fluid[5]. TAPS may occur spontaneously (spontaneous TAPS) in 2–5% of the monochorionic twin pregnancies or after laser surgery for chronic TTTS (post-laser TAPS) in 3–16% of the chronic TTTS cases.[6-9]

Distinction at birth between acute peripartum and TAPS may be difficult. In both cases, twins show a striking difference in skin color (a pale anemic donor and a plethoric polycythemic recipient twin) and a large difference in hemoglobin (Hb) levels (> 8 g/dL).[4, 5] Nevertheless, the required therapeutic approach is different in acute peripartum TTTS and TAPS. Therefore, distinction between the two conditions is of utmost importance. Measurement of the reticulocyte count ratio and injection of the placenta with color dye are two methods currently used to differentiate between acute peripartum TTTS and TAPS.[10-12] However, reticulocyte count is not always measured and placental injection is a complex and time-consuming procedure and is therefore only performed in specialized medical centers.

A previous study showed that measuring the color difference ratio (CDR) between the two placental shares of the maternal side can provide additional diagnostic information,[13] as TAPS placentas are characterized by a large CDR.

To date however, there are no reports on color differences in placentas from acute peripartum TTTS.

The aim of this study is to examine the CDR on the maternal side of acute peripartum TTTS placentas and to investigate whether this tool can help distinguish between acute peripartum TTTS and TAPS.

Methods

All monochorionic diamniotic twin placentas with a clear digital picture of the maternal side evaluated at our center between 2002–2016 were included in this retrospective study, and subdivided into three groups: 1.) acute peripartum TTTS placentas 2.) TAPS placentas (spontaneous and post-laser) and 3.) a control group of uncomplicated monochorionic twin placentas. Some of the cases we included were already used in a previous study.[13]

For the purpose of this study, digital pictures with insufficient quality or with incomplete Hb values were excluded. The quality of the picture was considered insufficient in case of unequal light exposure, low resolution, excessive light reflection or the presence of blood clots on the placenta.

TAPS was diagnosed using the following criteria: an inter-twin Hb difference > 8 g/dL and a reticulocyte count ratio > 1.7 or the presence of only miniscule anastomoses (diameter < 1 mm) detected through placental injection.[14] Diagnosis of acute peripartum TTTS was based on the presence of an inter-twin Hb difference > 8 g/dL and no signs of TAPS or chronic TTTS (according to the internationally accepted standardized antenatal ultrasound criteria for TTTS.[15]

The following obstetric and neonatal data were retrieved from our database: gestational age at birth, antenatal intervention, mode of delivery, sex, birth weight, Hb levels and reticulocyte count at birth and the presence of anastomoses. The presence of anastomoses was examined through placental color dye injection. The primary outcome of this study was the color difference ratio (CDR) between the different shares of the maternal side of the placenta. CDR was calculated using an image processing program called Image J version 1.57. A step-by-step tutorial on calculating the CDR using Image J created by our institution can be viewed at: https://www.youtube.com/watch?v=_OSd6utv2Bw

Data are reported as medians and interquartile rages (IQR). Since the size of the groups was small and data were not normally distributed, non-parametric tests were used. A Kruskal–Wallis test was applied to compare the results of the three different groups. To study the association between the inter-twin Hb differences and CDR the Spearman rank correlate on test was used. A p-value < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using IBM Statistics v23.0 (SPSS, Inc., an IBM company, Chicago, IL, USA).

Results

A total of 108 pictures of the maternal side were considered eligible for this retrospective study. We excluded 1 acute peripartum TTTS case due to an insufficient picture quality (blood clots and unequal light exposure). In the control group 23 cases were excluded because of insufficient picture quality (n = 2) and missing Hb values (n = 21). In total, 5 acute peripartum TTTS, 25 TAPS, and 54 control group placentas were analyzed. The TAPS group consisted of 14 spontaneous TAPS (56%) placentas and 11 post-laser TAPS placentas (44%). Figure 1 provides an overview of the selection of the study population.

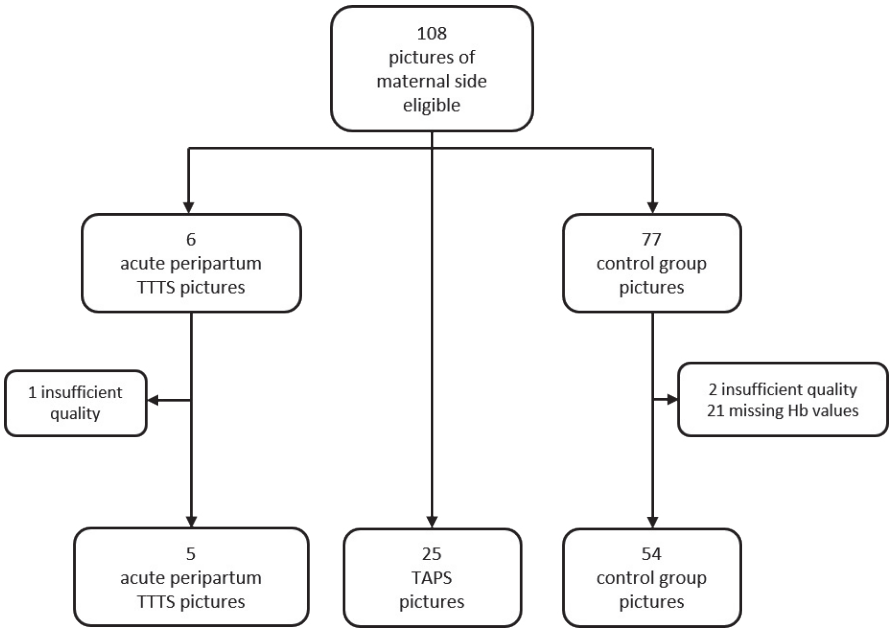


Figure 1. Description of the study population

The median gestational age in the acute peripartum TTTS group was 37 weeks (IQR 33–37 weeks), 32 weeks (IQR 30–35 weeks) in the TAPS group and 35 weeks (IQR 32–36 weeks) in the control group. Baseline characteristics of the three groups are presented in Table 1.

Table 1. Baseline characteristics

	Control group (n = 54)	**Acute peripartum TTTS (n =5)**	**TAPS (n = 25)**
Female	30/53 (57)	1/5 (20)	10/24 (42)
Gestational age at birth (weeks)	35 (32–36)	37 (34–37)	32 (30–35)
Cesarean Delivery	61/108 (57)	4/10 (40)	28/50 (56)
Birth weight (g)	2104(1610–2424)	2665 (1987–2850)	1722 (1223–2125)
Birthweight discordance	11 (5-21)	2 (0-8)	18 (10-31)
Post-natal TAPS stage			
Stage 1			6 (24)
Stage 2			8 (32)
Stage 3			4 (16)
Stage 4			4 (16)
Stage 5			3 (16)
Spontaneous TAPS			14 (56)
Antenatal diagnosis			9 (64)
Antenatal treatment (with IUT)			3 (21)
Post-laser TAPS			11 (44)
Antenatal diagnosis			8 (73)
Antenatal treatment (with IUT)			4 (36)

Data are median (IQR), n/N(%) or n (%)

Table 2 shows hematological characteristics and the CDR for the three different groups. Reticulocyte count ratio was measured in 60% (3/5) of the acute peripartum TTTS cases, 92% (23/25) of the TAPS cases and 41% (22/54) of the cases in the control group. In cases in which reticulocyte count ratio was not available, placental injection was used to fulfill the required diagnostic criteria for TAPS or acute peripartum TTTS. In agreement with the postnatal diagnostic criteria for TAPS, all TAPS cases had an inter-twin Hb difference > 8 g/dL, median 12.7 (IQR 10.5–18.1), and a reticulocyte count ratio > 1.7, median 3.7 (IQR 2.5–5.0). In the acute peripartum TTTS group, all 5 cases showed an inter-twin Hb difference > 8.0 g/dL and the median reticulocyte count ratio was 1.1

(IQR 1.0-1). In the control group, all 54 cases had an inter-twin Hb difference < 8 g/dL.

Table 2. Hematological differences and placental color differences (CDR)

	Control group (n = 54)	Acute peripartum TTTS (n = 5)	TAPS (n = 25)	P-values
Inter-twin Hb difference (g/dL)	1.4 (0.6–3.8)	10,2 (8.6–13.1)	12.7 (10.5–18.1)	< 0.01
Reticulocyte count ratio	1.05 (1.00–1.14)	1.1 (1.0-*)	3.7 (2.5–5.0)	< 0.01
Color difference ratio (CDR)	1.11 (1.05–1.22)	1.20 (1.05–1.20)	2.50 (1.85–3.45)	< 0.01

Data are median (IQR) or mean ± SD
*Since there were only three reticulocyte count ratios available for the acute peripartum TTTS group, the upper quartile could not be measured (reticulocyte count ratios were: 1.0, 1.1 and 1.4)

The median CDR in the acute peripartum TTTS group was 1.20 (IQR 1.05–1.20) compared to the median of 2.50 (IQR: 1.85–3.45) in the TAPS group and a median of 1.11 (1.05–1.22) in the control group (p < 0.01). There was no significant difference in CDR between spontaneous TAPS cases and post-laser TAPS cases (p = 0.149).

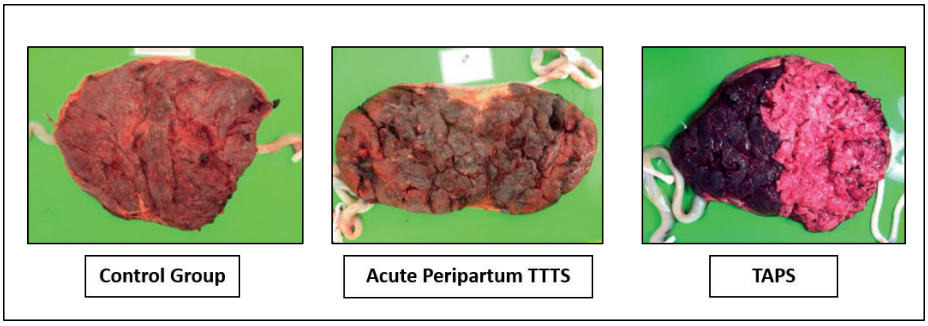


Figure 2. Maternal side of a control group placenta, an acute peripartum TTTS placenta and a TAPS placenta, illustrating the color difference in TAPS cases.

Figure 2 shows the maternal side of a control group placenta, acute peripartum TTTS placenta and a TAPS placenta. In Figure 3, pictures of the maternal side of the placenta are shown for ascending CDR values to illustrate the increasing difference in color intensity.

* Upper quartile could not be measured since only three reticulocyte count ratios (1.0, 1.1 and 1.4) were available.

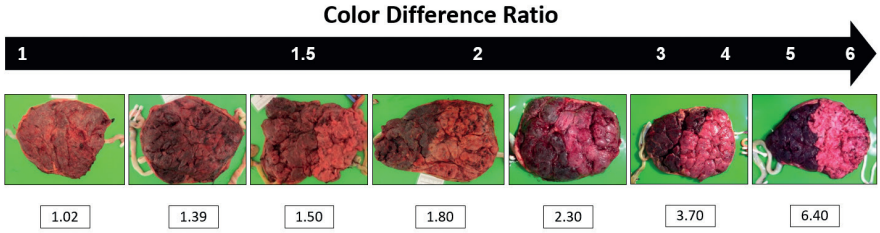


Figure 3. Pictures of the maternal side for ascending CDR values showing the increasing difference in color intensity between the two maternal shares.

In Figure 4, the relation between CDR and inter-twin Hb difference for the acute peripartum TTTS, TAPS and the control group is depicted. All the CDR values of the TAPS group were larger than 1.5, except for one post-laser TAPS case (CDR = 1.3). In this case an inter-twin Hb difference of 9.3 g/dL was found, corresponding with TAPS stage 1.[11] All control group cases showed a CDR < 1.5, with the exception of one case (CDR = 1.5). This placenta belonged to a twin with selective intra-uterine growth restriction (sIUGR), with an inter-twin Hb difference of 3.8 g/dL and a high reticulocyte count ratio (3.7). In all acute peripartum TTTS cases a CDR < 1.5 was found. Median CDR in the spontaneous TAPS group was 2.6 (IQR 2.0–4.7) and 2.1 (IQR 1.5–3.0) in the post-laser TAPS group ($p = 0.14$). As shown in Figure 4, there was no correlation between CDR and inter-twin Hb difference in the control group ($R = 0.18$, $p = 0.098$) or the acute peripartum TTTS group ($R = 0.63$, $p = 0.253$). In the TAPS group, there was a positive correlation between inter-twin Hb difference and CDR ($R = 0.58$, $p < 0.01$).

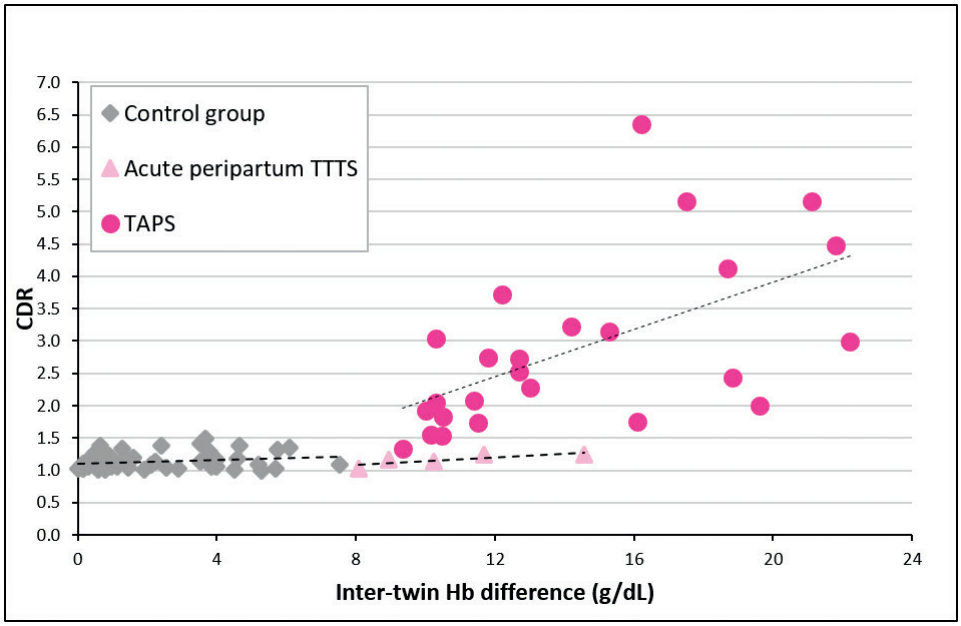


Figure 4. CDR versus inter-twin Hb difference in the control group, acute peripartum TTTS group and TAPS group. Correlation between CDR and inter-twin Hb difference in the control group, acute peripartum TTTS group and TAPS group is R = 0.18 (p = 0.098), R = 0.63, (p = 0.316) and R = 0.58 (p < 0.01), respectively.

Discussion

This is the first study reporting on color differences on the maternal side of acute peripartum TTTS placentas. We found a significantly lower median CDR in acute peripartum TTTS placentas compared to TAPS placentas ($p < 0.01$). Furthermore, all acute peripartum TTTS placentas had a CDR < 1.5, whereas almost every TAPS placenta (except one) had a CDR higher than 1.5.

Our study suggests that inspection of the maternal side of the placenta may help distinguish between acute peripartum TTTS and TAPS. Although twins with acute peripartum TTTS and TAPS present similarly at birth (highly discordant Hb values and the combination of a polycythemic plethoric recipient twin and an anemic pale donor twin), the two clinical conditions are different and require distinct neonatal management. Acute peripartum TTTS is characterized by an acute blood flow through large anastomoses during delivery leading to acute anemia and hypovolemic shock (in case of massive blood loss) in the donor and acute polycythemia in the recipient.[4] In contrast, TAPS is a result of slow and chronic blood transfusion through miniscule vascular anastomoses

(diameter < 1 mm) during the course of pregnancy, leading to chronic anemia in the donor and chronic polycythemia in the recipient.[5] Consequently, neonatal management in the donor twin of either the acute peripartum TTTS group or the TAPS group, calls for a different approach. Donors with acute peripartum TTTS suffer from acute blood loss and may thus need an acute blood transfusion within the first few hours after birth.[4] In contrast, since TAPS donors are diagnosed with a chronic form of TTTS, they would benefit from a more conservative therapeutic approach, with slower blood transfusion or, in case of sufficient erythropoiesis, even no blood transfusion at all.[16] In TAPS donors, acute blood transfusion is not only contra-indicated, it may even cause hemodynamic complications as these neonates are not hypovolemic. Therefore, a quick distinction between acute peripartum TTTS and TAPS shortly within one hour of birth could be helpful.

At the moment, there are two different methods available to distinguish between acute peripartum TTTS and TAPS. The first one includes calculating the reticulocyte count ratio by dividing the reticulocyte count of the donor by the reticulocyte count of the recipient.[12] In TAPS donors, the reticulocyte count is significantly increased, reflecting a constant high demand for erythrocytes due to chronic blood loss. Since blood transfusion in acute peripartum TTTS occurs rapidly, this compensating mechanism does not have time to take place, and therefore the reticulocyte count in the anemic twin is not increased.[4] Thus, an inter-twin reticulocyte count ratio > 1.7 is only indicative for the diagnosis of TAPS. The second criterion regards the size of the connecting vascular anastomoses detected through placental color dye injection.[14] In TAPS, only a few miniscule vascular anastomoses (diameter < 1 mm) at the placental surface are present.[11] On the contrary, in acute peripartum TTTS anastomoses with a large diameter are crucial to allow a rapid and large transfusion of blood.

However, reticulocyte count is not always measured and placental injection is a complex and time-consuming procedure and thus only performed by specialized medical centers. An additional quick and easy diagnostic tool could therefore be useful. In a previous study, we discovered that the maternal side of the placenta might contain important additional diagnostic information, by showing that TAPS placentas are characterized by a striking color difference on the maternal side.[13] The current study was set up to investigate whether this color difference was also present in acute peripartum TTTS cases. We conjectured

that there was no color difference on the maternal side in acute peripartum TTTS placentas, since blood transfusion only occurs acutely. Our results show indeed a significantly lower CDR in acute peripartum TTTS placentas compared to TAPS placentas. This finding underlines the idea that the visual examination of the maternal side of the placenta shortly after birth is an easy and quick way to distinguish between acute peripartum TTTS and TAPS.

The exact mechanism responsible for coloration (or discoloration) of the placenta remains unknown. Possibly, the level of erythrocytes and the time erythrocytes are present in the placenta play an important role. In the TAPS group, we found a positive correlation between inter-twin Hb difference and CDR, suggesting that the more discordant the hemoglobin values are, the more likely the placental mass was to change in color intensity. Furthermore, acute peripartum TTTS cases (in which a high inter-twin Hb difference is also seen) did not show color differences on the maternal side, supporting the idea that not only the degree of hemoglobin discordance, but also the time the placenta is exposed the low or high counts of erythrocytes is of influence. Unfortunately, placental histology is not routinely performed in our center. Histologic investigation of TAPS and uncomplicated monochorionic placentas could be of additional value in further unveiling the underlying mechanisms for coloration of the placental mass.

Our data should be interpreted with care due to the retrospective character of this study and the low sample size, especially in the acute peripartum TTTS group. Additional (prospective) studies with a larger group of acute peripartum TTTS placentas are required to help confirm the benefits of visual examination of the maternal side of the placenta for differentiation between TAPS and acute peripartum TTTS.

In conclusion, this study shows that there is a significant difference in CDR between acute peripartum TTTS placentas and TAPS placentas. TAPS placentas were characterized by a striking color difference whereas acute peripartum TTTS placentas showed no color difference on the maternal side. We strongly encourage caretakers in the obstetrical and neonatal field to examine the maternal side when a pale and plethoric monochorionic twin pair is delivered and obstetrical data is lacking or inconclusive. In contrast to reticulocyte count measurement and placental injection, visual inspection of color difference on the maternal side of the placenta can be performed on-site, shortly after

delivery of the placenta. Although the clinical presentation of the twins should be leading in determining the optimal neonatal management, the outcome of this study shows that color difference on the maternal side of the placenta could serve as an additional visual diagnostic tool, thus leading to better supported decision making regarding optimal neonatal care.

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