Modeling a hydropic recipient twin in twin-twin transfusion syndrome

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Wijngaard, Jeroen P. H. M. van den, Asli Umur, Raymond T. Krediet, Michael G. Ross, and Martin J. C. van Gemert. Modeling a hydropic recipient twin in twin-twin transfusion syndrome. Am J Physiol Regul Integr Comp Physiol 288: R799–R814, 2005. First published November 11, 2004; doi:10.1152/ajpregu.00635.2004.—We developed a mathematical model of twin-twin transfusion syndrome (TTTS) that includes a hydropic recipient twin, adding interstitial and intracellular fluid compartments, fetal congestive cardiac failure, and the dynamics of renin-angiotensin system (RAS) mediators to our previous TTTS model. Ten differential equations for each twin, coupled by the net fetofetal transfusion of blood and blood components, i.e., colloids, osmoles, and RAS mediators, describe the development of fetal arterial and venous blood volumes, blood osmolality and colloid osmotic pressure (COP), interstitial fluid volume and COP, intracellular fluid volume, amniotic fluid volume and osmolality, and RAS mediator concentration. We included varying placental anastomoses, placental sharing, and amnionicity. The 20 differential equations were solved numerically from 0 to 40 wk with a 0.6-s time step. Consistent with clinical experience, model predictions are as follows. Unidirectional arteriovenous anastomoses and arteriovenous anastomoses inadequately compensated by oppositely directed anastomoses cause severe TTTS that includes a hydropic recipient. Adequately compensated arteriovenous anastomoses simulated TTTS without hydrops. The probability that oppositely directed anastomoses prevent onset of a hydropic recipient after TTTS onset, i.e., the largest interval between onset of TTTS and onset of hydrops in the recipient, was best for a venovenous anastomosis, closely followed by an arterioarterial and finally an oppositely directed arteriovenous anastomosis. Hydropic recipients have decreased amniotic fluid volume. Unequal placental sharing and amnionicity modify hydrops onset. In conclusion, our model simulates a sequence of events that results in a hydropic recipient twin. Additional potential sequelae of TTTS are absence of donor bladder filling (TTTS stage II), additional abnormal umbilical flow in either twin (stage III), and congestive heart failure followed by hydrops in the recipient twin (stage IV). The end stage of TTTS is intrauterine fetal demise of either twin (stage V). Despite current opinions regarding the etiology and management of TTTS, controversy remains as to the optimal management of monozygotic twins, depending on the stage of TTTS severity and gestational age.

Mathematical TTTS models have been developed because study of human TTTS pathophysiology is virtually impossible. TTTS is rare, TTTS lacks an animal model, clinical presentation varies strongly and unpredictably, and the pathophysiology is complex. The first model, developed by Talbert et al. (50), consisted of two identical pulsating fetoplacental circulations, comparable to 28 wk of gestation, that are suddenly linked by unidirectional or bidirectional AV and by AA anastomoses (51). This model showed for the first time a chain of events that links net fetofetal transfusion to onset of the oligoanhydramnios vs. polyhydramnios sequence, the current definition of TTTS. However, this model was limited to a 28-wk pregnancy and required the fetuses to have equal shares of the combined placenta.

Our group developed two generations of TTTS models (57, 61), all based on nonpulsating fetoplacental circulations but including changes associated with fetoplacental growth. The first model (61) demonstrated that TTTS results from the normal development of vascular anastomoses vs. normal fetal

monochorionic twins; placental anastomoses; hydrops; cardiac failure; renin-angiotensin system

Address for reprint requests and other correspondence: M. J. C. van Gemert, Laser Center, Academic Medical Center, Univ. of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands (E-mail: m.j.vangemert@amc.uva.nl). The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
growth. The consequential TTTS pathophysiology is that AV fetofetal transfusion develops at a rate in excess of fetal growth, implying that the donor effectively loses blood volume vs. the opposite outcome for the recipient. The model explained why TTTS develops in some but not all monochorionic placentas. It predicted that a constant fetal discordance, even if large, implies that TTTS is unlikely to develop, a finding confirmed clinically (59). However, it lacked amniotic fluid dynamics, an essential element in the clinical definition of TTTS.

Subsequently, this model was extended (57) to include amniotic fluid dynamics, offering a description for TTTS stage I and II severity. It has now been shown that the placental angioarchitecture controls the onset and development of the pathological outcomes of TTTS (56), as well as the efficacy of TTTS therapy that includes amniotic fluid manipulation (58, 60). However, the model offers no description of increased TTTS severity stages. Although stage IV TTTS is notorious for high levels of mortality and morbidity, its underlying pathophysiology and response to therapy are incompletely understood. Stage IV TTTS includes an abnormal accumulation of interstitial fluid volume, congestive cardiac failure due to volume overload in the recipient, and the dynamics of the interstitial fluid volume, congestive cardiac failure due to volume overload.

The aim of this report is to present our third-generation model of TTTS, allowing the development of a hydropic recipient twin. To our previous model we have added growth of the interstitial fluid volume, congestive cardiac failure due to volume overload in the recipient, and the dynamics of the renin-angiotensin system (RAS).

METHODS

Our previous model (57) included 10 differential equations, 5 for each twin, to describe development of the volumes of fetal blood and amniotic fluid, the colloid osmotic pressure (COP) and osmolality of fetal blood, and the osmolality of the amniotic fluid. To include in this model fetal hydrops in the recipient, which develops because of elevated venous and hence capillary pressure caused by congestive cardiac failure, requires adding several other parameters. First, growth of the fetal interstitial fluid volume (dVInter/dt) and intracellular volume (dVIntra/dt) and increase of the colloid concentration of the interstitial fluid (dColloidsInter/dt) are essential to simulate hydrops. Second, allowing pathologically increased recipient arterial and venous blood pressures, necessary for producing congestive heart failure, requires including the dynamics of the RAS mediators (dRAS/dt). Third, congestive heart failure of the recipient twin implies excess blood volume in its venous circulation, which is caused by forward heart failure combined with the continuing net fetofetal transfusion of blood from donor to recipient along the anastomoses. Therefore, growth of the fetal total blood volume was separated into individual arterial and venous blood volumetric growth (dVart/dt and dVv/dt). Fourth, changes in amniotic fluid volume (dVamn/dt) and osmolality (dOsmamn/dt) and fetal blood osmolality (dOsmfet/dt) were basically included as in our previous model (57). Fifth, fetal cardiac output and venous return, as well as interstitial fluid pressures, are derived from flow-pressure or pressure-volume relations, similar to the blood pressure-volume relation used previously (61, 57).

Table 1 summarizes the parameters and their units used in the equations, and Table 2 summarizes the 10 parameters that are included in the present model for both twins to constitute the 20 differential equations. We use subscripts N and R to denote a normal, uncompromised fetus and either donor or recipient twin, respectively.

This analysis is organized such that deviations from normal development of fetal physiological parameters, e.g., changes in cardiac output due to changes in arterial and venous pressures, are shown in Figs. 1–9. The associated mathematical expressions used in the numerical code are presented in Table 3, including those of normal physiological behavior. In this way we hope that readers wishing to copy our model will be able to do so and that the paper will be as readable as possible.

Outline of Model

As before (57), we first use the model to simulate the normal physiology of fetal and amniotic fluid development and subsequently incorporate the effects of net fetofetal transfusion of blood and blood constituents, such as colloids, osmoles, and RAS mediators, from donor to recipient along the placental anastomoses.

The model of normal physiology assumes that volumetric growth of the amniotic fluid (dVamn/dt) and the fetal total body fluid (dTBF/dt) are caused by the net transplacental fluid flow (TransPlacenta) (50, 57) from the maternal blood to the fetoplacental circulation

\[
\text{TransPlacenta} = \frac{d\text{TBF}}{dt} + \frac{d\text{Vamn}}{dt} \quad (1)
\]

where \(L_p\) is the net transplacental filtration coefficient, \(P_{mat}\) is the mean arterial pressure of inter villous maternal blood, \(P_{amn}\) is the transmitted amniotic fluid pressure, \(P_{fet}\) is the fetoplacental capillary blood pressure, \(COP_{mat}\) is the COP of maternal blood and \(COP_{fet}\) is the COP of the fetal blood. Normal values of the parameters are summarized in Table 3. Because the normal pressures and net transplacental fluid flow for all gestational ages are known, \(L_p\) can be calculated and used subsequently for the donor and recipient twins (57). Furthermore, the rate of change of the amniotic fluid volume is given by

\[
\frac{d\text{Vamn}}{dt} = U + L - S - \text{IM} \quad (2b)
\]

where U is urine production, L is lung secretion, S is swallowing, and IM is the intramembranous flow, taken, identical to the previous model (57), as

\[
\text{IM}(t) = S_{IM} \cdot L_{IM} \cdot \left[ (P_{amn} - P_{fet}) - (\pi_{amn} - \pi_{fet}) \right] \quad (2c)
\]

where \(S_{IM}\) is the combined surface of the placenta at the fetal side, fetal skin, and umbilical cord as a function of gestation, \(L_{IM}\) is the filtration coefficient of the intramembranous pathway, \(P_{amn}\) is amniotic fluid pressure, and \(P_{fet}\) is fetal capillary blood pressure. The product has been determined as before (see Eq. M7e, Table 3). Parameters \(\pi_{amn}\) and \(\pi_{fet}\) denote the osmotic pressures of the amniotic fluid and fetal blood, respectively, using 1 mosmol/l.

In the new model, the fetal total body fluid (TBF) includes a blood (Vb), an interstitial (VInter), and an intracellular (VIntra) fluid compartment

\[
\text{TBF} = V_b + V_{\text{Inter}} + V_{\text{Intra}} \quad (3)
\]

Combining Eqs. 1 and 3 yields the growth of the total fetal blood volume as

\[
\frac{dV_b}{dt} = \frac{d\text{TBF}}{dt} - \frac{d\text{VIntra}}{dt} - \frac{d\text{VInter}}{dt} \quad (4)
\]

\[
= \text{TransPlacenta} - \frac{d\text{Vamn}}{dt} - \frac{d\text{VInter}}{dt} - \frac{d\text{VIntra}}{dt}
\]
Table 1. Overview of parameters used in model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Parameter Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA, AV, VA, VV</td>
<td>ml/wk</td>
<td>Arterioarterial, arteriovenous, venaarterial (opposite AV), and venovenous anastomosis</td>
</tr>
<tr>
<td>CardiacOutput</td>
<td>mmol</td>
<td>Fetal cardiac output</td>
</tr>
<tr>
<td>Colloidsarter</td>
<td>mmol</td>
<td>No. of colloids in fetal circulation</td>
</tr>
<tr>
<td>COParter</td>
<td>mmHg</td>
<td>Colloid osmotic pressure of fetal blood</td>
</tr>
<tr>
<td>COPinter</td>
<td>mmHg</td>
<td>Colloid osmotic pressure of fetal interstitial compartment</td>
</tr>
<tr>
<td>COPmat</td>
<td>mmHg</td>
<td>Colloid osmotic pressure of maternal blood</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>Donor (subscript)</td>
</tr>
<tr>
<td>ExColloidsarter</td>
<td>mmol/l</td>
<td>Excess colloid concentration in fetal vascular compartment</td>
</tr>
<tr>
<td>ExColloidsinter</td>
<td>mmol/l</td>
<td>Excess colloid concentration in fetal interstitial compartment</td>
</tr>
<tr>
<td>ExRAS</td>
<td>pg/ml</td>
<td>Excess RAS concentration</td>
</tr>
<tr>
<td>IM</td>
<td>ml/wk</td>
<td>Intramembranous flow</td>
</tr>
<tr>
<td>lext</td>
<td>ml/wk</td>
<td>Net fetofetal transfusion from donor to recipient (AV-VA-AA-VV)</td>
</tr>
<tr>
<td>Kf</td>
<td>ml·wk⁻¹·mmHg⁻¹</td>
<td>Fetal vascular-interstitial filtration coefficient</td>
</tr>
<tr>
<td>L</td>
<td>ml/wk</td>
<td>Lung fluid secretion</td>
</tr>
<tr>
<td>Lf</td>
<td>ml·wk⁻¹·mmHg⁻¹</td>
<td>Filtration coefficient for intramembranous pathway</td>
</tr>
<tr>
<td>Lp</td>
<td>ml·wk⁻¹·mmHg⁻¹</td>
<td>Fetal transplacental filtration coefficient</td>
</tr>
<tr>
<td>Lymph</td>
<td>ml/wk</td>
<td>Lymph clearance from interstitial to vascular space</td>
</tr>
<tr>
<td>N</td>
<td></td>
<td>Normal, uncompromised fetus (subscript)</td>
</tr>
<tr>
<td>Osman</td>
<td>mosmol/kgH₂O</td>
<td>Osmolality of amniotic fluid</td>
</tr>
<tr>
<td>Osfet</td>
<td>mosmol/kgH₂O</td>
<td>Osmolality of fetal blood</td>
</tr>
<tr>
<td>Parter</td>
<td>mmHg</td>
<td>Fetal arterial pressure</td>
</tr>
<tr>
<td>Pes</td>
<td>mmHg</td>
<td>Amniotic fluid pressure</td>
</tr>
<tr>
<td>Pf</td>
<td>mmHg</td>
<td>Fetal capillary blood pressure</td>
</tr>
<tr>
<td>Pinter</td>
<td>mmHg</td>
<td>Interstitial fluid pressure</td>
</tr>
<tr>
<td>Pmat</td>
<td>mmHg</td>
<td>Maternal placental capillary blood pressure</td>
</tr>
<tr>
<td>Pven</td>
<td>mmHg</td>
<td>Fetal venous pressure</td>
</tr>
<tr>
<td>R</td>
<td>mmHg·ml⁻¹·wk</td>
<td>Fetal peripheral resistance to blood flow</td>
</tr>
<tr>
<td>τ</td>
<td></td>
<td>Recipient (subscript)</td>
</tr>
<tr>
<td>RAS</td>
<td>pg/ml</td>
<td>Concentration of renin-angiotensin system mediators</td>
</tr>
<tr>
<td>S</td>
<td>ml/wk</td>
<td>Gating mechanism</td>
</tr>
<tr>
<td>Ssurf</td>
<td>m²</td>
<td>Combined surface of fetal placenta, fetal skin, and umbilical cord</td>
</tr>
<tr>
<td>t, t₀, t₁, t₂, t₃</td>
<td>wk</td>
<td>Gestational age</td>
</tr>
<tr>
<td>TBF</td>
<td>ml</td>
<td>Total body fluid volume</td>
</tr>
<tr>
<td>TransPlacenta</td>
<td>ml/wk</td>
<td>Transplacental fluid flow</td>
</tr>
<tr>
<td>TransVascular</td>
<td>ml/wk</td>
<td>Transvascular fluid flow</td>
</tr>
<tr>
<td>U</td>
<td>ml/wk</td>
<td>Urine production</td>
</tr>
<tr>
<td>Varter</td>
<td>ml</td>
<td>Fetal arterial blood volume</td>
</tr>
<tr>
<td>Vf</td>
<td>ml</td>
<td>Fetal venous blood volume</td>
</tr>
<tr>
<td>VfVen</td>
<td>ml</td>
<td>Volume of excess venous blood</td>
</tr>
<tr>
<td>VfVenExcess</td>
<td>ml</td>
<td>Fetal blood flow entering into the veins</td>
</tr>
<tr>
<td>VfIntra</td>
<td>ml</td>
<td>Intracellular fluid volume</td>
</tr>
<tr>
<td>VfInter</td>
<td>ml</td>
<td>Interstitial fluid volume</td>
</tr>
<tr>
<td>X</td>
<td></td>
<td>Represents donor (d) or recipient (r) (subscript)</td>
</tr>
<tr>
<td>σ</td>
<td></td>
<td>Osmotic reflection coefficient (0.8 used in model)</td>
</tr>
<tr>
<td>τ</td>
<td>wk</td>
<td>Time constant used in decay of colloids and RAS</td>
</tr>
</tbody>
</table>

Equations 3 and 4 imply that the fetal blood volume has no fixed relation any more to the fetal total body fluid volume [in the previous model (57), Vb was 10% of TBF].

Interstitial volumetric growth was modeled with Starling’s forces for capillary filtration of flow between the vascular and the interstitial compartment (44, 52). The transvascular flow (TransVascular) from the fetal blood to the interstitial fluid is driven by the hydrostatic pressure gradient (Pfet - Pinter) minus the COP gradient (COPfet - COPinter)

\[ \text{TransVascular} = K_f \cdot \left( [P_{\text{fet}} - P_{\text{inter}}] - \sigma (COP_{\text{fet}} - COP_{\text{inter}}) \right) \]  (5)

The osmotic reflection coefficient (σ) of the vascular wall for the blood proteins has been chosen as 0.8 (21). Kf is the hydraulic conductivity coefficient for the total vascular surface available for filtration. The dependence of Kf on gestational age for a normal fetus can be calculated with measured values for the right-hand-side parameters and measured values of TransVascular with normal interstitial and intracellular volumetric growth as well as normal lymph flow, combined with Eq. 6 below. Subsequently, these Kf values are used for donor and recipient twins.

Normal interstitial fluid volume was estimated to develop linearly from 54% at 11 wk of gestation to 25% of total fetal body fluid volume at 40 wk (44). Changes in the fetal interstitial space (dVinter/dt) follow from

\[ \frac{dV_{\text{inter}}}{dt} = \text{TransVascular} - \text{Lymph} - \frac{dV_{\text{intra}}}{dt} \]  (6)

where Lymph denotes the lymph flow from the interstitial to the vascular compartment. It was assumed that the endogenous colloids that leak from the blood into the interstitial space are transported back into the fetal circulation via the lymph flow. Normal lymph flow was estimated as 0.25 ml·min⁻¹·kg⁻¹ (12).

Normal intracellular volume was estimated to increase linearly from 36% at 11 wk to 65% of total fetal body fluid at 40 wk of
gestation (44). Experimentally estimated values for intracellular, interstitial, and total body fluid volumes are slightly lower than used in our model because other fluids, e.g., cerebrospinal fluid, are measured separately (44). However, for modeling purposes, our values are adjusted so that, according to Eq. 3, the volumetric sum of fetal blood, interstitial, and intracellular compartments equals the total body fluid volume. We assumed changes in intracellular fluid proportional to changes in the fetal blood volume.

Subsequently, we incorporated the effects of the net fetofetal transfusion (Inet), defined as the net transfusion of blood from the donor to the recipient along the anastomoses, i.e., AV-VA-AA-VV transfusion. As before (61, 57), this blood exchange increases the normal rate of increase of the fetal blood volume for the recipient twin and reduces the normal rate of the fetal blood volumetric increase for the donor twin. Comparable to our previous models (61, 57), overall changes of fetal blood volume become the anticipated normal fetal blood volumetric growth (Eq. 4) plus or minus the net fetofetal transfusion

\[
\frac{dV_b}{dt} = \text{TransPlacenta} - \frac{dV_{amn}}{dt} - \frac{dV_{Intra}}{dt} - \frac{dV_{Inter}}{dt} + I_{net} \tag{7}
\]

The plus sign before \(I_{net}\) represents the equation for the recipient and the minus sign the equation for the donor.

**Detailed Description**

**Intracellular fluid volume.** We scaled changes in the fetal intracellular volume (\(dV_{Intra}/dt\)), to the fetal blood volume (\(V_{b}\)), so

\[
\frac{dV_{Intra}}{dt} = \frac{V_{Intra}}{V_b} \cdot \frac{dV_b}{dt} \tag{8}
\]

where \(d = \text{d} \) or \(r \) and \(N = \text{normal} \).

**Cardiac output and venous return.** Venous return is normally identical to the fetal cardiac output. Therefore, for a normal fetus, overall vascular resistance to flow \(R_N\), as dependent on gestational age, can be calculated, dividing the normal difference between fetal arterial and venous pressures by the normal venous return

\[
R_N = \frac{P_{Art} - P_{Vamn}}{V_{VenExcess}} \tag{9}
\]

Venous return for either donor or recipient can subsequently be calculated from the actual pressure difference between the fetal arteries and the veins divided by resistance \(R_N\). The relation for \(R_N\) directly follows from Eqs. M3d and M6 in Table 3.

It has been demonstrated that the fetal heart operates near the maximal cardiac output plateau in the Frank-Starling curve (20, 22, 23). Furthermore, it has also been shown that fetal stroke volume of both ventricles increases with increasing atrial pressure, which is a consequence of increased preload. However, work from Gilbert (19) and also Thornburg and Morton (53, 54) indicated cardiac reserve to be extremely limited compared with adult physiology. In fetal lambs, Thornburg and Morton (53, 54) measured biventricular cardiac output sensitivity as depending separately on afterload and preload. We fitted their data, expressed by factors \(f_{AftLoad}\) and \(f_{Preload}\) in Eqs. M10 (Table 3), assuming, first, on afterload increase, that the fetal heart rate does not change significantly and biventricular output does not enhance significantly because of preload increase and, second, on preload increase, that the fetal cardiac output has a Frank-Starling response to venous blood pressure up to a value that exceeds the normal pressure, which is chosen arbitrarily at 1.1 times normal, and experiences a reduced cardiac output increase at higher venous pressures.

CardiacOut\(_X\) = CardiacOut\(_N\) \cdot f_{AftLoad} \cdot f_{Preload} \tag{10}

where \(X = \text{d} \) or \(r \). We used a normal fetal cardiac output of 425 ml/min \(^{-1}\) \(\cdot \) kg \(^{-1}\) as measured by Mielke and Benda (37). The behaviors of \(f_{AftLoad}\) and \(f_{Preload}\) are shown in Fig. 1 and summarized in Eqs. M10 (Table 3).

In the new model, the venous return and cardiac output are calculated separately. At onset of recipient cardiac failure, the cardiac output becomes smaller than the venous return. Then the difference between the two flows determines growth of the excess blood volume that stays behind in the venous circulation (\(dV_{VenExcess}/dt\)),

\[
\frac{dV_{VenExcess}}{dt} = \text{VenousReturn}_X - \text{CardiacOut}_X \tag{11}
\]

\(V_{VenExcess}\) is added to the venous blood volume and subtracted from the arterial blood volume.

**Arterial and venous blood volumes.** In the previous model, the ratios of arterial and venous blood volumes divided by the total blood volume were constant. However, in the current model the blood volume ratios are variables. Combining Eqs. 7 and 11, changes in both the arterial and venous blood volumes for donor and recipient twins can be written as (leaving out subscript \(X\) in all parameters)

\[
\frac{dV_{bArt}}{dt} = -V_{VenExcess}
\]

\[
\frac{dV_{bVen}}{dt} = V_{VenExcess}
\]

where \(V_b = V_{bArt} + V_{bVen}\). Blood pressure vs. blood volume relations. Previously, the blood volume of the recipient twin did not exceed 1.5 times the normal blood volume. Therefore, arterial hypertension also remained limited. In the current model, vascular compliance for high blood pressures, i.e., those exceeding 1.1 times normal, was modeled differently at

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Table 2. Ten model parameters for each twin that constitute twenty differential equations of present model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Parameter Description</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>dV_{Art}/dt</td>
<td>ml/wk</td>
<td>Growth of fetal arterial blood volume</td>
<td>12a</td>
</tr>
<tr>
<td>dV_{Ven}/dt</td>
<td>ml/wk</td>
<td>Growth of fetal venous blood volume</td>
<td>12b</td>
</tr>
<tr>
<td>dV_{Intra}/dt</td>
<td>ml/wk</td>
<td>Growth of fetal intracellular blood volume</td>
<td>6</td>
</tr>
<tr>
<td>dV_{Inter}/dt</td>
<td>ml/wk</td>
<td>Growth of fetal interstitial fluid volume</td>
<td>8</td>
</tr>
<tr>
<td>dV_{amn}/dt</td>
<td>ml/wk</td>
<td>Growth of amniotic fluid volume</td>
<td>2b</td>
</tr>
<tr>
<td>dColloidsIntra/dt</td>
<td>mmol/wk</td>
<td>Growth of fetal blood colloid concentration</td>
<td>17g</td>
</tr>
<tr>
<td>dOsmamn/dt</td>
<td>mosmol/kg H(_2)O (^{-1}\cdot)wk (^{-1})</td>
<td>Growth of fetal blood osmolality</td>
<td>Ref 57, Eq. 15</td>
</tr>
<tr>
<td>dOsmfet/dt</td>
<td>mosmol/kg H(_2)O (^{-1}\cdot)wk (^{-1})</td>
<td>Growth of amniotic fluid osmolality</td>
<td>Ref 57, Eq. 5</td>
</tr>
<tr>
<td>dColloidsInter/dt</td>
<td>mmol/wk</td>
<td>Growth of fetal interstitial fluid colloids</td>
<td>17h</td>
</tr>
<tr>
<td>dRAS/dt</td>
<td>pg/ml (^{-1}\cdot)wk (^{-1})</td>
<td>Growth of fetal blood renin-angiotensin system concentration</td>
<td>22e</td>
</tr>
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Table 3. Summary of mathematical expressions used in model for various parameters

<table>
<thead>
<tr>
<th>Expression</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{SN} = 149.0(t/31)^3 )</td>
<td>Normal parameters, blood volume, ml</td>
</tr>
<tr>
<td>( V_{SN} = 95.5 + 39.3 \sqrt{t - 29.1} )</td>
<td>Normal parameters, amniotic fluid volume, ml</td>
</tr>
<tr>
<td>( V_{amn} = 525.6 - 117.2t + 8r^2 - 0.1237r^3 )</td>
<td>Normal parameters, anastomotic resistances, mmHg</td>
</tr>
<tr>
<td>( P_{mat} = 40 )</td>
<td>Normal parameters, amniotic, interstitial, and blood hydrostatic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ttn} = -3(t/40) )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ret} = P_{ven} + (P_{aen} - P_{ven})/3 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ven} = 60(t - 5)/35 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ven} = 7.5(t - 5)/35 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( V_{InterN} = 27.530 - 0.367t + 0.056t^2 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{mat} = 40 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ttn} = -3(t/40) )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ret} = P_{ven} + (P_{aen} - P_{ven})/3 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ven} = 60(t - 5)/35 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( P_{ven} = 7.5(t - 5)/35 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( V_{mat} = 0.0137t^3 - 0.044t^2 + 11.509t - 85.873 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( \log S_0(t) = 0.044t + 1.105 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( \log S_0(t) = 0.044t + 1.105 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( L_N(t) = 0.0005t + 0.0538t^2 - 1.7447t^2 + 23.5t - 112.07 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( S_{min} = 0.588y - 0.6596 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( S_{min} = 0.588y - 0.6596 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
<tr>
<td>( \text{Resist}(t) = \text{Resist}(40 \text{ wk})/(40 - 4)t/(t - 4)^3 )</td>
<td>Normal parameters, colloid osmotic pressures, mmHg</td>
</tr>
</tbody>
</table>

### Actual parameters

**Equation 10**
- \( f_{preload} = (1.22 - 0.22P_{mat}/P_{ven}) \)
- \( f_{preload} = (0.29 + 1.29P_{aen}/P_{ven}) \)
- \( f_{preload} = (1.08 + 0.044P_{aen}/P_{ven}) \)

**Equation 13**
- \( f_{bloodVolume} = 1.247V_{SN}/V_{SN} \)
- \( f_{bloodVolume} = 0.4 + 0.6V_{SN}/V_{SN} \)
- \( f_{bloodVolume} = 12(V_{SN}/V_{SN})^2 - 25.8V_{SN}/V_{SN} + 14.92 \)

**Equation 14**
- \( f_{CO} = 5.5 \)
- \( f_{CO} = -9\text{COPa}/\text{COPN} + 10 \)
- \( f_{CO} = 1 \)

**Equation 16**
- \( f_{volInter} = 1.9 \)
- \( f_{volInter} = -9V_{InterN}/V_{InterN} + 10 \)
- \( f_{volInter} = 1 \)

**Equation 19**
- \( z = (P_{ven} - P_{ttn})/(P_{ven} - P_{ttn}) \)
- \( f_{lymph} = 3.94 \)
- \( f_{lymph} = (0.66 - 0.66z) \)

**Equation 20**
- \( f_y = (10/3)(P_{arx}/P_{aen})^2 - 3(P_{arx}/P_{aen}) + 2/3 \)
- \( f_y = 0 \)
- \( f_{Colloid} = 1 \)
- \( f_{Colloid} = -0.8\text{COPa}/\text{COPN} + 1.8 \)

**Equation 21**
- \( F_{RAS} = 3.1917 \)
- \( F_{RAS} = [5.322.1(P_{arx}/P_{aen})^2 - 8.5154P_{arx}/P_{aen} + 3.40772] \)
- \( F_{RAS} = (-0.05P_{arx}/P_{aen} + 1.05) \)
- \( F_{RAS} = (-0.5P_{arx}/P_{aen} + 1.5) \)
- \( F_{RAS} = 0 \)
larger blood volumes, where the new relations are now continuous in function and derivative. The previous blood pressure vs. blood volume relations (57) were replaced by

\[
\text{Part, ven}_N = \frac{\text{Part, ven}_X}{\text{BloodVolume}^f}\tag{13}
\]

see also Fig. 2 and Eq. M13 (Table 3).

COP of fetal blood and interstitial fluids. The net colloid production in the vascular compartment of each fetus was calculated proportional to the normal colloid production and to the ratio of actual to normal blood volumes, as in the previous model (57). We propose that the condition of the donor twin is essentially similar to the nephrotic syndrome, where large amounts of protein are removed from the vascular compartment by loss in the urine (25, 64). Zanetti et al. (64) speculated that a reduced plasma osmotic pressure regulates albumin production at the hepatocyte level. Thus, to account for the observed upregulation of colloid production in the fetal blood, as assumed to occur at low blood COP, we additionally included a parameter \( f_{\text{COP}} \), which is a function of \( \text{COP}_f \)

\[
\frac{d\text{Colloids}_f}{dt} = \frac{d\text{Colloids}_N}{dt} \cdot \frac{V_{hx}}{\text{COP}_f} \cdot f_{\text{COP}}
\tag{14}
\]

\( f_{\text{COP}} \) is shown in Fig. 3 and expressed in Eq. M14 (Table 3), where \( \text{COP}_X \) follows from

\[
\text{COP}_X = 19.6 \cdot \text{Colloids}_X V_{hx}
\tag{15}
\]

We assume that 1 mmol of colloids per liter equals 19.6 mmHg at 37°C.

We assumed that the normal interstitial fluid colloid osmotic pressure (\( \text{COP}_{\text{Inter}N} \)) grows linearly from 1.38 mmHg at 11 wk of gestation to 5 mmHg at 40 wk, which is similar to the range of experimental values (9). The net colloid production in the interstitial compartment of each twin is calculated similar to that in the blood (Eq. 14), i.e., proportional to the normal colloid production, the fetal blood volume divided by normal, and a function of fetal interstitial size, expressed by parameter \( f_{\text{VolInter}} \)

\[
\frac{d\text{Colloids}_{\text{Inter}X}}{dt} = \frac{d\text{Colloids}_{\text{Inter}N}}{dt} \cdot \frac{V_{hx}}{\text{VolInter}} \cdot f_{\text{VolInter}}
\tag{16}
\]

\( f_{\text{VolInter}} \) is shown in Fig. 4 and represented by Eq. M16 (Table 3). This approach prevents fetal anemia in the donor from leading to an increased interstitial volume, even leading to hydrops, which would contradict clinical observations.

As mentioned previously, in the absence of anastomoses, we assume that the number of colloids entering the fetal interstitium equals the colloids removed by the lymph flow. However, in normal
controls, observations from Kayser and Schoenfeld (28) indicate the ratio of plasma albumin mass and extravascular albumin mass to be 0.7. In addition, albumin loading experiments in mammals showed extravasation of albumin (6, 47) and also protein (36) to be significant. In our model, we pragmatically included the effects of extravasation in the recipient by distributing 33% of the colloids transfused from the donor over the recipient’s vascular compartment and 67% over its interstitial space. Accordingly, 67% of colloids removed from the donor’s circulation by AV transfusion is taken from the donor interstitial space. We were forced to include this type of solution because the control mechanisms involved are unknown. Furthermore, to prevent the donor interstitial COP from decreasing beyond pathological unrealistic values we assumed donor lymphatics to contain no colloids when COPinter is reduced below 0.25 times normal.

Fetofetal transfusion as well as fetal growth may produce colloids in excess of their normal value (ExColloids), expressed as excess millimoles per liter, in both the vascular and interstitial compartments, where

\[
\begin{align*}
\text{ExColloids}_{\text{fet}} &= (\text{COP}_{\text{hx}} - \text{COP}_{\text{hxN}})/19.6 \\
\text{ExColloids}_{\text{inter}} &= (\text{COP}_{\text{interN}} - \text{COP}_{\text{inter}})/19.6
\end{align*}
\]

We assumed such excess colloids to have a finite lifetime and have chosen an exponential decay with a time constant of \(\tau = 10\) wk (which equals a half-lifetime of 7 wk). For albumin, the fractional synthesis rate (the percentage of production compared with the total pool) for healthy controls is reported between 3 and 8% (15, 64), indicating a life span of between 5 and 2 wk. When albumin concentrations significantly surpass the normal concentration, we assume that the fractional synthesis rate is <3%, and therefore the decay of albumin is longer than 5 wk, making the life span close to the value used in the model. Furthermore, \(\tau\) is comparable to the measured fetal red blood cell mean life span of ~9 wk (11).

At gestational age \(t > t_0\), the excess colloids at \(t\), as a consequence of the excess colloids at \(t_0\), follow from

\[
\text{ExColloids}(t) = \text{ExColloids}(t_0) \cdot e^{\frac{(t-t_0)}{\tau}}
\]

Thus the influence at \(t\) of all ExColloids\((t_0)\) at all previous times \(t_0\) follows as

\[
\text{ExColloids}(t) = \int_0^t \text{ExColloids}(t_0) \cdot e^{\frac{(t-t_0)}{\tau}} dt_0
\]

In the model, Eq. 17d is numerically solved as

\[
\text{ExColloids}(t + \delta t) = \text{ExColloids}(t) \cdot e^{\frac{\delta t}{\tau}} \approx \text{ExColloids}(t) \cdot \left(1 - \frac{\delta t}{\tau}\right)
\]

which follows directly from Eq. 17d by substituting \((t + \delta t)\) for \(t\). We used time increment \(\delta t = 10^{-6}\) wk ~ 0.6 s, hence, \(\delta t/\tau < < 1\), required for Eq. 17e to be valid. From Eq. 17e, we derive the rate of change of ExColloids\((t)\) straightforwardly as

\[
\frac{\text{dExColloids}(t)}{\delta t} = \frac{\text{dExColloids}(t)}{\tau} = \frac{-\text{ExColloids}(t)}{\tau}
\]

Thus the differential equations for the colloids in the vascular and interstitial compartments become

\[
\begin{align*}
\frac{d\text{Colloids}_{\text{fet}}}{dt} &= \frac{d\text{Colloids}_{\text{fetN}}}{dt} \cdot \frac{V_{\text{hx}}}{V_{\text{hxN}}} \cdot \text{COP} \\
+ \frac{3}{\tau} \cdot \text{ColloidFetofetalTransfusion}_{\text{hx}} &= - \frac{\text{ExColloids}_{\text{fet}}}{\tau} \cdot V_{\text{hx}} \\
\frac{d\text{Colloids}_{\text{inter}}}{dt} &= \frac{d\text{Colloids}_{\text{interN}}}{dt} \cdot \frac{V_{\text{hx}}}{V_{\text{hxN}}} \cdot \text{COP}_{\text{interN}} \\
+ \frac{3}{2} \cdot \text{ColloidFetofetalTransfusion}_{\text{inter}} &= - \frac{\text{ExColloids}_{\text{inter}}}{\tau} \cdot V_{\text{interN}}
\end{align*}
\]

The recipient equation includes the plus sign and the donor equation the minus sign. Both the first right-hand-side terms denote colloid production, i.e., Eqs. 14 and 16. The last term in Eq. 17g is an addition compared with our previous model (57). The resulting COPs then follow from Eq. 15. The factors 1/3 and 1/(3/2) in the second right-hand-side terms express that colloids transfused by or removed from the donor imply 1/3 is associated with the vascular and 2/3 with the interstitial compartment.

Control of interstitial hydrostatic pressure. Normal interstitial hydrostatic pressure (\(P_{\text{interN}}\)) decreases linearly from a negative −0.83 mmHg at 11 wk of gestation to a value of −3 mmHg at 40 wk. These values are within the range measured by Brace et al. (9) in various mammals. Actual interstitial hydrostatic pressure (\(P_{\text{inter}}\)) depends on the interstitial volume (\(V_{\text{inter}}\)) and the compliance of the interstitial space. After hemorrhage and intravenous saline infusion in fetal lambs, interstitial compliance was estimated to be 45 ml/mmHg kg⁻¹ kg⁻¹ (10). Comparable to adult values, we assumed that edema and hydrops develop when the interstitial compartment is enlarged by 18% (25). In the model, we assumed the interstitial compliance to be 100 ml/mmHg kg⁻¹ kg⁻¹ (24) after an interstitial volume increase of 18%; additionally, we assumed that fetal interstitial compliance reduces sharply when the fetal tissues are stretched by edema, and a compliance of 20 ml/mmHg kg⁻¹ kg⁻¹ was arbitrarily chosen for fetal interstitial space that exceeded 1.5 times normal (see Fig. 5).

As previously (61), normal fetal weight (kg) is taken to be proportional to normal fetal blood volume (ml), using a proportionality factor of 10 (57), and, to convert kilograms into milliliters, to the density of the fetus, assumed to be 1/1000 kg/ml. Thus

\[
\text{WeightNormalFetus} = 10 \cdot V_{\text{hxN}}/1000
\]

In equations, Fig. 5 implies

\[
P_{\text{inter}} - P_{\text{interN}} = \frac{1}{45} \cdot \frac{(V_{\text{inter}} - V_{\text{interN}})}{\text{WeightNormalFetus}} \cdot (V_{\text{inter}} - V_{\text{interN}}) < 0.18 \cdot V_{\text{interN}}
\]

\[
\Delta P/\Delta V = (1/20) \text{ mmHg·kg/ml}
\]

\[
\Delta P/\Delta V = (1/100) \text{ mmHg·kg/ml}
\]

\[
(\text{Interstitial Volume - Normal}) / \text{Weight (ml / kg)}
\]

\[
\frac{\Delta P}{\Delta V} = (1/20) \text{ mmHg·kg/ml}
\]

\[
\frac{\Delta P}{\Delta V} = (1/100) \text{ mmHg·kg/ml}
\]

\[
(\text{Interstitial Volume - Normal}) / \text{Weight (ml / kg)}
\]

Fig. 5. Curve used for interstitial pressure (P) minus normal vs. interstitial volume (V) minus normal divided by fetal weight (Eq. 18).
To explain the second and third parts of the curve in Fig. 5, it is convenient to introduce parameters \(x\) and \(y\) and the points \(x_1, y_1\) and \(x_2, y_2\) and replace Eq. 18b by the identical, abbreviated form

\[
y = C \cdot x \quad C = 1/45 \quad x < x_1 \tag{18c}
\]

\[
x = \frac{(V_{\text{int}N} - V_{\text{int}})}{\text{WeightNormalFetus}}
\]

and

\[
y = \frac{P_{\text{int}N} - P_{\text{int}}}{0.18 \cdot V_{\text{int}N}} \tag{18d}
\]

\[
x_1 = \frac{1 \cdot V_{\text{int}N}}{\text{WeightNormalFetus}} \tag{18e}
\]

When edema develops, \(\Delta P/\Delta V\) decreases to 1/100 mmHg \(\cdot \) kg \(^{-1}\) \(\cdot\) ml \(^{-1}\) (24). Using \(x_1, y_1\) as the connecting point between the two curves, the second part of the curve is

\[
y - y_1 = C_1 \cdot (x - x_1) \quad C_1 = 1/100 \quad x > x_1 \tag{18f}
\]

Next, choosing \(x_2, y_2\) as the new connecting point for volumes exceeding 1.5 times normal, the third part of the curve is

\[
y - y_2 = C_2 \cdot (x - x_2) \quad C_2 = 1/20 \quad x > x_2 \tag{18g}
\]

\[
x_2 = \frac{1.5 \cdot V_{\text{int}N}}{\text{WeightNormalFetus}} \tag{18h}
\]

**Control of lymph flow.** Lymph flow, from the interstitial to the venous compartment, depends on both the interstitial and venous hydrostatic pressures. Increasing the venous pressure will lower the lymph flow. Decreasing the venous pressure will enhance the lymph flow until it reaches its maximal value, as demonstrated experimentally (8, 13, 18). In the model, the pressure difference between the venous and the interstitial space \((P_{\text{ven}} - P_{\text{int}})\) regulates the lymph flow. We used fetal lamb measurements of lymph flow by Brace (8) in dependence of venous pressure. Because lymph flow is a function of \(P_{\text{ven}} - P_{\text{int}}\), we added 2.66 mmHg, which represents in the model the assumed normal interstitial pressure at 133 days of gestation, to the venous pressures \((P_{\text{ven}})\) measured by Brace (8). Subsequently, we normalized the data at 133 days of gestation by the normal value of \(P_{\text{ven}} - P_{\text{int}}\), being 2.9 + 2.66 = 5.56 mmHg. The scaled data obtained from Brace can be represented as in Fig. 6 and described by Eqs. 19 and 19 (Table 3).

\[
\text{Lymph}_f = \text{Lymph}_0 \cdot f_{\text{lymph}} \tag{19}
\]

Normal lymph flow was 0.25 ml \(\cdot\) min \(^{-1}\) \(\cdot\) kg \(^{-1}\) as estimated from Reference 12.

**Control of urine production by arterial pressure, colloids, and RAS mediators.** In the previous model, fetal urine production depended on mean arterial pressure only. In the current model, we also incorporate the influence of the fetal blood COPfet, as well as the influence of the circulating peptides, represented by the RAS mediators, which constrict efferent renal arteries, thus limiting urine production. The fetal urinary output can be represented as

\[
U_f(t) = U_g(t) \cdot f_r \cdot f_{\text{Colloid}} \cdot f_{\text{RAS}} \tag{20}
\]

Where \(f_r\) denotes the pressure-diuresis curve used previously (57), \(f_{\text{Colloid}}\) the control function for colloids, and \(f_{\text{RAS}}\) the control function for the peptides, all summarized in Eq. M20 (Table 3) and the latter two defined below and shown in Figs. 7 and 8.

**Colloids and urine production.** Normal filtration of blood across the glomerular capillary membrane is driven by the hydrostatic pressure gradient and, because the membrane is impermeable to colloids, is affected by the colloid concentration of the blood plasma, where increased colloid concentration will decreaseglomerular filtration rate (GFR) (30). It is assumed that urine production reflects GFR, i.e., tubular reabsorption can be neglected.

Infusing autologue plasma proteins for 8 days in dogs, Manning (35) investigated the chronic effects of hyperproteinemia on mean arterial pressure and urine output. At elevated COP, mean arterial pressure and urine production rose significantly, although mean arterial pressure rise with normo-COP would normally increase urine production to a larger degree. In the model, a high COP will limit urine production; however, we assume that a low COP does not increase urinary output. We interpreted the data by Manning as shown in Fig. 7 and expressed in Eqs. M20c–e (Table 3).

**RAS mediators and urine production.** During fetal life the major components included in the RAS are present, albeit with different activities than in adults (44). As in the adult, angiotensin II has potent pressor pressor effects and acts to reduce urine production (44). The marked upregulation of renin synthesis noted in TTTS donor kidneys (32) is likely due to the reduced perfusion (38, 43). In contrast to the donor twin, renin synthesis in the recipient is markedly decreased, a result of hypervolemia and concomitant hypertension (29, 32). Similarly, significant differences were found between donor and recipient blood concentrations of renin and angiotensin I (39). Although arginine vasopressin levels parallel the changes in angiotensin II (4), the RAS has been speculated to be the key mechanism implicated in TTTS pathophysiology (29, 32, 33). In our model we included the effects of angiotensin II to embody the effects of RAS mediators (Figs. 8 and 9; Eqs. M20f–j and M21, Table 3). In contrast, atrial natriuretic factor (ANF), which increases urine production, was shown to be markedly elevated in the recipient twin (39, 63). As ANF increases in response to vascular pressure, we have continued (57) to incorporate the effects of ANF by the pressure-diuresis factor \(f_r\) (Eqs. 20 and M20a,b, Table 3).

In the model, \(f_{\text{RAS}}\) (Eq. 20) is regulated by the total concentration of circulating peptides (RASs) divided by the normal concentration (RASsN). Urinary volumetric output, depending on angiotensin II concentration, was scaled from adult sodium intake and output curves (25). Here, we assumed that the urine sodium concentration does not change significantly, and the urinary volumetric output as depending on angiotensin II has been fitted from these curves (Fig. 8), using \(f_{\text{RAS}}\) from Eqs. M20f–j (Table 3).

**RAS mediator concentrations.** We have chosen the normal concentration of all combined vasconstrictive peptides to be 35 pg/ml for all.
gestational ages, resembling the concentration for angiotensin II (17). So,

\[ \text{RAS}_S(t) = 35 \]  

(21a)

The influence of variations in arterial pressure on renin activity was investigated by Binder and Anderson (7) in fetal lambs. A linear relationship between the arterial pressure and the log concentration of the renin activity was established, albeit with significant error bars. Faber and Anderson (17) assumed the angiotensin II concentration to be proportional to the renin activity and transformed this relation to their Eq. 3. For modeling purposes, we interpreted the observations of Binder and Anderson as the production of RAS mediators. We assumed that RAS production hardly increases when fetal arterial pressure is still above 0.8 times normal. In contrast, the assumed that RAS production hardly increases when fetal arterial pressure is below 0.8 times normal. Addition-
only. The rate of change of excess recipient RAS due to fetofetal transfusions along the anastomoses is (omitting the t dependence of the parameters)

$$\frac{d\text{ExRAS}_r}{dt} = \left[ \frac{I_{AV} \text{RAS}_d}{V_w} - (I_{VA} + I_{AA} + I_{VV}) \right] \frac{\text{RAS}_r}{V_w} - \frac{\text{ExRAS}_r(i)}{\tau}$$

where \text{RAS}_d and \text{RAS}_r are the RAS concentrations in donor and recipient blood volumes, respectively. Finally, from Eqs. 22a,c,d, the differential equation for recipient RAS is

$$\frac{d\text{RAS}_r}{dt} = \frac{\text{dRAS}_r}{dt} = \frac{\text{dRAS}_r(P_{\text{Net}})}{dt}$$

We omitted the t dependence of the terms within the square brackets.

Additional model parameters. Additional model parameters, i.e., fetal swallowing, urine osmolality, fetal lung fluid secretion, fetal blood osmolality, amniotic fluid osmolality, transplacental flow, and fetal intramembranous flow, were left identical to those in the previous model (57).

Model input parameters and iterative time step. Input parameters in the model are left identical to those in the previous models (57, 61), i.e., vascular anastomotic radii of AV, VA, AA, and VV anastomoses and the degree of placental sharing between donor and recipient twin. In our models, radius and length of all anastomoses increase linearly with gestation, implying that their values at 40 wk determine the anastomotic resistances at all gestational ages (61, 57), i.e., Eq. M8 (Table 3). In our models, anastomotic radii are converted to resistances, based on Poiseuille’s law of laminar flow. The differential equations were solved by a standard forward finite difference method, using a time step of $10^{-6}$ wk, which is comparable to 0.6 s. This is 100 times shorter than in the previous model, required to prevent the numerical solution to include an oscillatory component. The numerical code was programmed in Borland Delphi 5.0. One computer simulation on our Pentium 2-GHz 512-MB PC takes approximately 9 min.

RESULTS

Single AV Anastomosis with Severe TTTS and Hydrops in Recipient Twin

A single AV anastomosis was selected to have a resistance that generates an anhydramniotic “stuck” donor twin at 22 wk of gestation and a polyhydramniotic recipient at 19.9 wk (Fig. 10A), where polyhydramnios was defined as an amniotic fluid volume of twice the normal volume (57). Fetofetal transfusion before 22 wk reduces the increase of the donor twin’s blood volume (Fig. 10B) and total body fluid volume (Fig. 10C), leading to hypotension (Fig. 10D) and a reduced urine production. In the recipient twin, increased growth of the blood volume leads to mild hypertension (Fig. 10D), increased urine production, increased COP, increased transplacental flow, and polyhydramnios (Fig. 10A). Subsequently, a stuck donor twin develops, hence the onset of TTTS stage 1. After 22 wk, the inability of the donor twin to swallow amniotic fluid aggravates its hypotension, leading to a strong increase of RAS production (Fig. 10E), which results in an increased transfusion of RAS mediators to the recipient twin. The recipient’s polyuria now becomes mitigated by the transfused RAS mediators, which strongly increase the recipient’s venous and hence capillary blood pressures (Fig. 10D). At 24.4 wk the recipient twin’s total interstitial volume has increased 18% above normal for gestational age, our definition of fetal hydrops (Fig. 10F).

AV Plus Inadequately Compensating AA Anastomosis Causes TTTS and Hydrops in Recipient Twin

An AV anastomosis, inadequately compensated by an AA anastomosis, with resistances selected to produce a stuck donor twin at 22 wk (resistances at 40 wk are $0.16 \text{mmHg}\cdot\text{ml}^{-1}\cdot\text{h}$ for AV and 0.13 mmHg·ml⁻¹·h for AA). In this case, all parameters exhibit behavior similar to that in the previous case of a single AV anastomosis, including the development of hydrops at 32.4 wk of gestation in the recipient twin (data not shown).

AV Plus Adequately Compensating AA Anastomosis Causes TTTS Without Hydrops in Recipient Twin

An AV anastomosis, adequately compensated by an AA anastomosis, was chosen with resistances that generate a stuck donor twin at 22 wk (resistances at 40 wk are 0.10 and 0.05 mmHg·ml⁻¹·h for AV and AA, respectively). In the model, the donor arterial pressure remains above 0.75 times normal, preventing both a strong increase of RAS production and the development of hydrops in the recipient twin (data not shown).

AV Plus Compensating VV Anastomoses

Two cases with an AV anastomosis inadequately (resistances at 40 wk are 0.16 and 0.02 mmHg·ml⁻¹·h for AV and VV, respectively) or adequately (resistances at 40 wk are 0.07 and 0.003 mmHg·ml⁻¹·h for AV and VV, respectively) compensated by a VV anastomosis, were chosen so the donor twin becomes stuck at 22 wk. Here, hydrops in the recipient develops for inadequate compensation at 32.8 wk but not for adequate compensation (data not shown).

Compensation of AV by VA, AA, or VV Anastomoses

Results from anastomotic compensation of AV by VA, AA, or VV anastomoses are summarized in Table 4. Our simulations show that the VV anastomosis has the largest interval between the onset of TTTS and the onset of hydrops, closely followed by the AA and finally by the VA anastomosis.

Polyhydramnios vs. Hydrops

In the model, the increased maternofetal transplacental fluid flow to the recipient twin, caused by excess colloids, can either exit through the recipient bladder, contributing to polyhydranmios, or into the fetal interstitial space, contributing to hydrops. Figure 11 shows amniotic fluid volumes of two anastomotic patterns, the single AV of Fig. 10 and an AV + VV, with anastomotic resistances at both produce a stuck donor twin at 22 wk, but where the single AV causes hydrops at 24.4 wk and the AV + VV (resistances of the inadequate compensation of AV + VV as above) at 32.8 wk. Figure 11 shows that development of hydrops causes a reduction in the recipient’s amniotic fluid volume, mitigating the severity of polyhydranmios.

Varying Placental Sharing

In our model, unequal placental sharing affects outcome as in the previous model (57). Figure 12 shows amniotic and interstitial fluid development for the single AV anastomosis of
Fig. 10, using a donor-recipient placental sharing of 0.75:0.25 (Fig. 12, A and C) and 0.25:0.75 (Fig. 12, B and D). A large donor placental part delays onset of TTTS (40) and hydrops compared with equal sharing and the opposite effect for a small donor part.

**Monoamniotic Twins**

Figure 13 shows the interstitial fluid volume using the single AV anastomosis of Fig. 10 for monoamniotic twins. Monoamnionicity was incorporated as before (58, 60). As in the previous model, monoamniotic donor twins will continue to swallow amniotic fluid until the fetal blood osmolality has decreased at least by 4% compared with normal, causing cessation of thirst. Consequently, donor hypotension will not develop as quickly in the presence of fetal swallowing, so hydrops will be delayed compared with the same anastomotic pattern in diamniotic twins, in the example of Fig. 13 by 2.3 wk. For less severe TTTS cases, the influence of amnionicity on the onset and development of TTTS is not as strong as in Fig. 13, basically as the predictions of our previous model (58, 60). Furthermore, introducing monoamnionicity for the inadequately compensated AV + AA case described above postponed hydrops by ~0.5 wk, rendering the beneficial effect of monoamnionicity negligible.
outcome of these simulations. The gestational age at which a hydropic recipient develops is the consequence of an AA, VA, or VV anastomosis, producing a stuck donor at 20 and 25 wk, respectively, and with compensation mechanisms that address maternal hypertension and venous return. Thus our model strongly supports recent findings by Mahieu-Caputo et al. (32–34), which suggested that insufficient maternal hypertension and venous return are not excessive. The strongly increased colloids cause an excess transplacental fluid flow from the maternal to the recipient circulation, which exits to a larger extent through the bladder, causing polyhydramnios, than through the capillary walls into the interstitial compartment. The severity of TTTS remains limited to stages I or II if the rate of increase of the net fetofetal transfusion stabilizes compared with the rate of increase of fetal growth. Second, TTTS stage IV severity may develop if the net fetofetal transfusion continues to increase at a rate that exceeds the increase of fetal growth of each twin. Then, the sequence of events develops that was explained in the previous paragraph. As a result, the hydrostatic pressure gradient in the transvascular flow (Eq. 5) increases, whereas the COP gradient hardly changes, implying that the excess transplacental flow now exits primarily into the interstitial space at the cost of exiting through the bladder. Therefore, onset of hydrops coincides with reduction of polyhydramnios (Fig. 11), in agreement with clinical observations reported by Trespudi et al. (55) in their Fig. 1.

Previously (61, 57), we stressed that incomplete information is available on the normal cardiovascular function and amniotic fluid homeostasis, let alone when such developments are complicated by fetofetal transfusion. Equally so, incomplete information is available on the new mechanisms that contribute to the onset of forward cardiac failure, i.e., the physiology of fetal interstitial and intracellular fluid development, the dynamics of colloids, as well as the pathophysiology of hypertension and RAS mediator dynamics. Thus, as before, we were forced to improvise, using a simplified and sometimes empirical or

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single AV</th>
<th>AV + AA</th>
<th>AV + VA</th>
<th>AV + VV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastomotic resistance, mmHg/ml^−1·24 h</td>
<td>0.13 (AV)</td>
<td>0.13 (AV)</td>
<td>0.13 (AV)</td>
<td>0.13 (AV)</td>
</tr>
<tr>
<td>Anastomotic resistance, mmHg/ml^−1·24 h</td>
<td>0.14 (AA)</td>
<td>0.70 (VA)</td>
<td>0.02 (VV)</td>
<td></td>
</tr>
<tr>
<td>Stuck donor, wk</td>
<td>18</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hydropic recipient, wk</td>
<td>20.3</td>
<td>28.5</td>
<td>23.9</td>
<td>30.3</td>
</tr>
<tr>
<td>Time between stuck and hydrops, wk</td>
<td>2.3</td>
<td>8.5</td>
<td>3.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Anastomotic resistance, mmHg/ml^−1·24 h</td>
<td>0.28 (AV)</td>
<td>0.28 (AV)</td>
<td>0.28 (AV)</td>
<td>0.28 (AV)</td>
</tr>
<tr>
<td>Stuck donor, wk</td>
<td>22</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Hydropic recipient, wk</td>
<td>24.4</td>
<td>32.5</td>
<td>28.5</td>
<td>33.1</td>
</tr>
<tr>
<td>Time between stuck and hydrops, wk</td>
<td>2.4</td>
<td>7.5</td>
<td>3.5</td>
<td>8.1</td>
</tr>
</tbody>
</table>

Stuck donor was simulated with a single AV anastomosis of 2 resistances, producing a stuck donor at 18 and 20 wk, respectively, and with compensation by an AA, VA, or VV anastomosis, producing a stuck donor at 20 and 25 wk, respectively. The gestational age at which a hydropic recipient develops is the outcome of these simulations.

**DISCUSSION**

**Model**

To our knowledge, this mathematical model is the first to quantify a sequence of events that leads to the onset and development of hydrops in the recipient twin in cases of severe TTTS. The model combines our previous TTTS model (57) with clinical results of Mahieu-Caputo et al. (32) and Kilby et al. (29), modeling by Faber and Anderson (17), and fetal lamb experiments by Gilbert (19) and Thornburg and Morton (53, 54). Three essential elements had to be included, without which a hydropic recipient could not be modeled. The first is vasoconstrictive peptides, described as the RAS. Here, the severely hypotensive donor produces excessive RAS mediators to limit its fluid loss by urination. Then, the net fetofetal transfusion propagates the excessive donor RAS concentration toward the recipient, also creating excessive recipient RAS mediators, which mitigates recipient polyuria, aggravating its hypertension. The second essential element is the limited capacity of the fetal heart to increase its cardiac output beyond normal values after abnormally increased blood volume (19, 53, 54), leading to a state of high-output cardiac failure. Then, the continuing net fetofetal transfusion primarily enters the recipient’s venous circulation, resulting in an excess venous blood volume and venous hypertension. The third element is an interstitial fluid compartment. Once venous hypertension has developed in the recipient, a large volume of fluid propagates from the vascular capillaries into the interstitial compartment, causing an increased interstitial fluid volume and hence development of hydrops. Thus our model strongly supports recent findings by Mahieu-Caputo et al. (32–34), which suggested recipient hypertension in severe TTTS and circulating vasoconstrictive peptides as implicated in the mechanisms that cause hydrops. It also supports an older study in which significant differences were found between donor and recipient blood concentrations of renin and angiotensin I (39). Furthermore, our approach to simulating hydrops in TTTS recipient twins is supported by Faber and Anderson (17), who showed fetal cardiac failure to be the strongest stimulus for the formation of hydrops compared with infusion of angiotensin II, constriction of the fetal suprarenal aorta, or anemia. Finally, it is well established that venous hypertension either induced artificially by atrial pacing (42), lymphatic ligation, or excision (3) or caused by structural defects is a known contributor to hydrops (27).

From the viewpoint of pathophysiological mechanisms, our model is clear and simple (Fig. 14). First, stages I and II TTTS develop if the net fetofetal transfusion increases at a rate in excess of fetal growth of each twin. A stuck donor and strongly increased colloids in the recipient follow, albeit that recipient hypertension and urine production are not excessive. The strongly increased colloids cause an excess transplacental fluid flow from the maternal to the recipient circulation, which exits to a larger extent through the bladder, causing polyhydramnios, than through the capillary walls into the interstitial compartment. The severity of TTTS remains limited to stages I or II if the rate of increase of the net fetofetal transfusion stabilizes compared with the rate of increase of fetal growth. Second, TTTS stage IV severity may develop if the net fetofetal transfusion continues to increase at a rate that exceeds the increase of fetal growth of each twin. Then, the sequence of events develops that was explained in the previous paragraph. As a result, the hydrostatic pressure gradient in the transvascular flow (Eq. 5) increases, whereas the COP gradient hardly changes, implying that the excess transplacental flow now exits primarily into the interstitial space at the cost of exiting through the bladder. Therefore, onset of hydrops coincides with reduction of polyhydramnios (Fig. 11), in agreement with clinical observations reported by Trespudi et al. (55) in their Fig. 1.

![Fig. 11. Amniotic fluid volumes divided by normal for the single AV anastomosis of Fig. 10 and the AV anastomosis inadequately compensated by a venousovenous (VV) anastomosis as discussed in the text. Both anastomotic patterns produce a stuck donor twin at 22 wk. An amniotic fluid volume ratio exceeding 2 indicates polyhydramnios.](http://ajpregu.physiology.org/)

Downloaded from [http://ajpregu.physiology.org/]

*Fig. 11. Amniotic fluid volumes divided by normal for the single AV anastomosis of Fig. 10 and the AV anastomosis inadequately compensated by a venousovenous (VV) anastomosis as discussed in the text. Both anastomotic patterns produce a stuck donor twin at 22 wk. An amniotic fluid volume ratio exceeding 2 indicates polyhydramnios.*

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A pragmatic description of fetal, amniotic fluid and blood component pathophysiology. Examples are as follows.

First, albumin and protein extravasation into the interstitial fluid is observed to be significant (6, 36, 47). However, mechanisms that control extravasation of colloids are lacking, so in Eqs. 17g,h we pragmatically modeled this mechanism, creating interstitial colloid concentrations comparable to reported observations. In addition, increasing extravasation from 50% to 75%, model outcomes varied only slightly, i.e., at 75%, hydrops occurred by 10 wk earlier after the development of a stuck donor twin than at 67%, the value used in our model. Furthermore, the decay time for excess colloids, chosen to be 10 wk, is not a critical parameter in our model. Varying \( \tau \) between 5 and 15 wk gave essentially the same results of onset of polyhydramnios and hydrops.

Second, the ability of the donor to upregulate the concentration of circulating peptides to limit its urine output as a consequence of chronic hypotension is incompletely known. Here, the multitude of compounds involved, and the incomplete data on type, properties, and function of these substances, prompted us and others (29, 32–34) to use the generic term RAS mediators. Interestingly, the values selected for decay time (20 min) and steady-state RAS concentrations (Fig. 9) mutually affected the model predictions. However, as long as the product of \( \tau F_{\text{RAS}} \) for arterial pressures below 0.8 times normal (Eqs. M21a,b, Table 3) was kept constant, model output remained virtually identical. We varied \( \tau \) between 1 min and 4 ha tconstant \( \tau F_{\text{RAS}} \) and found no differences in the gestational ages at onset of a stuck donor and recipient polyhydramnios and hydrops. Interestingly, this behavior directly follows from the differential equation Eq. 22e, because the terms including parameters \( \text{RAS}_d \) and \( \tau \) are much larger than the other terms, particularly for shorter values of \( \tau \). Also, the difference between the two terms is much smaller than each of the terms, implying from standard physics that \( dRAS/dt \) can be set to zero. Then \( \text{ExRAS} \), directly follows from the algebraic relation, indeed showing proportionality to the product \( \tau F_{\text{RAS}} \).

Therefore, because donor RAS concentrations during hypotension are unknown, the value chosen for the decay of excess RAS in our model is not critical. Our choice for \( \tau F_{\text{RAS}} \) is supported by Kilby et al. (29), who found a donor-to-recipient ratio of renin-producing renal glomerulus cells in stillborn twin pairs to be as large as 500 for severe TTTS cases. In our model,
the ratio of donor to recipient RAS concentrations in the fetal blood is ~180 at onset of hydrops (Fig. 10E). Furthermore, our predictions give donor vs. recipient angiotensin II concentrations of 8.8 vs. 0.05 ng/ml at onset of hydrops. Our data match within a factor of about two with the 2.1 and 3.8 vs. 0.16 and 0.08 ng/ml measured by Nageotte et al. (39) in two cases that included abdominal ascitis and pleural effusion in the recipient, respectively. Here, we converted the data of Nageotte et al. on angiotensin I, assuming that the cleaving of angiotensin I to angiotensin II by ACE implies that angiotensin II has an approximate weight of 0.8 times that of angiotensin I.

As previously, therefore, in view of the incomplete pathophysiological information requiring improvised solutions, our model can only provide possible trends to illustrate the general concepts. However, as long as the various mechanisms are modeled in an essentially correct way, the underlying concepts are likely realistic, implying that our model “sharpens the intuition” in understanding the sequence and significance of the mechanisms involved that cause a hydropic recipient in severe TTTS.

As before, we tried to limit the number of model variables to those that seemed essential in causing clinically realistic development of recipient hydrops. Consequently, we did not include the discordant pathological development of the placental villi, oxygenation of fetal organs, cardiac hypertrophy, the influence of RAS mediators on the placental vasculature (2) and fetal myocardium (26), tricuspid valve regurgitation, or the discordant development of the blood viscosity. Nevertheless, and despite these simplifications, we acknowledge the significantly increased complexity of the present model compared with the previous models (57, 61).

**TTTS**

Our model simulated onset and development of recipient hydrops related to the pattern of placental anastomoses. Important predictions are as follows. First, none of the anastomotic patterns we tried gave spontaneous resolution of hydrops. Basically, RAS mediators transfused from the strongly hypotensive donor essentially contribute to onset of hydrops in the recipient. As long as the donor cannot improve its cardiovascular status, excess donor RAS mediators will be produced and transfused to the recipient, which therefore cannot improve its cardiovascular status either, so hydrops sustains. Although we acknowledge that this result may be in contradiction to occasional cases (1), placental details were lacking in this report, implying that other, unidentified events not included in our model could have been responsible for the reversal of the hydrops. A possible example is thrombosis of one or more anastomoses that were responsible for causing the hydrops. Thrombosis of chorionic vessels was seen in 2 of 22 cases in normal placentas (16), and 2 such cases, recently described (41, 51), caused severe TTTS in previously uneventful monochorionic twin pregnancies. Additionally, because the donor twin experiences a strong upregulation of albumin and therefore also fibrinogen (15), which is a major determinant of plasma viscosity and erythrocyte aggregation (46), the recipient twin experiences increased fibrinogen levels too, because of anastomotic transfusion. Thus we speculate that the thrombosis rate found in uneventful singleton pregnancies may even be increased in recipients of severe TTTS cases. So, because chorionic vascular thrombosis has not been excluded in cases describing spontaneous resolution of hydrops (1), our model predictions of irreversible hydrops may be realistic.

Second, we predict that VV anastomoses, by producing the longest interval between a stuck donor twin and a hydropic recipient twin, protect best against development of hydrops in the recipient after TTTS onset, closely followed by AA and finally by VA anastomoses. Although perhaps at first surprising, the need for the venous pressure to increase strongly before onset of hydrops makes compensatory efficacy by a VV anastomosis obvious. This model confirms again that lack of superficial anastomoses is an adverse anatomic sign in TTTS cases.

Third, a thought-provoking model prediction may be that once stage II TTTS severity has developed deterioration to stage IV severity often will follow soon. The underlying mechanism is that cessation of donor urine production parallels solid increase of donor RAS concentrations, which, transfused to the recipient, aggravates its hypertension to levels at which the transvascular flow often increases sufficiently to cause
hydrops. Here, our choice that donor RAS levels increase excessively at donor arterial pressures <0.8 times normal and our selection of actual RAS values compared with normal cause TTTS stage II to progress into stage IV. However, reducing the arterial pressure at onset of donor upregulation, e.g., from 0.8 to 0.7 times normal, resulted in TTTS stage II cases that sustained for as long as 10 wk. In addition, by varying the \( F_{\text{RAS}} \) function at the beginning of donor upregulation, onset of a stuck donor twin could be simulated to coincide with cessation of urine production, i.e., simultaneous onset of stage I and II TTTS severity. Therefore, the current uncertainty in the dynamics of RAS mediators makes it challenging to search for prognostic criteria that predict whether TTTS severity stabilizes or progresses. Finding such criteria would be exceedingly important for severe TTTS cases, particularly when presenting at the beginning of the third trimester and laser therapy is not usually offered.

In conclusion, our model simulates a variety of realistic manifestations of onset and development of fetal hydrops in the recipient twin in cases of severe TTTS during pregnancy related to the placental angioarchitecture. The model results add to the growing evidence that recipient hydrops is due to limited cardiac preload reserve aggravated by the fetofetal transfusion of RAS mediators from the donor twin. We hypothesize that our model can aid to the optimal management of monochorionic twin pregnancies complicated by TTTS that includes a hydropic recipient twin by an assessment of current therapeutic interventions for TTTS, including laser obliteration of all anastomoses followed by amniotic fluid reduction and stand-alone amniotic fluid manipulations.

Perspectives

Monozygotic twinning has an incidence of 3.5 per 1,000 pregnancies, with 75% of these cases sharing one monochorionic placenta in which their fetoplacental circulations are coupled in 96% by one or more placental anastomoses. TTTS complicates monochorionic twin pregnancies in 10–15% of cases, with a significant incidence of preterm birth, perinatal mortality, and persistent morbidity. Occurrence of a hydropic recipient twin as a consequence of circulatory volume overload indicates the highest level of TTTS severity in two live fetal twins. Despite current opinions regarding the underlying pathophysiology and therapy of TTTS, controversy remains as to the optimal management of monochorionic twins, depending on gestational age and the stage of TTTS severity. The mathematical model developed in the present study may enable an improved understanding of TTTS pathophysiology in the most severe cases and identify the sequence of events that determines the progression of TTTS severity and the efficacy and outcome of current and potential therapeutic interventions.

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