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Chapter 9

Intrauterine transfusion combined
with partial exchange transfusion for
twin anemia polycythemia sequence:
modelling a novel technique



Abstract

Introduction:

Twin anemia-polycythemia sequence (TAPS) is a newly described disease in monochorionic twin pregnancies, characterized by large inter-twin hemoglobin differences. Optimal management for TAPS is not clear. One of the possible treatment modalities is intrauterine blood transfusion (IUT) in the donor with or without combination of partial exchange transfusion (PET) in the recipient.

Methods:

We applied a computational model simulation to illustrate the mechanism of IUT with and without PET in TAPS occurring after laser surgery for twin-twin transfusion syndrome (TTTS). Model simulations were performed with the representative anastomotic pattern as observed during laser intervention, and after placental dye injection.

Results:

The model was tested against different cases where IUT was combined with PET for the treatment of post-laser TAPS. Model simulations using the observed anastomotic pattern showed a significant reduction of hyperviscosity in the recipient after IUT/PET compared to IUT without PET.

Discussion:

In this model simulation we show that the addition of PET to IUT reduces the severity of polycythemia in the recipient. PET may thus be important to prevent complications of hyperviscosity.

Conclusion:

This model simulation shows the beneficial effect of PET for the recipient in TAPS cases treated with IUT.

Introduction

Monochorionic twin pregnancies can be complicated by the twin anemia-polycythemia sequence (TAPS), which is a chronic form of feto-fetal transfusion. TAPS is characterized by large inter-twin hemoglobin (Hb) differences but without signs of the oligo-polyhydramnios sequence. TAPS placentas are characterized by the presence of only few, miniscule vascular anastomoses [1]. The incidence of TAPS varies between 1-5% in spontaneous TAPS [2-5] and up to 16% in post-laser TAPS [6;7]. TAPS can be diagnosed antenatally or postnatally. “Prognosis of TAPS can vary from two healthy neonates with transient hematological problems to severe neonatal morbidity, such as limb necrosis, severe cerebral injury or perinatal death.” Antenatal management options include expectant management, induction of labor, intrauterine blood transfusion (IUT) with or without combination of partial exchange transfusion (PET), selective feticide or (repeat) fetoscopic laser surgery [8-11]. Treatment with IUT at least temporarily improves the condition of the donor twin, however, the transfer of transfused red cells to the already polycythemic recipient may worsen its hyperviscosity and increases the risk for associated complications such as limb necrosis and severe cerebral injury [6;12]. The PET procedure implies replacement of the polycythemic fetal blood with saline solution and leads to a reduction of hyperviscosity. In this study we tested a model simulation against different cases of IUT in combination with PET. With this model we illustrate the mechanism of IUT with PET compared to IUT without PET.

Methods

We selected different post-laser TAPS cases treated with IUT in combination with PET with full details of vascular anastomotic pattern during laser treatment and from postnatal placental injection studies[13]. Details on IUT and PET were recorded, including the amount of blood transfused and exchanged. Simulations of the effect of IUT and PET were performed in our computational model of monochorionic twin pregnancies [11].

Mathematical model simulation

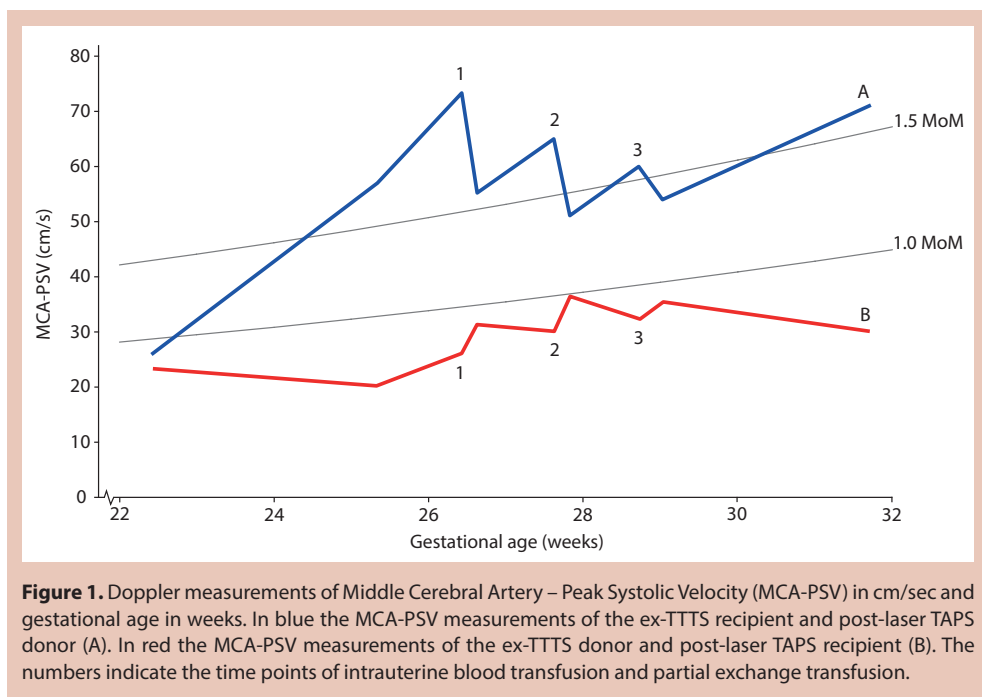
The model as used for the simulations was based on the previous TTTS models with nonpulsating circulations [14;15] as was previously applied to predict development of hydrops in the TTTS recipient [16] and the presence of a discordant hematocrit in the presence of normal amniotic fluid volumes after incomplete laser therapy of vascular anastomoses [11]. In brief, the model applies 13 coupled differential equations for each twin

to describe changes in volumes of fetal arterial and venous blood, volumes of interstitial, intracellular, and amniotic fluid, colloid osmotic pressures of fetal blood and interstitial fluid, osmolality of fetal blood and amniotic fluid, the concentration of vasoconstrictive peptides in the fetal blood, blood hematocrit, arterial wall elastin content, arterial wall thickness, as well as measures of brain and placental vascular resistances. The differential equations of the nonpulsatile model are programmed in Delphi 5.0 (Borland Interprise Corp., Cupertino, CA) and are numerically solved for 12 to 36 weeks with a time step of approximately 0.6 sec. Input variables for computation of anastomotic flow include the type of anastomosis, i.e. arterio-venous (AV), veno-arterial (VA), arterio-arterial (AA) or veno-venous (VV) and the anastomosis resistances. Following the application of Ohm's law of each of the resistances, multiple parallel placental anastomoses of identical type can be computationally represented by a single corresponding replacement resistance. Laser intervention of a set of anastomoses combined with amnioreduction is simulated as cessation of fetofetal transfusion of blood and constituents through the anastomoses and the normalization of the recipient amniotic fluid volume. IUT as well as PET are simulated by instantaneous increase or replacement of blood volume and its constituents respectively with blood of normal properties.

Results

Vascular anastomotic pattern at time of laser for TTTS, amount of blood transfused or exchanged were available in four post-laser TAPS cases and are reported in Table 1. Figure 1 shows the middle cerebral artery – peak systolic velocity (MCA-PSV) measurements of case 1. Placenta injection with color dye of case 1 showed the presence of 1 miniscule AV anastomosis (diameter 0.2mm) from the anemic twin to the polycythemic twin (figure 2).

Model simulations were performed using as input variables the anastomotic pattern as observed during laser intervention and after placental injection analysis. Hence, in the model, prior to laser intervention, large bidirectional arteriovenous flow was simulated whereas after laser intervention only one small uncompensated arteriovenous anastomosis from ex-recipient to ex-donor was simulated. Placental sharing between the twins was set as equal and all interventions were modelled at identical gestational ages and blood volumes used for IUT and PET as performed clinically. A model simulation for case 1 and 2 showing computed hematocrit as a function of gestational age is shown in Figure 3. Model simulations were performed for IUT with and without PET of the TAPS recipient for all the reported post-laser TAPS cases. Model simulations were comparable for these four cases, model simulation for case 1 and 2 are shown in Figure 3. The model simulation shows the difference in hematocrit



in the recipient with and without the combination of PET. Figure 4 shows for case 1 the blood flow for TTTS recipient (TAPS donor) to TTTS donor (TAPS recipient) in ml per day. Net blood flow before laser resulted in TTTS, and after laser the net blood flow through the miniscule remaining AV anastomosis resulted in post-laser TAPS.

Discussion

We showed theoretically that including PET with IUT for the recipient in TAPS has a strong beneficial effect compared to IUT without PET, as illustrated in a model simulation. This is the first study that shows the importance of PET, confirming previous case-reports which suggested a possible advantage of PET [6;9]. The advantage of model simulation is that with the same patient characteristics hematocrit levels can be given for two treatment options (IUT with and without combination of PET).

Our model simulation shows that the addition of PET to IUT reduces the hyperviscosity in the TAPS recipient. Also shown in this model is that the risk of severe polycythemia and hyperviscosity increases with repeated IUTs when performed without PET. Hyperviscosity is associated with complications such as ischemic limb necrosis and severe cerebral injury.

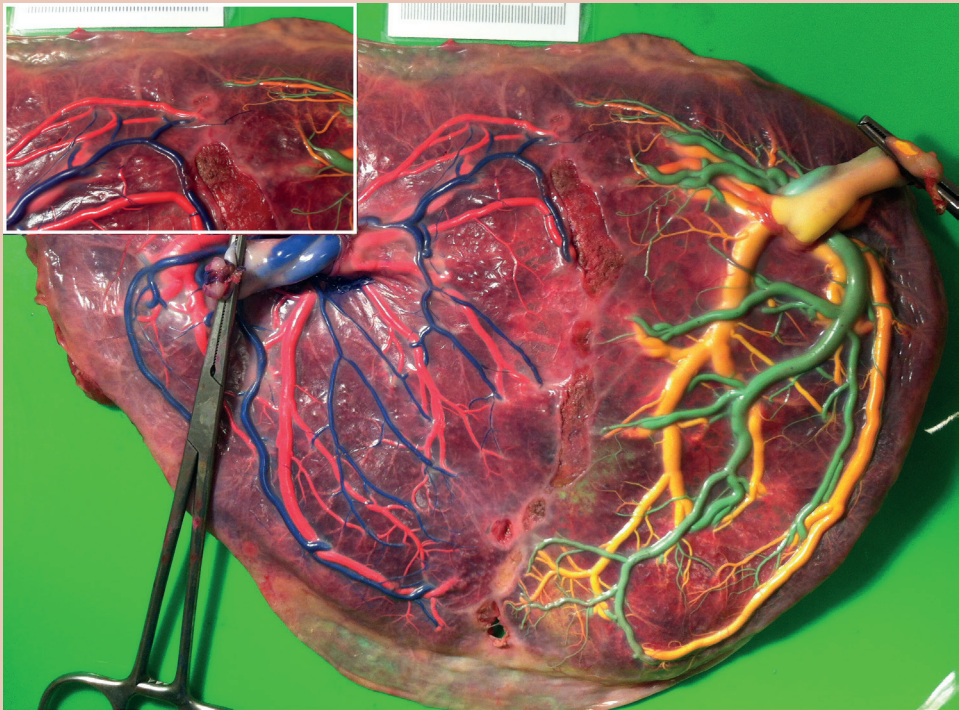


Figure 2. Post-laser TAPS placenta after color dye injection. Blue and green dye was used to stain the arteries and yellow and pink was used to stain the veins. The placenta share of the TAPS donor is on the left side of the picture and the placenta share of the TAPS recipient is on the right side. At the top and in the enlargement one residual arterio-venous anastomoses in seen which caused post-laser TAPS.

Our model also shows the differences that occur in the development of TTTS compared with TAPS. Net blood flow from donor to recipient is much higher in TTTS compared to the small amount of blood transfused from donor to recipient in TAPS.

Our findings thus strongly support the use of IUT combined with PET in the management of TAPS. However, IUT with or without PET is a symptomatic treatment for TAPS because it does not solve the underlying problem, which are small (residual) anastomoses. In a recent publication by our group, results suggested that laser treatment for TAPS may improve survival and neonatal outcome by prolonging the pregnancy [10]. Prolonging the pregnancy is of paramount importance for neonatal outcome. If laser surgery is not feasible, IUT in combination with PET might be a good alternative to prolong the pregnancy while temporarily improving the condition of both twins.

A recent long-term follow-up study on post-laser TAPS cases showed that low gestational age at birth and low birth weight are important risk factors for cognitive delay [17]. A subgroup

analysis on antenatally detected post-laser TAPS cases showed that the lowest median cognitive scores were in the IUT-group (without PET). Whether the lower scores were due to

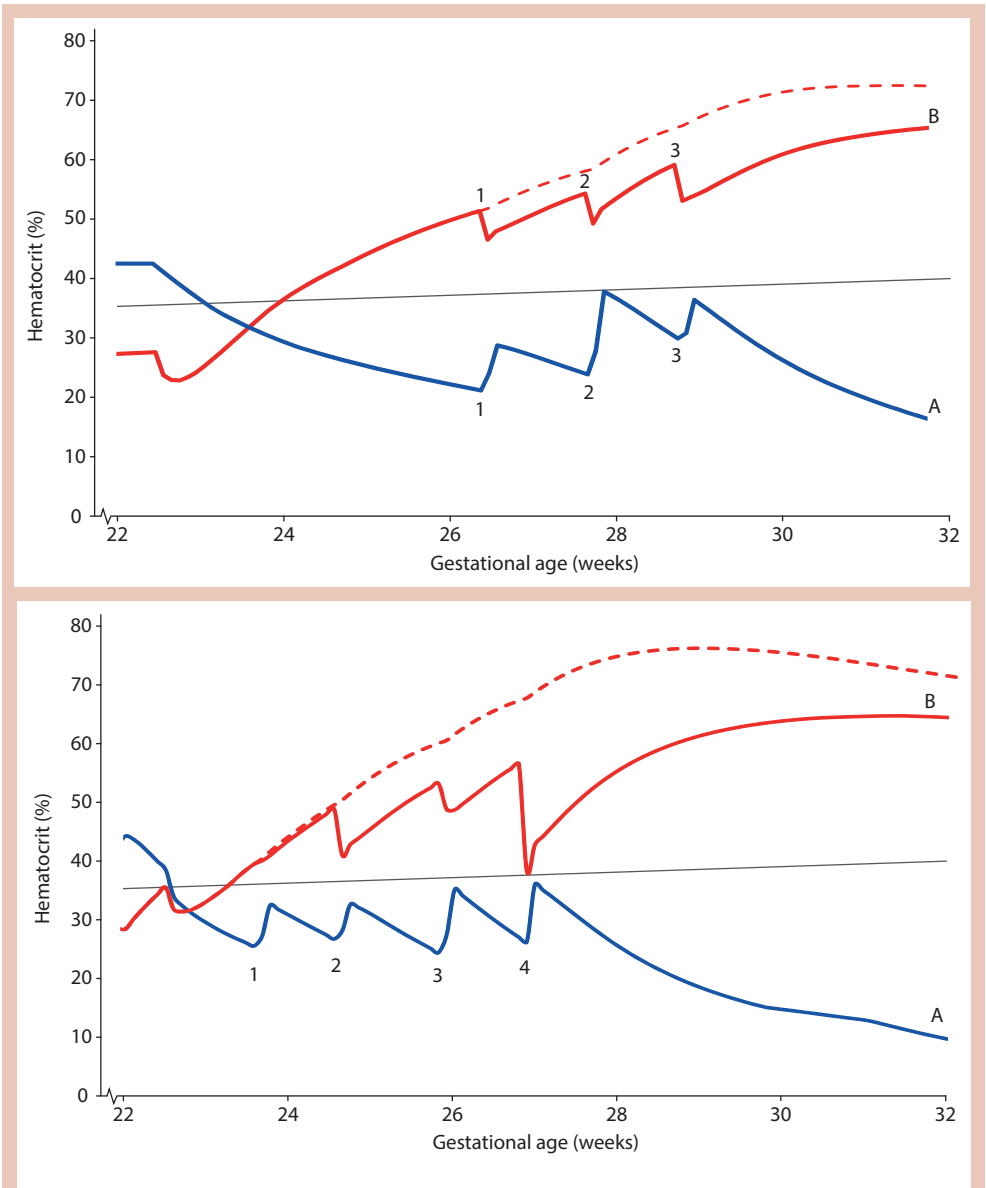
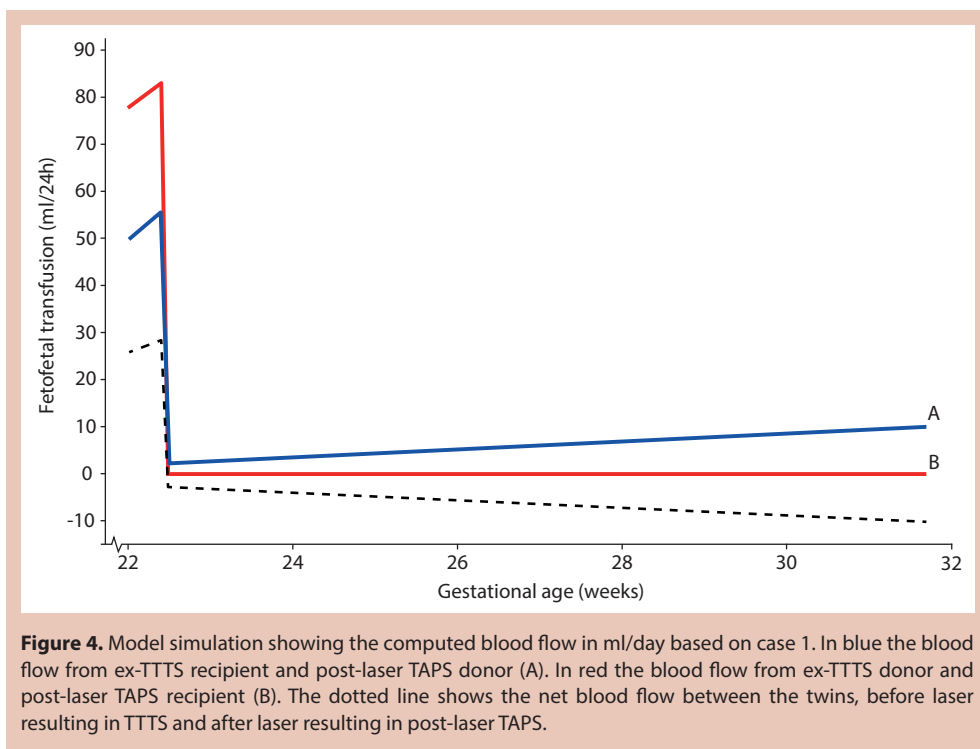


Figure 3. Model simulation showing the computed hematocrit (%) as a function of gestational age (weeks). In blue the percentage of hematocrit in the ex-TTTS recipient and post-laser TAPS donor (A). In red the percentage of hematocrit in the ex-TTTS donor and post-laser TAPS recipient. The red dotted line indicates the model outcome in case of no simulated PET. The first shows the model for case 1, and the second shows the model for case 2.

GA (weeks)	anastomotic pattern during laser for TTTS	Intervention	twin A Hb before	twin A Hb after	Birthweight twin A	Amount of blood ex- changed (ml)	twin B Hb before	twin B Hb after	Birthweight twin B	Amount of blood transfused (ml)
Case 1										
22+2 (laser for TTTS)	2 AV, 4 VA									
26+3		1st IUT & PET	18.2	15.0		32 out + 32 in	5.0	8.0		23 iv + 20 ip
27+5		2nd IUT & PET	17.4	13.9		38 out + 40 in	6.6	10.9		47 iv + 30 ip
28+6		3rd IUT & PET	16.3	14.6		26 out + 20 in	10.9	13.1		27 iv + 10 ip
31+5 (at birth)			23.4		1445 gram	reticulocyte count 28% _{oo}	9.3		1715 gram	reticulocyte count 115% _{oo}
Case 2										
21+5 (laser for TTTS)	4 AV, 3 VA									
23+4		1st IUT & PET	17.9	n/a		6ml out, 5ml in	1.9	7.5		N/A
24+4		2nd IUT & PET	19.3	11.2		50ml	2.6	8.6		12ml
25+6		3rd IUT & PET	18.6	17.6		30ml out, 25ml in	3.7	10.7		N/A
26+6		4th IUT + PET	20.6	13.1		94ml out, 100ml in	3.5	11.5		50ml iv +30 IP
27+5 (at birth)			21.5		980 gram	reticulocyte count 39% _{oo}	9.3		1235 gram	reticulocyte count 143% _{oo}
Case 3										
25+1 (laser for TTTS)	4 AV, 4 VA									
27+2		1st IUT + PET	18.9	15.0		30ml out, 30ml in	4.3	9.3		30ml IV + 25ml IP
29+3		2nd IUT + PET	-	-		-	7.0	9.3		20ml IV + 30ml IP
32+3 (at birth)			23.0		1664 gram	reticulocyte count 43% _{oo}	12.8		1615 gram	reticulocyte count 94% _{oo}
Case 4										
15+3 (laser for TTTS)	2 AV, 3 VA									
28+2		1st IUT + PET	18.2	14.7		55ml out, 55ml in	5.0	13.8		65ml IV + 50ml IP
29+1		2nd IUT + PET	17.8	14.6		57ml out, 45ml in	9.6	13.6		45ml IV + 50ml IP
31+1 (at birth)			26.1		1520 gram	reticulocyte count 29% _{oo}	12.0		1759 gram	reticulocyte count 108% _{oo}

GA: gestational age; AV: arterio-venous anastomosis; VA: veno-arterial; IUT: intrauterine transfusion; PET: partial exchange transfusion; Hb: hemoglobin (g/dL); iv: intravenous; ip: intraperitoneal

Table 1: Hematological measurements and management information.



the lower gestational age or due to severe anemia and polycythemia in this subgroup could not be established.

In conclusion, when IUT is considered as treatment option for TAPS, our model simulations strongly suggest to add PET, to reduce the risk of severe polycythemia and the possible complications due to hyperviscosity. More clinical, prospective studies are needed to confirm our theoretical findings.

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