A mathematical model of twin-twin transfusion syndrome with pulsatile arterial circulations

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Van den Wijngaard JP, Westerhof BE, Ross MG, van Gemert MJ. A mathematical model of twin-twin transfusion syndrome with pulsatile arterial circulations. Am J Physiol Regul Integr Comp Physiol 292: R1519–R1531, 2007. First published December 7, 2006; doi:10.1152/ajpregu.00534.2006.—The twin-twin transfusion syndrome (TTTS) is a severe complication of monochorionic twin pregnancies caused by a net transfusion of blood from one twin (the donor) to the other (the recipient) through placental anastomoses. To examine the pathophysiology of TTTS evolving through clinical stages I to IV, we extended our mathematical model to include pulsating circulations propagating along the arterial tree as well as placental and cerebral vascular resistances, and arterial wall thickness and stiffness. The model demonstrates that abnormal umbilical arterial flow (TTTS stage II) in the donor twin results from increased placental resistance as well as reduced resistance in the cerebral arteries. In contrast, recipient twin abnormal umbilical arterial flow requires a significantly greater increase in placental resistance, resulting from the compressive effects of high amniotic fluid pressure. Thus simulated abnormalities of donor umbilical arterial pulsations occur in the donor more commonly and earlier than in the recipient. The “normal” staging sequence (I, II, III, IV) correlates with the presence of compensating placental anastomoses, constituting the majority of monochorionic twin placentas. However, TTTS stage III may occur before manifestations of stage II (lack of donor bladder filling), in our model correlating with severe TTTS from a single arteriovenous anastomosis, an infrequent occurring placental angioarchitecture. In conclusion, this mathematical model describes the onset and development of the four stages of TTTS, reproduces a variety of clinical manifestations, and may contribute to identifying the underlying pathophysiology of the staging sequence in TTTS.

stage III; quintero staging sequence

TTTS is believed to progress through four worsening stages of severity with both twins alive (36). Stage I TTTS is diagnosed by the oligo-polyhydramnios sequence, where the donor has almost no amniotic fluid and the recipient simultaneously has excess amniotic fluid. More severe stages of TTTS often develop subsequently: stage II includes lack of donor bladder filling; stage III, abnormal umbilical flows in either twin (i.e., reduced or reversed end-diastolic flow) (21); and stage IV, congestive cardiac failure and hydrops in the recipient.

The syndrome has a largely inaccessible pathophysiology, because invasive fetal study is unethical and an animal model is lacking. Accordingly, mathematical models of TTTS have been developed to aid in identifying the pathophysiology of the various TTTS presentations (42, 43, 46, 50) and the response to therapy (44, 47). However, none of these models described TTTS stage III, probably the most complex of the four stages, because the abnormal umbilical flows can occur in either or both of the twins. Therefore, stage III pathophysiology likely comprises a variation of different mechanisms that may develop independently in each of the twins (4, 23, 26, 33, 37). We hypothesized that multiple cardiovascular abnormalities [e.g., in blood viscosity, arterial pressure, arterial wall stiffness (10, 18), redistribution of arterial blood flow to the brain, vasoconstrictive peptides, and placental resistance] contribute to the onset of stage III TTTS.

We recently modeled (48) pulsating arterial flow of the fetoplacental circulation, using viscoelastic tube segments and three-element windkessels to simulate the arteries and fetal organs, respectively. In the present study, we sought to extend the TTTS model, including our model of pulsating arterial circulations and multiple cardiovascular parameters, to simulate the onset and development of abnormal umbilical arterial pulsations (stage III) and to examine the progression of TTTS from stage 1 to stage IV in relation to the placental angioarchitecture.

METHODS

The present model is based on combining two previous mathematical models. First, our pulse arterial propagation model (48), and second, our TTTS model with nonpulsating circulations (46). The resulting new model incorporates 13 differential equations for each twin, coupled by the net fetofetal transfusion of blood volume and blood constituents, i.e., colloids, osmoles, and vasoconstrictive peptides. These 26 equations describe the development of and interactions

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occurring between the volumes of fetal arterial and venous blood, interstitial fluid, intracellular fluid and amniotic fluid, the colloid osmotic pressures of fetal blood and interstitial fluid, the osmolarities of fetal blood and amniotic fluid, the concentration of vasoconstrictive peptides in the fetal blood, generically referred to as renin-angiotensin-system (RAS) mediators, the blood hematocrit, and the elastin content and thickness of the arterial walls. Output parameters of the TTTS model, i.e., cardiac output, arterial wall thicknesses and Young’s moduli (stiffness related to the elastin content), placental and cerebral vascular resistances, and blood viscosities related to blood hematocrits, at a certain gestational age, are used as input for the pulse propagation model to compute the donor and recipient pulsating flow waves in their respective arterial trees at that gestational age. An overview of both models is schematically given in Fig. 1. Possible differences in diameter and length of arterial segments as a consequence of discordant developing donor and recipient twins were neglected because differences in blood volume as large as a factor of two, for example, would cause a much smaller difference of a factor of 2\(^{1/3} = 1.26\) in diameters and lengths.

Below, we briefly describe the arterial pulse propagation model (48), followed by a description of the new additions in our TTTS model (46), i.e., the dynamics of blood hematocrit, arterial wall thickness and elastin content, and the placental and cerebral vascular resistances. The appendix gives a brief overview of our TTTS model and the underlying differential equations. Table 1 summarizes the symbols used in this article.

Model of the pulsatile fetoplacental circulation. As described previously (48, 54, 55), the fetal arterial tree was constructed using 13 viscoelastic tubes representing the arteries and 9 three-element windkessels representing the peripheral organ beds. Details on anatomical parameters, i.e., arterial lengths and radii, wall thicknesses and viscoelastic wall properties, and blood viscosity, all as a function of gestational age, were adapted from the literature (20, 32, 48). The model uses a normal cardiac flow waveform entering the ascending aorta. With the use of the frequency spectrum of this cardiac pulse, the usual approach to compute propagation and attenuation of frequency components was followed, resulting in changes in phase and amplitude of the harmonic waves at the different sites of the arterial tree. To obtain the time domain pulse waveform at the sites of interest, we used the inverse Fourier transform.

Analysis showed placental and cerebral resistances to have the highest influence on the pulse waveforms along the fetal arterial tree. In addition, blood viscosity and vessel wall stiffness had a much smaller influence, whereas organ, i.e., windkessel, compliance had negligible influence. The model of pulsatile flow and pressure is written in Mathematica 4.0 (Wolfram Research, Champaign, IL) and uses 25 harmonics, multiples of the normal fetal heart rate, to compute the frequency spectrum of the input flow waveform. One computer run took ~2.5 min on a Pentium 4.8 GHz personal computer. Details of the model can be found elsewhere (48).

Blood hematocrit dynamics. The normal fetal blood hematocrit, \(\text{Hct}_{N}(t)\), as a percentage at gestational age \(\text{t}\) (weeks), is given by (53)

\[
\text{Hct}_{N} = t \cdot 0.405 + 25.9
\]

and ranges from ~30% at 10 wk to 42% at 40 wk. Because it is the ratio of the volume of red blood cells, \(V_{\text{RBC}}\), to total blood volume, \(V_b\), the normal volume of red blood cells can be written as

\[
V_{\text{RBC}} = \left( t \cdot 0.405 + 25.9 \right) / 100 \cdot V_b
\]

When fetal hematocrit is lower than normal, e.g., in anemia, the production of red blood cells is upregulated by erythropoietin from the fetal kidneys (35). The maximal increase of red blood cell production in acutely hemorrhaged fetal lambs was two- to threefold (19, 41). In addition, a similar upregulation follows from the results of reticulocyte count (19). In a recent study in human fetuses with the twin anemia polycythemia sequence (25), the donor had a 2.2–2.7 times larger absolute reticulocyte count than the recipient. Because the exact amount of upregulation due to chronic blood loss is unknown, the maximal upregulation was chosen as 1.5. We further assumed that this upregulation has a time constant of \(\tau_1 = 3\) wk after onset of a lower hematocrit than normal so that the upregulation is 1.25 after ~2 wk vs. 1.4 after 7 wk. Using \(\Delta t\) (weeks) as the time period between the gestational age considered and that where the hematocrit became reduced, the dynamics of upregulation for donor and recipient have been described as

\[
\frac{dV_{\text{RBC},N}}{dt} = \frac{dV_{\text{RBC},N}}{dt} \cdot \frac{V_b}{V_{\text{RBC}}}[1.5 - \exp(-\Delta t / \tau_1)] \quad X = \text{D,R}
\]

The time derivative of \(V_{\text{RBC},N}\) follows directly from Eq. 2, and D and R represent donor and recipient, respectively. For clarity, the time dependence in the parameters was omitted.

In case of an excess hematocrit at gestational age \(\text{t}_0\), defined as

\[
\text{ExHct}_{D,R}(\text{t}_0) = \text{Hct}_{D,R}(\text{t}_0) - \text{Hct}_{N}(\text{t}_0) \quad X = \text{D,R}
\]

the excess red blood cells are removed from the circulation by an exponential function with a time constant of \(\tau_2 = 7.2\) wk, corresponding to the actual measured maximal life span of 10 wk (8) and hence a half-life time of 5 wk. As shown previously (46), this can be expressed as

\[
\frac{d\text{ExHct}_{D,R}(\text{t})}{dt} = - \frac{\text{ExHct}_{D,R}(\text{t})}{\tau_2} \quad X = \text{D,R}
\]

The differential equation of donor and recipient hematocrit can now be written as

\[
\text{ExHct}_{D,R}(\text{t}) = \text{Hct}_{D,R}(\text{t}) - \text{Hct}_{N}(\text{t}) \quad X = \text{D,R}
\]
normal resistances of the fetal brain, the periphery, and the placenta.

The normal total resistance to consist of the parallel circuit of the periphery), and 30% to the placenta (48); see Fig. 2. We considered the normal total resistance to consist of the parallel circuit of the normal resistances of the fetal brain, the periphery, and the placenta. Thus

\[ R_{\text{TotalN}} = \frac{P_{\text{artN}} - P_{\text{venN}}}{\text{CON}} \]  

(7)

where \( P_{\text{artN}} \) and \( P_{\text{venN}} \) are the normal mean arterial and venous pressures (mmHg), and \( \text{CON} \) (ml/wk) is the normal combined cardiac output (31). Under normal conditions, we assumed that 70% of the cardiac output perfuses the fetal body, of which 25% is directed to the fetal brain, 45% to the rest of the body (for convenience, called periphery), and 30% to the placenta (48); see Fig. 2. We considered the normal total resistance to consist of the parallel circuit of the normal resistances of the fetal brain, the periphery, and the placenta. Thus

\[ R_{\text{TotalN}} = R_{\text{BrainN}} + R_{\text{PeripheryN}} + R_{\text{PlacentaN}} \]

(8a)

The normal placental resistance is the sum of the precapillary and postcapillary resistances, \( R_{\text{PlacentaPreN}} \) and \( R_{\text{PlacentaPostN}} \). Thus, using fetoplacental capillary blood pressure, \( P_{\text{capN}} \), it follows that

\[ R_{\text{PlacentaN}} = R_{\text{PlacentaPreN}} + R_{\text{PlacentaPostN}} \]

(9a)

Placental resistance in donor and recipient depending on their RAS, blood viscosity, and amniotic fluid pressure. In the model, the placental resistance depends on the blood RAS mediators, which influence the precapillary, although not postcapillary, placental resistance by causing vasoconstriction of the cotyledonic arteries (1, 2, 3, 15). Placental resistance also may be increased by increased blood viscosity, as well as compression of the placental vessels resulting from increased amniotic fluid pressure associated with polyhydramnios (Refs. 9, 16; unpublished observations). The viscosity of the fetal blood for either twin (in N s m\(^{-2}\)) is related to their hematocrit via the relation derived by Welch et al. (53) as

\[ \text{ViscosityX} = \frac{1}{HctN} \cdot \text{Viscosity} \]

where \( HctN \) and \( HctD \) are the normal and donor hematocrits, respectively.

### Table 1. List of parameters used in the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Parameter Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFN, AFp, AFr</td>
<td>mmHg</td>
<td>Normal, donor, and recipient amniotic fluid pressure</td>
</tr>
<tr>
<td>COaN, COpN, COPNC</td>
<td>ml/wk</td>
<td>Normal cardiac output</td>
</tr>
<tr>
<td>COPcapN, COPcapX</td>
<td>mmHg</td>
<td>Colloid osmotic blood pressures of maternal and fetal blood of either twin</td>
</tr>
<tr>
<td>D, R</td>
<td></td>
<td>Donor and recipient subscript</td>
</tr>
<tr>
<td>EHthoAON</td>
<td>mmHg</td>
<td>Thoracic aorta Young’s modulus</td>
</tr>
<tr>
<td>FPlacentaX</td>
<td>ml/wk</td>
<td>Placental flow of either twin</td>
</tr>
<tr>
<td>hsc, hth</td>
<td></td>
<td>Normal and recipient arterial wall thickness</td>
</tr>
<tr>
<td>HcSN, HcSD, HctR</td>
<td></td>
<td>Normal, donor, and recipient Hct</td>
</tr>
<tr>
<td>IAV, IVA, IAA, IVV</td>
<td>ml/wk</td>
<td>Flow through AV, VA, AA, and VV anastomoses</td>
</tr>
<tr>
<td>k</td>
<td></td>
<td>Adjustable parameter to increase effect of polyhydramnios</td>
</tr>
<tr>
<td>LP</td>
<td>ml/wk ( ^{-1} ) mmHg ( ^{-1} )</td>
<td>Transplacental filtration coefficient</td>
</tr>
<tr>
<td>PAF</td>
<td>mmHg</td>
<td>Amniotic fluid pressure</td>
</tr>
<tr>
<td>PAWN, PAWX</td>
<td>mmHg</td>
<td>Normal and of either twin arterial pressure</td>
</tr>
<tr>
<td>PcapN</td>
<td>mmHg</td>
<td>Normal fetoplacental capillary blood pressure</td>
</tr>
<tr>
<td>PWN, PWX</td>
<td>mmHg</td>
<td>Normal and of either twin venous pressure</td>
</tr>
<tr>
<td>RASN, RASX</td>
<td>pg ml ( ^{-1} )</td>
<td>Normal concentration and concentration of either twin of renin-angiotensin system mediators</td>
</tr>
<tr>
<td>RPlacentaN, RBrainX</td>
<td>mmHg ml ( ^{-1} ) wk</td>
<td>Normal and of either twin brain resistance to mean blood flow</td>
</tr>
<tr>
<td>RPlacentaPreN</td>
<td>mmHg ml ( ^{-1} ) wk</td>
<td>Normal periphery resistance to mean blood flow</td>
</tr>
<tr>
<td>RPlacentaPostN</td>
<td>mmHg ml ( ^{-1} ) wk</td>
<td>Normal placental resistance to mean blood flow</td>
</tr>
<tr>
<td>RTotalN</td>
<td>mmHg ml ( ^{-1} ) wk</td>
<td>Normal total resistance to mean blood flow</td>
</tr>
<tr>
<td>t, ( \Delta t ), ( \tau_1 )</td>
<td>wk</td>
<td>Gestational age, time difference, time increment</td>
</tr>
<tr>
<td>TransPlacentaX</td>
<td>ml/wk</td>
<td>Maternofetal flow for either twin</td>
</tr>
<tr>
<td>VSN, VAX</td>
<td>ml</td>
<td>Normal blood volume, blood volume of donor or recipient</td>
</tr>
<tr>
<td>VBrainN, VBrainX</td>
<td>ml</td>
<td>Normal volume of red blood cells, volume of red blood cells of donor or recipient</td>
</tr>
<tr>
<td>ViscosityN</td>
<td>N ( ^{-1} ) s ( ^{-1} ) m ( ^{-2} )</td>
<td>Blood viscosity of either twin</td>
</tr>
<tr>
<td>WthoAon, WthoAod</td>
<td>g</td>
<td>Normal and donor weight of elastin</td>
</tr>
<tr>
<td>WCollN, WCollD</td>
<td>g</td>
<td>Normal and donor weight of collagen</td>
</tr>
<tr>
<td>WthoAon</td>
<td>g</td>
<td>Normal thoracic aorta wall weight</td>
</tr>
</tbody>
</table>

AV, arteriovenous; VA, opposite arteriovenous; AA, arterioarterial; VV, venovenous.
To develop the relation between increased amniotic fluid volume/pressure and placental resistance, we used clinical data obtained from two amnioreductions of a TTTS polyhydramniotic recipient, where the umbilical venous flow was found to increase immediately following amnioreduction (unpublished observations). On average, placental flow increased 1.5-fold, implying a 1.5-fold reduction in placental resistance. Assuming that polyhydramnios increases the sum of the amniotic fluid volumes at least three times, based on normal AFV values of \(~0.4 \text{ liter at } 20 \text{ wk, and the amnioreductions remove } \sim 1 \text{ liter, Eq. } 13\) predicts the amniotic fluid pressure to increase to at least 15 mmHg. This can subsequently be used to correlate with the decrease in umbilical flow of 1.5 times. Because polyhydramnios shows a large variation in amniotic fluid pressures (16, 51), the relation of \(f_{\text{AFP}}\) with amniotic fluid pressure includes the adjustable parameter \(k\) as follows

\[
\begin{align*}
\frac{f_{\text{AFP}}}{f_{\text{AFP},N}} &= 1 + k \cdot \left(\frac{P_{\text{AFP}} - P_{\text{AFN},N}}{P_{\text{AFN},N}}\right) \quad P_{\text{AFN},N} \geq P_{\text{AFN}} \quad (14)
\end{align*}
\]

and with \(f_{\text{AFP}} = 1\) otherwise. In the simulations below, the adjustable parameter \(k\) was chosen as one and five, where \(k = 1\) implies that \(f_{\text{AFP}} = P_{\text{AFP},N}/P_{\text{AFN},N}\); hence, the placental resistance is proportional to the actual amniotic fluid pressure. With \(k = 5\), a significantly stronger influence of amniotic fluid pressure on placental resistance is assumed, i.e., a twofold increased amniotic fluid pressure increases the placental resistance sixfold. In the model, the placental resistance is then roughly increased 2.5-fold at 22 wk due to the predicted level of polyhydramnios in a severe case of TTTS (single AV, stuck donor at 20 wk).

Cerebral resistance for donor and recipient depending on their placental flow. Consistent with “brain sparing” blood flow responses, Jensen et al. (22) showed that cerebral perfusion in fetal lambs increased 0.6\% when placental perfusion decreased by 1\%. Following Myers and Capper (32), we decreased cerebral resistance accordingly when the placental resistance was increased, also resulting in decreased placental flow, \(F_{\text{Placenta}}\). With \(X = D, R\), we used

\[
R_{\text{Brain}} = R_{\text{Brain}N} \quad F_{\text{Placenta}} = \text{normal} \quad (15a)
\]

\[
R_{\text{Brain}} = R_{\text{Brain}N} \cdot \left(0.6 \cdot \frac{F_{\text{Placenta}}}{F_{\text{Placenta}N}} + 0.4\right) \quad F_{\text{Placenta}} \leq \text{normal} \quad (15b)
\]

\[
F_{\text{Placenta}} = \frac{P_{\text{AF}} - P_{\text{AFN}}}{P_{\text{AFN}}} \quad R_{\text{Placenta}} \quad (15c)
\]

Vascular Young's moduli in donors. Hypovolemia and growth retardation in the donor twin leads to a decreased elastin deposition in the large arteries (29, 30) and hence increased Young's moduli (stiffer arterial walls). Previously, the normal Young's modulus (in mmHg) for the thoracic aorta was derived as (48)

\[
E_{\text{ThorAor}} = 3.8 \times 10^2 \cdot r^2 + 4.7 \times 10^3 \cdot t + 1.5 \times 10^4 \quad (16a)
\]

where we combined measured pulse wave velocities (17) with estimated anatomical values for vessel wall radius and thickness from literature data (48). From the latter data and using an arterial wall tissue density of 1.05 g/ml (12), we assessed the weight of the thoracic aorta wall (in g) as (48)

\[
W_{\text{ThorAor}} = 1.3 \times 10^{-4} \cdot r^3 + 2.2 \times 10^{-4} \cdot r^2 + 9.7 \times 10^{-3} \cdot t \quad (16b)
\]

From measurements by Berry et al. (7), we fitted the normal weight content of collagen, \(W_{\text{Coll},N}\), and elastin, \(W_{\text{Elast},N}\), in the thoracic aorta wall as
Subsequently, using the normal vascular Young’s modulus and the weight contents of elastin and collagen of the thoracic aorta, we could fit the following relation for the normal Young’s modulus:

\[ E_{\text{ThorAoN}} = 1.24 \times 10^6 \cdot W_{\text{ColN}} - 1.28 \times 10^6 \cdot W_{\text{ElaN}} + 5.9 \times 10^3 \]  

(18)

with an \( R^2 \) value of 0.994 (Microcal Origin, version 6.0; Northampton, MA).

Fetal elastin synthesis is abnormal in cases of a blood volume smaller than normal (in donor twins). We modeled this as

\[ W_{\text{ElaR}} = W_{\text{ElaN}} \]  

\[ \frac{dW_{\text{ElaD}}}{dt} = \frac{dW_{\text{ElaN}}}{dt} \cdot \left( 2 \cdot \frac{V_{\text{MD}}}{V_{\text{NN}}} - 1 \right) \]  

(19a)

\[ W_{\text{ElaD}} = W_{\text{ElaN}} \]  

(19b)

\[ W_{\text{ElaD}} = W_{\text{ElaN}} \]  

(19c)

where \( \frac{dW_{\text{Ela}}}{dt} \) follows from Eq. 17. Subsequently, from Eq. 18, the donor Young’s modulus of the thoracic aorta can be calculated by replacing the normal elastin weight with \( W_{\text{ElaD}} \). Solving from Eq. 19. In recipient twins, the Young’s modulus remained as given by Eq. 18.

This approach produces an increased Young’s modulus in hypovolemia or growth retardation in TTTS donors, approximating the observations described in the literature (18, 29). The factor of increase in thoracic aorta Young’s modulus was subsequently used to increase the Young’s moduli of the other arteries correspondingly (48).

**Arterial wall thickness in recipients.** Clinical data suggest that severe hypertension may develop in the recipient twin (27). According to experiments in the hypertensive rat (56) and fetal sheep (6), severe hypertension may develop in the recipient twin (27). According to experiments in the hypertensive rat (56) and fetal sheep (6), severe hypertension may develop in the recipient twin (27). According to experiments in the hypertensive rat (56) and fetal sheep (6), severe hypertension may develop in the recipient twin (27). According to experiments in the hypertensive rat (56) and fetal sheep (6), severe hypertension may develop in the recipient twin (27).

We dropped the \( X = D, R \) in all terms and used \( F_{\text{Placenta}} \) as defined in Eq. 15c. An increase in the precapillary resistance indeed decreases the capillary pressure, i.e., statement 1.

As described previously (43), the maternofetal flow (transplacental flow) depends on the \( P_{\text{cap}} \) as

\[ \text{TransPlacenta} = L_{\text{pl}} \left( P_{\text{mat}} - (P_{\text{AFX}} + P_{\text{cap}}) \right) - (C_{\text{OPmat}} - C_{\text{OPfet}}) \]  

where \( X = D, R \), where \( L_{\text{pl}} \) is the placental filtration coefficient in ml\( \cdot \)wk\(-1\)\cdot mmHg\(-1\), \( P_{\text{mat}} \) is the maternal hydrostatic villous blood pressure, and \( C_{\text{OPmat}} \) and \( C_{\text{OPfet}} \) are the maternal and fetal colloid osmotic blood pressures (in mmHg). A decreased \( P_{\text{cap}} \) indeed increases the transplacental flow, i.e., statement 2.

By allowing a low capillary hydrostatic pressure to develop in the donor twin as a consequence of RAS-mediated increased precapillary resistance, the maternofetal flow to the donor is increased compared with the previous model (43, 46). This stimulates development of polyhydramnios, which is confirmed by the observation that low-dose infusions of angiotensin produce polyhydramnios (15).

**Description of TTTS staging in the model.** The clinical stages of TTTS are defined as follows. The first stage is a stuck donor twin and simultaneously occurring polyhydramnios in the recipient. In our model, this is defined as a donor amniotic fluid volume of 10 ml and a recipient amniotic fluid volume of at least twice the normal volume. TTTS stage II commences when donor urine production has become zero. TTTS stage III, i.e., abnormal umbilical flow, is characterized by absent or reversed end-diastolic flow in the distal umbilical artery (48). TTTS stage IV is defined by hydrops in the recipient, defined at least an 18% increase of the interstitial fluid volume.

**Model simulations.** Model simulations included three selected cases (Table 2), all with an equally shared placenta. Case I has one single uncompensated AV anastomosis; this angioarchitecture represents severe TTTS (45). We used \( k = 1 \) in Eq. 14. The radius of the AV anastomosis was varied until the model outcome predicted a stuck

### Table 2. Data used as input in the TTTS model and the predicted staging sequence for the three simulated cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Anastomotic Pattern</th>
<th>Anastomotic Resistances at 40 wk, mmHg ( \cdot ) ml(^{-1})\cdot h(^{-1})</th>
<th>( k ) (Eq. 14)</th>
<th>Predicted Staging Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AV</td>
<td>AV = 0.31</td>
<td>( k = 1 )</td>
<td>I-III(D)-II-IV</td>
</tr>
<tr>
<td>2</td>
<td>AV + VA + AA</td>
<td>AV = 0.10</td>
<td>( k = 1 )</td>
<td>I-II-III(D)-IV</td>
</tr>
<tr>
<td>3</td>
<td>AV + VA + AA</td>
<td>AV = 0.10</td>
<td>( k = 5 )</td>
<td>I-III(D)-II-III(R)-IV</td>
</tr>
</tbody>
</table>

TTTS, twin-twin transfusion system.
donor twin at 22 wk of gestation. Case 2 has an AV anastomosis, inadequately compensated by one oppositely directed smaller VA anastomosis and one small AA anastomosis. This placental angioarchitecture, i.e., an AV inadequately compensated by opposite anastomoses, is found in a large number of TTTS placentas (11). In this case, we increased the AV radius ∼1.3-fold compared with the previous case; thus the AV resistance was reduced 3-fold (from 1/1.3^2), and compensating VA and AA anastomoses were included so that a stuck donor twin also developed at 22 wk. An example of a non-TTTS placenta with this type of anastomoses is depicted in Fig. 3. Compared with case 1, this angioarchitecture allows for return of colloids, osmoles, and hematocrit from the recipient to the donor, causing milder TTTS (34). We used k = 1. Case 3 has the anastomotic pattern of case 2, but the influence of amniotic fluid pressure on the placental resistance was increased. We used k = 5 in Eq. 14. As a result, a stuck donor twin developed at 22.5 wk.

RESULTS

Case 1. Table 3 summarizes some of the outcomes of donor and recipient parameters of case 1 as well as a normal fetus. Polyhydramnios in the recipient sac occurs at 19.9 wk, and the donor twin becomes stuck at 22 wk (stage I). Donor anuria develops at 22.5 wk (stage II). However, donor twin absent end-diastolic flow in the distal umbilical artery occurs slightly earlier than stage II, at 22.4 wk (stage III), which ultimately develops into reversed end-diastolic flow (see Fig. 4). In the recipient, although reversed end-diastolic flow does not develop in the umbilical artery, flow amplitudes are severely reduced compared with normal, a consequence of the increased placental resistance and increased blood viscosity (Table 3). Hydrops in the recipient develops at 27.2 wk (stage IV). Donor and recipient blood viscosity develop severely discordantly, and Young’s moduli develop somewhat discordantly (Table 3). In this case, the sequence of TTTS stages are I, III(D), II, and IV (Table 2).

Case 2. Polyhydramnios develops in the recipient amniotic sac at 19.8 wk and a stuck donor at 22 wk. The donor twin ceases to produce urine at 28.1 wk (stage II). Subsequently, increased levels of RAS develop in the donor twin’s blood, and when combined with recipient polyhydramnios, the donor placental resistance is increased (not shown). Absent and reversed end-diastolic flows develop in the donor’s umbilical artery at 28.2 wk (stage III). Subsequently, hydrops develops in the recipient twin at 33.7 wk (stage IV). Model outcomes of umbilical arterial and middle cerebral artery flow for donor and recipient can be found in Fig. 5. The sequence of TTTS stages are I, II, III(D), and IV (Table 2).

Case 3. Polyhydramnios develops at 20 wk, and the donor becomes stuck at 22.5 wk (stage I). The strongly increased placental resistance in donor and recipient twins (not shown) causes abnormal umbilical flows to develop in both twins. At 24.8 wk, reversed end-diastolic flow develops in the donor (stage III). Donor anuria subsequently develops at 28.5 wk (stage II). In the recipient, reversed end-diastolic flow develops at 32.3 wk and hydrops at 33.1 wk (stage IV) (see Fig. 6). The sequence of TTTS stages is I, III(D), II, III(R), and IV (Table 2).

DISCUSSION

We present the first mathematical model that describes the sequence of the four TTTS pathophysiology stages with two live twins. In the current study, we added several equations to our existing model of TTTS, describing the dynamics of the fetal blood hematocrit, the placental and cerebral resistances, the arterial wall Young’s modulus (stiffness), and the arterial wall thickness. These parameters subsequently were used in our model of the pulsating fetal arterial circulation (48) to yield flow waves propagating down the arterial tree with emphasis on umbilical and cerebral arterial flow. The model provides insight into the pathophysiology of donor vs. recipient stage III TTTS, and the sequence of the various stages, in relation to the placental angioarchitecture.

In our model, abnormal umbilical artery flows (stage III) develop in the donor twin more commonly and earlier than in the recipient. This results from an increased donor placental vascular resistance in conjunction with decreased cerebral vascular resistance. The increased placental resistance occurs in both donor and recipient twins from two primary mechanisms: 1) increased levels of RAS developing in the hypotensive donor that are transfused by the AV anastomosis to the recipient, which increases the precapillary resistance of the cotyledons; and 2) placental sponging due to polyhydramnios-induced increased amniotic fluid pressure, which is distributed equally to both placentas. A third mechanism, which increases placental resistance only in one twin, is the increased blood viscosity of the polycythemic recipient. In addition, although not addressed in the present report, unequal placental sharing increases donor or recipient placental resistance, depending on which twin has the smaller placental part. In our model,
abnormal umbilical flows, developing only in the recipient and not in the donor, would result from a small recipient placental part. We assume the placenta can be described by a set of parallel capillary resistances; hence, a smaller placenta contains less capillaries, and its resistance is inversely proportionally increased. In addition, our model indicates a decreased mean umbilical blood flow for donor twins compared with recipient twins, which is comparable to clinical observations (5).

In contrast to the similar effects of RAS and polyhydramnios on both twins, effects of viscosity differ greatly. As the decreased donor blood viscosity (anemia) increases the arterial pulse wave amplitude (48), the donor twin more readily develops reduced or absent end-diastole flow. In addition, the “normal” staging sequence where stage II precedes stage III additionally requires that donor anemia is limited as a result of mechanisms that affect the pulsations in opposite directions, namely, reduced cerebral vascular resistance and increased blood viscosity. Reduced cerebral vascular resistance reduces the reflection of the pulsatile blood flow against the brain vascular bed; hence, both the pulse amplitude and the mean flow in the middle and anterior cerebral arteries increase (48). In contrast, an increased blood viscosity increases the cerebral arterial stage III develops more frequently in the donor than in the recipient, i.e., 15 of 110 vs. 1 of 110 cases of TTTS, respectively. In addition, stage III in recipients virtually always refers to venous instead of arterial flow abnormalities such as reversed flow in the ductus venosus or pulsatile umbilical venous flow. Of 110 cases of TTTS, at least 30 recipients developed ductus venosus reversed flow during atrial contraction, and at least 33 developed pulsatile umbilical venous flows, compared with 1 recipient with arterial stage III (28). Pulitating umbilical venous or ductus venosus flows may develop as a consequence of an impaired relaxation of the right ventricle (40), resulting from a decreased compliance of the myocardium. Our model obviously cannot simulate the significant presentation of abnormal venous flows in recipients at the present time, because venous circulations were not included.

Second, the current model demonstrates that stage III TTTS (in the donor) may develop before stage II (lack of donor bladder filling). Although TTTS stages are based on clinical observations, it is clear that not all pregnancies follow the consecutive pattern of stage I through IV. Simulation of donor stage III preceding stage II required conditions of severe TTTS (i.e., a single AV anastomosis without compensating anastomoses, cases with severe polyhydramnios, or a small placental fraction). Thus stage III preceding stage II is prognostic for severe cases of TTTS. Clinically, these cases occur infrequently.

Interestingly, our simulations suggest that under conditions of high blood viscosity and severe blood flow redistribution, recipient middle cerebral arterial flow nevertheless may be normal. This is the result of two simultaneous pathological mechanisms that affect the pulsations in opposite directions, namely, reduced cerebral vascular resistance and increased blood viscosity. Reduced cerebral vascular resistance reduces the reflection of the pulsatile blood flow against the brain vascular bed; hence, both the pulse amplitude and the mean flow in the middle and anterior cerebral arteries increase (48).
vascular resistance but reduces the mean flow through the brain as well as the amplitudes of arterial pulsations. Thus, in our model, the degree of severity of the recipient’s condition is not reflected by abnormal cerebral arterial pulsations.

Our model has several limitations. First, we included only the fetal arterial circulation to simulate stage III TTTS in donor twins, obviously with a limited number of arteries and organs and an estimated flow distribution (20, 32). Because we have used our previous pulsatile model (48), the same limitations as previously apply. One important simplification is the fixed distribution of the combined cardiac output, which, in the in vivo situation, changes during gestation (38). A model analysis with flow distribution depending on gestational age was, however, included in the sensitivity analysis (see below). Second, our model simulates a highly complex and still incompletely understood syndrome that affects many parameters of pathophysiology in both fetuses, often in opposite ways, and at different points in time. Therefore, as discussed previously (43, 46, 50), we were sometimes forced to include a simplified and at times even empirical or pragmatic description of fetal pathophysiological mechanisms. Examples are described below.

First, the influence of the blood viscosity on the placental resistance was not considered, where low blood viscosity in the donor twin has not been simulated to reduce the placental resistance. This results from two opposite and simultaneous mechanisms, both of which increase the placental resistance, i.e., a reduced number of cotyledonic capillaries as well as delayed villous maturations (52). Second, other examples include pragmatic choices of parameter development in mechanisms that are essentially correct but not known in sufficient detail: 1) the placental resistance is increased by excess concentrations of RAS and increased amniotic fluid pressures; 2) hypovolemia and growth retardation reduces the production of elastin in arterial walls, which increases the Young’s moduli, and 3) hypertension causes an increased thickness of recipient arterial walls. Third, possible differences in diameter and length of arterial segments as a consequence of abnormal donor and recipient development were not accounted for, because differences in linear dimensions are much smaller than in, for example, blood volume, i.e., length/diameter develop proportional to the one-third power of volume. Fourth, circulatory adaptations such as cardiac hypertrophy as a response to the increased preload in the recipient twin due to volume loading have not been accounted for, resulting in a somewhat lower combined cardiac output for recipients compared with clinical observations (5).

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<th>Gestation (weeks)</th>
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Fig. 4. Model flow waves for case 1 (single AV) in the distal umbilical artery (UA) and middle cerebral artery (MCA) for donor and recipient twins as a function of gestational age. Normal flows are indicated with dashed lines. The predicted staging sequence is I, III(D), II, and IV.

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We performed a sensitivity analysis. First, varying the maximal hematocrit upregulation between zero and fivefold caused slight differences in donor blood viscosity. Increased hematocrit upregulation of more than threefold in case 1 prevented early development of abnormal umbilical artery flow in the donor, i.e., before anuria. In the recipient, upregulation caused a strongly increased viscosity that reduced the placental flow. The staging sequence remained unchanged for hematocrit upregulation of threefold or less. In cases 2 and 3, increased hematocrit increased both donor and recipient blood viscosities, but without altering the staging sequence. Second, the influence of amniotic fluid pressure in cases 2 and 3, with $k_{H} = 1$ and $k_{H} = 5$ in Eq. 14, respectively, increased the placental resistance 1.2- and 1.9-fold at 12 mmHg amniotic fluid pressure (at 22 wk) and 1.6- and 3.8-fold at 16–17 mmHg (32 wk). The overall result of increased placental resistance due to $k$ variation as illustrated by cases 2 and 3 is earlier onset of abnormal donor umbilical artery flows and occurrence of abnormal umbilical flows in the recipient when $k$ was 4 or higher. Third, excluding changes in vessel wall thickness and stiffness, and, fourth, excluding changes in brain resistance, produced the normal staging sequence in cases 1 and 2 and unchanged staging in case 3. Fifth, we included that a percentage of the combined cardiac output, depending on gestation, enters the pulmonary circulation (38). This part of the combined cardiac output was removed from the ascending aorta flow. In addition, placental flow and descending aorta flow were modified according to clinical measurements (13, 14) to respectively 25 and 50% of the combined cardiac output, retaining ~3% that enters each kidney as measured by Guettouche et al. (20). To account for the change in pulmonary flow, we varied carotid artery flow between 20 and 31% during gestation. As a result of the modified flow distribution, abnormal umbilical artery flows presented earlier, leaving the staging sequence in cases 1 and 3 unchanged. In case 2, however, onset of absent end-diastolic flow in the distal umbilical artery presented earlier than donor twin anuria. Overall, however, severe cases present with abnormal flows in the umbilical artery earlier. Interestingly, therefore, subtle differences in fetal parameters, within natural physiological variation, cause large variability in TTTS staging, confirming that clinical TTTS presentation often is perceived as widely variable and at times unpredictable.

In conclusion, our mathematical model of TTTS is the first that describes the sequence of TTTS stages I, II, III, and IV. The model explains the more common finding of donor vs. recipient stage III TTTS and predicts that the majority of TTTS pregnancies progresses in the normal consecutive staging sequence I through IV, but some have an abnormal sequence, i.e., donor stage III preceding stage II. These findings may be applied to the prospective assessment and management of TTTS pregnancies, providing clinicians with insight into both pathophysiology and prognosis, and aiding in guiding therapeutic decisions.

**Perspectives**

Monozygotic twins result from embryonic splitting of a fertilized ovum producing identical twins in two amniotic sacs,
although often, i.e., in 75% of cases, competing for one monochorionic placenta. Monochorionic twin placentas virtually always include vascular anastomoses, which may result in TTTS, from a chronic net fetofetal transfusion from donor to recipient twin, with significant cardiovascular consequences to either or both twins. For clinical management and prediction of outcome, TTTS has been categorized into four stages of worsening severity: stage I exhibits oligo- and polyhydramnios; stage II includes lack of donor bladder filling; stage III includes abnormal umbilical flows in either twin; and stage IV includes congestive cardiac failure and hydrops in the recipient. Stage III likely is the most complex of these, because it refers to abnormal umbilical arterial or venous pulsations in either or both twins. So far, the underlying pathophysiology of these abnormal pulses in the donor or recipient, as well as the order of appearance of the various stages, has not been identified. Therefore, we present our mathematical model on abnormal donor and recipient umbilical arterial pulsations, which enables an improved understanding of the TTTS pathophysiology and may identify the sequence of events that determines the progression of TTTS stages as well as the efficacy and outcome of TTTS therapies.

APPENDIX: OVERVIEW OF NONPULSATILE TTTS MODEL

The first part of the model describes the normal physiology of fetal and amniotic fluid development. The second part incorporates the consequences of the net fetofetal transfusion of blood and blood constituents along the anastomoses. The growth equations of donor and recipient blood volumes are the essential equations. Growth of fetal total body fluid volume, TBF, together with the interstitial and intracellular volumes, $V_{\text{Inter}}$ and $V_{\text{Intra}}$, as follows:

$$V_{\text{b}} = TBF - V_{\text{Inter}} - V_{\text{Intra}} \quad (A1)$$

Normal growth of the fetal total body and amniotic fluids is caused by the net transplacental fluid flow from the maternal to the fetoplacental circulation. We described this flow by Starling forces as the difference between the fetal and maternal hydrostatic ($P_{\text{fet}}$ and $P_{\text{mat}}$) and colloid osmotic pressure ($COP_{\text{fet}}$ and $COP_{\text{mat}}$) gradients in the intervillous space. Thus

$$\frac{dTBF}{dt} = \text{TransPlacenta} - \frac{dV_{\text{amn}}}{dt} \quad (A2)$$

TransPlacenta = $L_{\text{pl}} \cdot \{[P_{\text{mat}} - (P_{\text{amn}} + P_{\text{cap}})] - (COP_{\text{mat}} - COP_{\text{amn}})\}$

$$\quad (A3)$$

Including the net fetofetal transfusion ($I_{\text{net}} = I_{\text{AV}} - I_{\text{VA}} - I_{\text{AA}} - I_{\text{VV}}$), growth of fetal blood volumes is described from Eqs. A1 and A2 as

$$\frac{dV_{\text{b}}}{dt} = \left(\text{TransPlacenta} - \frac{dV_{\text{amn}}}{dt} - \frac{dV_{\text{Inter}}}{dt} - \frac{dV_{\text{Intra}}}{dt}\right) \pm I_{\text{net}} \quad (A4)$$

The plus sign is the recipient equation, the minus sign is the donor equation. The rate of change of the amniotic, interstitial, and intracellular fluid volumes is given by

$$\frac{dV_{\text{amn}}}{dt} = U + L - S - IM \quad (A5)$$

$$\frac{dV_{\text{Inter}}}{dt} + \frac{dV_{\text{Intra}}}{dt} = \text{TransVascular} - \text{Lymph} \quad (A6)$$

where $U$ is urine production, $L$ is lung secretion, $S$ is swallowing, and $IM$ is the intramembranous flow. Interstitial and intracellular volumetric growth was modeled by Starling forces between the vascular

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Fig. 6. Model flow waves for case 3 (AV, VA, and AA; $k = 5$ in Eq. 15) in the distal UA and MCA for donor and recipient twins as a function of gestational age. Normal flows are indicated with dashed lines. The predicted staging sequence is I, III(D), II, III(R), and IV.
and the interstitial compartment, comparable to Eq. A3, and including the lymph flow from the interstitial to the vascular compartment. To separately calculate the interstitial volume, we assumed the rate of change of intracellular fluid is its normal rate of change times the volume of the interstitial compartment. The lymph flow from the interstitial to the vascular compartment is calculated similarly. To separate the lymph flow from the lymphatic system, we assumed the rate of change of the lymph volume, which is the lymph flow from the interstitial to the vascular compartment. To separate the lymph flow from the lymphatic system, we assumed the rate of change of the lymph volume, which is the lymph flow from the interstitial to the vascular compartment. To separate the lymph flow from the lymphatic system, we assumed the rate of change of the lymph volume, which is the lymph flow from the interstitial to the vascular compartment. 

Changes to the arterial and venous blood volumes, which is the correct description included in the numerical code. These changes produce new pressures, osmoles, colloids, and RAS in the vascular system. The changes in the arterial and venous blood volumes are incorporated in control functions of U and L, and amniotic fluid volumes are added equations for blood hematocrit (Eq. 6). The ratio term at the right-hand side assures that it becomes 1 at t = 40 wk. Anastomotic resistances at 40 wk, based on their length and diameters, are one of the input parameters in the model. 

We used simple algebraic descriptions of the normal values of all model parameters, summarized in tables in our previous reports (Table 4 of Ref. 50, Table 1 of Ref. 43, Table 3 of Ref. 46). Also, we used (other) simple algebraic relations to express the abnormal development of various parameters, divided by their normal values, vs. another parameter, also divided by its normal value, taking these relations independent of gestation. Nevertheless, gestation is included, because the normal values of the parameters depend on gestation. An example is abnormal arterial and venous blood pressures vs. abnormal blood volumes (i.e., Fig. 2 of Ref. 46). Input parameters in the model are vascular anastomotic radii at 40 wk, anastomotic lengths of 15 cm at 40 wk, the degree of placental sharing between donor and recipient twin, and the amniocidity.

In our first model (50), an initial condition was that all donor and recipient parameters are zero at zero gestational age, the moment of embryonic splitting. The later models, including the present one, use the output of the first model at 11 wk as well as added estimated or measured values of all other parameters. Thus all parameters at 11 wk are known, including the Inet. A short time step later, a small blood volume, equal to the product of Inet and the time step, is subtracted from the donor blood volume and added to that of the recipient. These new blood volumes also generate new pressures, osmoles, colloids, Inet, RAS, and other parameters, at that slightly later gestational age. This process continues, beginning at 11 wk and ending at 40 wk.

The 26 coupled differential equations were solved by a standard forward finite-difference method, using a time step of 10^−4 wk, which is comparable to 0.6 s. The computer program is written in Delphi 5.0 (Borland Enterprise, Cupertino, CA). One computer run, from 0 to 40 wk, took about 9 min on a Pentium 4 GHz personal computer, and an additional 2.5 min for each run of the pulse model (thus simulating the pulse propagation waveforms for 5 gestational ages, as in Fig. 4, took 21.5 min).

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