Amniotic fluid and hemodynamic model in monochorionic twin pregnancies and twin-twin transfusion syndrome

ASLI UMUR, MARTIN J. C. VAN GEMERT, AND MICHAEL G. ROSS

1Laser Center and Department of Obstetrics and Gynecology, Academical Medical Center, University of Amsterdam, 1105 Amsterdam, The Netherlands, 2Department of Obstetrics and Gynecology, Harbor University of California-Los Angeles Medical Center, Torrance, California 90502

Received 17 July 2000; accepted in final form 10 January 2001

Amniotic fluid and hemodynamic model in monochorionic twin pregnancies and twin-twin transfusion syndrome. Am J Physiol Regulatory Integrative Comp Physiol 280: R1499–R1509, 2001.—We developed a mathematical model of monochorionic twin pregnancies and twin-twin transfusion syndrome (TTTS), combining both fetal fluid dynamics and fetoplacental growth and circulation alterations and assuming that transplacental fluid flow from mother to fetus accounts for normal fetal and amniotic fluid volumes. Ten coupled differential equations, describing fetal total body and amniotic fluid volumes, their osmolalities, and fetal blood colloid osmotic pressure, for both donor and recipient twins, were solved numerically. Amniotic flows are controlled by fetal plasma osmolarity and hydrostatic and colloid osmotic pressures. We included varying placental anastomoses and placental sharing of the circulations. Consistent with clinical experience, model predictions are: fetofetal transfusion from unidirectional arteriovenous anastomoses cause oligo-polyhydramnios, a normal size recipient but hypovolemic donor; compensating oppositely directed deep and superficial anastomoses moderate discordant development; and anhydramnios results from mild and severe TTTS, where milder forms may even present earlier in gestation than severe TTTS. Unequal placental circulatory sharing may exacerbate discordant development. In conclusion, our model simulates a wide variety of realistic manifestations of amniotic fluid volume and fetal growth in TTTS related to placental angioarchitecture. The model may allow an assessment of the efficacy of current therapeutic interventions for TTTS.

fetoplacental growth; placental anastomoses; circulatory and amniotic fluid imbalance; mathematical model

MONOCHORIONIC TWINS COMPLICATED by the twin-twin transfusion syndrome (TTTS) commonly develop discordant amniotic fluid volume and often but not always discordant fetal weight, with presentation between 16 and 34 wk of gestation. As a result of imbalanced fetofetal transfusion along vascular anastomoses, the donor twin becomes oliguric and hypertensive and develops oligohydramnios, while the polyuric, hypertensive recipient develops polyhydramnios (13, 20). Despite these accepted concepts, predictive abilities, early diagnosis, and treatment options remain markedly limited.

Because there is no appropriate animal model of TTTS, computer models have been developed to aid in understanding the pathophysiology (31, 34). Talbert et al. (31) developed a mathematical model of monochorionic twin fetoplacental units utilizing numerous interrelated hemodynamic, osmotic, and metabolic physiological variables. This model of the acute onset of unidirectional arteriovenous (AV) anastomotic blood flow identified a sequence of events resulting in oligo- and polyhydramnios. However, the model was limited to a 27-wk twin gestation of previously concordant twins occupying an equally shared placenta and only including AV anastomoses. In view of the enormous variability in clinical presentation of TTTS and the significant influence of superficial anastomoses and unequal placental sharing (2, 9, 34), it is unlikely that the acute introduction of uni- or bidirectional AV anastomoses in an otherwise normal 27-wk concordant twin pregnancy is a realistic picture of clinical TTTS.

Our laboratory subsequently derived a computer model (34) of TTTS that predicted twin fetal growth discordance resulting from placental angioarchitecture and fetoplacental circulation alterations. Physiological realities including gestational growth of anastomoses and unequal placental sharing of the circulations were incorporated in model equations. Model simulation indicated that fetofetal transfusion from unidirectional (donor to recipient) AV anastomoses causes progressive and irreversible fetal discordance with advancing gestation and fetoplacental growth, because AV transfusion occurs at a rate in excess of fetal growth. Steady-state discordant growth may develop if AV anastomotic transfusion is compensated by oppositely directed transfusion, either from other deep oppositely directed AV or superficial arterioarterial (AA) or, less frequently, venovenous (VV) anastomoses. Although the fetal growth predictions of this model are highly consistent with clinical observations (23, 35, 37, 39), the model did not include an assessment of amniotic fluid dynamics.

http://www.ajpregu.org 0363-6119/01 $5.00 Copyright © 2001 the American Physiological Society R1499
In the present study, we sought to combine mathematical models of both fetal fluid dynamics (8, 31) and fetoplacental growth and circulation alterations (34) throughout gestation of monochorionic twin pregnancy to predict the clinical manifestations of amniotic fluid volume disturbances in TTTS.

METHODS

Outline of the model. Model development consisted of two phases: phase 1 was the model of normal physiology of fetal and amniotic fluid development; phase 2 incorporated the effects of fetofetal transfusion of blood along placental anastomoses into the phase 1 model.

The model of normal physiology of fetal and amniotic fluid development is based on the assumption that the growing fetus acquires water and nutrient molecules from the maternal circulation to maintain its volume of total body fluid (TBF in ml) as well as its amniotic fluid volume (Vamn in ml), which may be viewed as an extension of the fetal extracellular volume. It follows that growth of fetal TBF [i.e., its rate of change, d(TBF)/dt, where t is gestational age in wk] can be assumed to be the difference between the total net flux of fluid across the placenta from mother to fetus (Trans in ml/wk) and growth of amniotic fluid volume, d(Vamn)/dt (Eq. 1).

\[ \frac{d(TBF)}{dt} = Trans - \frac{d(V_{amn})}{dt} \] (1)

We tacitly assumed that the fetoplacental circulation can incorporate all maternal fluids transferred across the placenta; hence, Trans is the rate-limiting step of fetal growth.

The second model phase incorporates the effects of net fetofetal transfusion of blood (34) (I_{net} in ml/wk), from donor to recipient along the placental anastomoses. As addressed previously (34), this blood exchange augments the normal rate of increase of the fetal blood volume (Vb) for the recipient twin and reduces the normal rate of blood volume increase for the donor twin.

We have assumed that 10% of the TBF constitutes the blood volume of the fetus (3). Thus comparable to our previous model (34)

\[ \frac{dV_b}{dt} = \frac{1}{10} \frac{d(TBF)}{dt} + I_{net} \] for recipient twin \hspace{1cm} (2A)

\[ \frac{dV_b}{dt} = \frac{1}{10} \frac{d(TBF)}{dt} - I_{net} \] for donor twin \hspace{1cm} (2B)

Further, I_{net} also changes the blood (hydrostatic) pressure and colloid osmotic pressures of both twins, influencing Trans (Eq. 1) and, subsequently, all other parameters that control the development of fetal and amniotic fluid volumes. Hence, through these mechanisms, I_{net} additionally affects fetal growth of both twins.

Detailed description. Table 1 summarizes the main relations used for the physiological parameters for normal fetal and amniotic fluid development.

Transplacental fluid flow. Trans (Eq. 1) is assumed to depend on a dynamic balance between the hydrostatic pressures and colloid osmotic pressures across the placenta (31)

\[ Trans = L_p\left[\left(P_{mat} - (P_{amn} + P_{fet})\right) - (COP_{mat} - COP_{fet})\right] \] (3)

where \( L_p \) (ml·wk\(^{-1}\)·mmHg\(^{-1}\)) is the net transplacental filtration coefficient, \( P_{mat} \) is the maternal mean arterial blood pressure in the intervillous space, \( P_{amn} \) is the transmitted amniotic fluid pressure, and \( P_{fet} \) is the fetal capillary blood pressure (Eq. 11, below) assumed equal to the fetal capillary pressure in the placental villi. Within the fetal body, the transmitted amniotic fluid pressure adds equally to arterial and venous pressures, so it is added to the fetal capillary pressure. COP_{mat} and COP_{fet} are the colloid osmotic pressures of the maternal blood and fetal blood, respectively (see Blood pressures, COPs, and osmolality of fetus).

For practical reasons, we empirically assumed that nutrients are transported via fluid flow from mother to fetus and we set the osmolality of the transplacental flow (Trans) to 280 mosmol/kgH\(_2\)O, the value for normal plasma osmolality in humans.

Placental filtration coefficient. For a hemodynamically unconnected twin (i.e., an uncomplicated pregnancy), \( L_p \) can be determined as a function of gestation. First, all parameters within the brackets on the right-hand side of Eq. 3, as well as \( V_{amn} \) and TBF (Eq. 1), are known from literature data (4, 8,

Table 1. Model equations used for various parameters for normal fetuses as a function of gestational age

<table>
<thead>
<tr>
<th>Model Equation used for Parameters</th>
<th>Gestational Age (wk)</th>
<th>Equation No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloid osmotic pressures, mmHg (Ref. 38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COP_{mat} = 27.530 - 0.367·t + 0.056·t(^2)</td>
<td></td>
<td>(m1)</td>
</tr>
<tr>
<td>COP_{fet} = -4.70 + 0.58·t</td>
<td></td>
<td>(m2)</td>
</tr>
<tr>
<td>Amniotic fluid volume, ml (Ref. 4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V_{amn} = 525.6 - 117.2·t + 8·t(^2) - 0.1237·t(^3)</td>
<td>t ≥ 11</td>
<td>(m3)</td>
</tr>
<tr>
<td>Urine production (Ref. 25; ml/h) and osmolality, mosmol/kgH(_2)O (Ref. 21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>log [U(t) + 3] = 0.088 + 0.041·t</td>
<td>t &lt; 33</td>
<td>(m4)</td>
</tr>
<tr>
<td>OsmU(t) = 1.98·10(^{-2})·t(^{0.328} - 0.019·t + 18.02</td>
<td>t ≥ 33</td>
<td>(m5)</td>
</tr>
<tr>
<td>OsmU(t) = OsmU(3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swallowing (ml/day)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$S(t) = 0.0137·t^{-3} - 0.4044·t^{-2} + 11.509·t - 85.873$</td>
<td>t ≤ 30</td>
<td>(m6)</td>
</tr>
<tr>
<td>$S(t) = 10^{1.0644·t + 1.105}$</td>
<td>t &gt; 30</td>
<td>(m7)</td>
</tr>
<tr>
<td>Parameter for intramembranous flow, ml·day(^{-1})·mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S_{IML}(t) = 0.0588·t - 0.6596</td>
<td>t ≥ 11</td>
<td>(m7)</td>
</tr>
<tr>
<td>Lung fluid secretion, ml/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$L(t) = -0.0065·t^4 + 0.0538·t^3 - 1.7447·t^2 + 23.5·t - 112.07$</td>
<td></td>
<td>(m8)</td>
</tr>
</tbody>
</table>

COP_{mat} and COP_{fet}, colloid osmotic pressures of maternal and fetal blood, respectively; V_{amn}, amniotic fluid volume; t, gestational age; U, urine production; S, swallowed volume; L, lung fluid; IM, intramembranous flow.
34, 38). Consequently, Trans and, therefore, Lpl follow from Eq. 1. Because Lpl is a placental parameter, we assumed that hemodynamically connected twins have the same Lpl.

**Amniotic fluid.** The two primary sources of amniotic fluid production are fetal urine production \([U(t)]\) and lung liquid secretion \([L(t)]\). Amniotic fluid removal is by fetal swallowing \([S(t)]\) and intramembranous flow \([IM(t)]\), which is the absorption of water into fetal blood perfusing the fetal surface of the placenta (4, 8). The latter route has been generalized to include all exchanges between amniotic fluid and fetal blood that may occur across other surfaces such as fetal skin and the umbilical cord (4). All these flows are expressed in milliliters per week. So, the rate of change (growth) of \(V_{amn}\) can be expressed as

\[
\frac{dV_{amn}(t)}{dt} = U(t) + L(t) - S(t) - IM(t) \tag{4}
\]

The amniotic fluid osmolality is also calculated for each time interval. The rate of change in the total number of osmoles contained in the amniotic fluid is equal to the number of osmoles entering the amniotic fluid minus the number of osmoles disappearing out of the amniotic fluid. Because the product of osmolality \((\text{mosmol/kgH}_2\text{O})\) and volume constitutes the total number of osmoles in the amniotic fluid, its rate of change can be expressed as

\[
\frac{d(\text{Osm}_{amn} \cdot V_{amn})}{dt} = \text{Osm}(U) \cdot U(t) + \text{Osm}(L) \cdot L(t) - \text{Osm}(S) \cdot S(t) - \text{Osm}(IM) \cdot IM(t) \tag{5}
\]

where \(\text{Osm}(X)\) is the osmolality of the corresponding flow \(X\).

Amniotic pressure is defined as the ratio of total amniotic fluid volume and uterine compliance. We have calculated the uterine compliance as a function of gestation using normal amniotic volumes for both twinning (4, 6) and an amniotic pressure of 10 mmHg for an uncomplicated pregnancy (14).

**Urine production.** We related the actual fetal urine production to normal singleton urine production rates \([U_N(t)]\) and assumed that it is controlled by a pressure diuresis curve \([U_{cont}(P_{ax})]\). Thus

\[
U(t) = U_N(t) \cdot U_{cont}(P_{ax}) \tag{6}
\]

where \(U_N(t)\) was derived from Rabinowitz et al. (25) (Eq. m4; Table 1). \(P_{ax}\) is the mean arterial pressure of the hemodynamically connected twin \((x = d \text{ or } r \text{; representing donor or recipient})\). The function \(U_{cont}(P_{ax})\) was derived from adult physiology (16), where urine output is zero at a mean arterial pressure of 50 mmHg, at 100 mmHg it is normal, and at 200 mmHg it is about eight times larger than normal (16). We scaled these data to fetal mean arterial pressures.

\[
U_{cont}(P_{ax}) = \frac{10}{3} \left( \frac{P_{ax}}{P_{ax0}} \right)^2 - 3 \left( \frac{P_{ax}}{P_{ax0}} \right) + \frac{2}{3}, \quad \text{if } P_{ax} > \frac{P_{ax0}}{2} \tag{7A}
\]

\[
U_{cont}(P_{ax}) = 0, \quad \text{if } P_{ax} \leq \frac{P_{ax0}}{2} \tag{7B}
\]

where \(P_{ax0}\) (mmHg) is the mean arterial pressure of the uncomplicated twin (at the same gestational age).

Urine osmolality decreases as gestation progresses (21) (Eq. m5; Table 1).

**Swallowing.** Because there are no available data for swallowed volumes throughout gestation, we used the values calculated by Curran et al. (8) \([S_N(t)]; \text{Eq. m6}; \text{Table 1}]\). Swallowed volume is considered to be directly proportional to the size of the fetus, so we included a factor \(f\), which is the ratio of TBF of a hemodynamically connected twin over the TBF of a normal uncomplicated twin. In addition, we assumed that swallowed volumes are controlled by blood osmolality of the fetus (22, 27), expressed as control function \(S_{cont}\). Thus

\[
S(t) = S_N(t) \cdot S_{cont}(\text{Osm}_{fetx}) \cdot f \tag{8}
\]

Here, \(S_{cont}\) is a second degree control parameter of fetal osmolality. Assuming that a 4–7% decrease in osmolality is sufficient to stop drinking in rats (30), the swallowed volume has been set equal to lung liquid secretion when fetal blood osmolality \((\text{Osm}_{fetx})\) of fetus \(x\) has decreased by 4%, i.e., when \(\text{Osm}_{fetx}\) has become 96% of its normal value \((\text{Osm}_{fetN})\).

The osmolality of the swallowed volume is equal to amniotic fluid osmolality.

**Intramembranous flow.** Intramembranous flow is defined as the water transfer between the amniotic cavity and fetal blood. Gilbert et al. (15) showed that intramembranous absorption of water occurs and plays an important role in rhesus monkey amniotic fluid volume regulation. We neglected the potential intramembranous solute exchange (i.e., the reflection coefficient is assumed to be 1) and assumed that only free water moves across the intramembranous pathway, driven by osmotic and hydrostatic pressures gradients.

\[
IM(t) = S_{IM}(t) \cdot L_{IM}(t) \cdot [(P_{AP} - P_{av}) - (\pi_{AP} - \pi_{fet})] \tag{10}
\]

where \(\pi_{AP}\) and \(\pi_{fet}\) are the osmotic pressures of the amniotic fluid and fetal blood, respectively \((1 \text{ mosmol/l } = 19.6 \text{ mmHg at } 37^\circ \text{C}; \text{Ref. 16})\), and \(P_{AP}\) and \(P_{fet}\) are hydrostatic pressures of the amniotic fluid and fetal blood volume, respectively. \(S_{IM}(t)\) \((\text{m}^2)\) denotes the combined surface of the placenta at the fetal side, fetal skin, and umbilical cord as a function of gestation. \(L_{IM}(t)\) is the filtration coefficient of the intramembranous pathway.

We have calculated the product of \(S_{IM}(t) \cdot L_{IM}(t)\) for an uncomplicated pregnancy (Eq. m7; Table 1) from Eq. 10, using intramembranous flow values calculated by Curran et al. (8), amniotic fluid osmolality determined for a singleton pregnancy by Brace and Edward (4), and assuming a fetal plasma osmolality of 280 mosmol/kgH\(_2\)O.

**Lung fluid.** Because no human fetal data are available for lung fluid secretion, we used values from Curran et al. (8) that were derived from ovine studies (Eq. m8; Table 1). Because 50% of the lung liquid produced is swallowed before excretion into the amniotic fluid (4), the values given by Eq. m8 are 50% of normal lung liquid production. Lung fluid osmolality is assumed to be isotonic to fetal plasma osmolality throughout gestation (8).

**Blood pressures, COPs, and osmolality of fetus.** \(P_{max}\) is set to 40 mmHg (12). Fetal capillary blood pressure \((P_{cap})\) is calculated by using fetal mean arterial \((P_a)\) and venous \((P_v)\) blood pressures as (12)
\[ P_{\text{net}} = P_v + \frac{1}{2} (P_a - P_v) \]  

Eq. 11

Fetal mean arterial and venous blood pressures during gestation are calculated from fetal blood volumes as described previously (34).

Colloid osmotic pressures (COP in mmHg) for mother and uncomplicated fetus are calculated according to Wu (38) (Eqs. m1 and m2; Table 1). For hemodynamically connected twins, colloid osmotic pressures are calculated as follows. COP is given by (24)

\[ \text{COP} = 19.6 \cdot \text{total colloids/fetal blood volume} \]  

Eq. 12

Equation 12 was combined with the available curves of COP vs. gestation (38) and fetal blood volume vs. gestation (34), determining the total number of colloids in a singleton as a function of gestation. The time derivative gave us the net colloid production of a singleton fetus as a function of gestation. Furthermore, the net colloid production of each twin is considered to be directly proportional to the twin’s size. Thus, for the twins, the colloid production of a singleton was multiplied by the function f, as was done for swallowing (Eq. 8).

Total amount of colloids in the blood compartment of each fetus changes not only with the net colloid production but also with exchange of blood through anastomoses.

\[ \frac{d(\text{total colloids})}{dt} = \text{net colloid production} + \text{colloid transfusion recipient} \]  

Eq. 13A

\[ \frac{d(\text{total colloids})}{dt} = \text{net colloid production} - \text{colloid transfusion donor} \]  

Eq. 13B

The number of colloids transfused through the anastomoses was calculated as

\[ \text{colloid transfusion} = I_{\text{AV}}(t) \times \text{blood colloid concentration of donor} \] - \text{colloid transfusion recipient} \]

\[ \text{of donor} - [I_{\text{AA}}(t) + I_{\text{VA}}(t) + I_{\text{XV}}(t)] \]  

\[ \times \text{blood colloid concentration of recipient} \]

where \( I_{\text{XV}}(t) \) (ml/wk) is the blood flow through the corresponding XY anastomosis.

Finally, from Eq. 13, the number of total colloids and, subsequently from Eq. 12, the COP of both twins were calculated.

The number of osmoles in the fetal total body fluid volume also changes with 1) transplacental fluid transfer and amniotic flows and 2) amniotic blood transfusion from donor to recipient.

\[ \frac{d(TBF \cdot \text{Osm}_{\text{osmol}})}{dt} = \text{Trans} \cdot \text{Osm}(\text{Trans}) - \frac{d(\text{Osm}_{\text{amn}} \cdot V_{\text{amn}})}{dt} + \text{osmoles transfused recipient} \]  

Eq. 15A

\[ \frac{d(TBF \cdot \text{Osm}_{\text{osmol}})}{dt} = \text{Trans} \cdot \text{Osm}(\text{Trans}) - \frac{d(\text{Osm}_{\text{amn}} \cdot V_{\text{amn}})}{dt} - \text{osmoles transfused donor} \]  

Eq. 15B

The number of osmoles transfused from donor to recipient can be calculated as in Eq. 14 replacing blood colloid concentration with blood osmolality.

Unequal placental circulatory sharing We assumed that the number of available cotyledons for the twins, representing their placental circulatory fractions, remains constant throughout pregnancy (34). For IM flow across the fetal skin (prior to keratinization), we have also assumed that fetal skin surface is proportional to its placental surface [i.e., \( L_{\text{pl}} = \frac{X \cdot L_{\text{pl}}}{} \) for \( \text{Trans} \) and \( \text{S}_{\text{IM}}(t) \cdot L_{\text{IM}}(t) = \frac{X \cdot \text{S}_{\text{IM}}(t) \cdot L_{\text{IM}}(t)}{} \) for IM, where \( X \) is the normalized placental fraction (34) defined as \( X_1 + X_2 = 2 \), subscripts 1 and 2 denote fetuses 1 and 2].

Model description Essential to the model is our previous assumption that each anastomosis grows in volume proportionately with the placental volume, approximately proportional to gestational age to the third power (34). As a consequence, we derived that each anastomotic resistance decreases proportional to \( t^{-4} \) to the third power, where \( t \) is gestational age (wk) and blood vessels become functional at 4 wk of gestation (34). Therefore, anastomotic resistance can be expressed as

\[ \text{resistance}(t) = \text{resistance}(40 \text{ wk}) \times \left( \frac{40 - 4}{t} \right)^3 \]  

Eq. 16

where Eq. 16 implies that the resistance value at 40 wk completely determines resistance values throughout pregnancy.

Because the mechanisms of fetal and amniotic fluid dynamics before 11 wk of gestation are significantly different from those of the second and third trimester, the model is initiated at 11 wk. Fetal blood volume and pressures before 11 wk were calculated on the basis of our previous model (34) using as input parameters: 1) degree of placental sharing, 2) types of anastomoses, and 3) their resistance during gestation defined by the values chosen at 40 wk (Eq. 16). At 11 wk, our model starts with the assumption of equal amniotic fluid volumes of 40 ml for both twins and osmolality of amniotic fluid and blood of 280 mosmol/kgH2O.

The model program runs for both uncomplicated and for hemodynamically connected twins. First, normal twin data are deduced from the run of the uncomplicated twin. Second, all amniotic fluid flows (U, L, S, IM), transplacental flow (Trans), and \( I_{\text{net}} \) are calculated. From these flows, new blood volumes, pressures, osmolalities, and COPs for the twins and osmolalities and pressures for the amniotic fluid result. We solved the 10 coupled differential equations between 11 and 40 wk gestation by a standard numerical forward finite difference method with a total time step of 1/10,000 wk (−1 min).

RESULTS

Uncomplicated twins (no vascular anastomoses). The amniotic fluid volume as predicted by our model for an uncomplicated twin fetus is shown as the curve labeled “Normal” in Fig. 1. Normal amniotic fluid volume steadily increases until 35 wk of gestation and decreases throughout the remainder of the pregnancy, with values well within the normal range of widely varying volumes (quoted as 39–257% of the mean volume for any given gestational age; Ref. 4). Normal amniotic and fetal blood parameters predicted by our model are summarized in Table 2.

Twins with unidirectional AV anastomoses. Blood transfusing along the AV anastomosis from donor to recipient, which occurs at a rate in excess of fetal growth (34), reduces the donor twin’s blood volume, blood pressures resulting in hypotension (20), urine production rate, blood osmolality, and COP. The decrease in fetal COP is greater than the decrease in total capillary pressure of the donor, so the total net fluid flux across the placenta will decline (Trans; Eq. 3). The
Table 2. Amniotic and fetal parameters throughout gestation as predicted by the model

<table>
<thead>
<tr>
<th>Gestation, wk</th>
<th>Trans, ml/wk</th>
<th>U, ml/wk</th>
<th>L, ml/wk</th>
<th>S, ml/wk</th>
<th>IM, ml/wk</th>
<th>Osm_{amn}, mosmol/kg H_2O</th>
<th>V_{min}, ml</th>
<th>P_{a}, mmHg</th>
<th>P_{v}, mmHg</th>
<th>V_{b}, ml</th>
<th>Osm_{fet}, mosmol/kg H_2O</th>
<th>COP_{fet}, mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>32</td>
<td>77</td>
<td>70</td>
<td>70</td>
<td>256</td>
<td>289</td>
<td>40</td>
<td>10.3</td>
<td>1.3</td>
<td>7</td>
<td>250</td>
<td>1.7</td>
</tr>
<tr>
<td>15</td>
<td>73</td>
<td>367</td>
<td>29</td>
<td>303</td>
<td>56</td>
<td>279</td>
<td>147</td>
<td>17.1</td>
<td>2.1</td>
<td>17</td>
<td>281</td>
<td>4.0</td>
</tr>
<tr>
<td>20</td>
<td>114</td>
<td>928</td>
<td>73</td>
<td>669</td>
<td>280</td>
<td>278</td>
<td>374</td>
<td>25.7</td>
<td>3.2</td>
<td>40</td>
<td>282</td>
<td>6.9</td>
</tr>
<tr>
<td>25</td>
<td>145</td>
<td>1,736</td>
<td>212</td>
<td>1,161</td>
<td>732</td>
<td>276</td>
<td>643</td>
<td>34.3</td>
<td>4.3</td>
<td>78</td>
<td>283</td>
<td>9.8</td>
</tr>
<tr>
<td>30</td>
<td>164</td>
<td>2,836</td>
<td>492</td>
<td>1,813</td>
<td>1,465</td>
<td>274</td>
<td>909</td>
<td>42.9</td>
<td>5.4</td>
<td>135</td>
<td>284</td>
<td>12.7</td>
</tr>
<tr>
<td>35</td>
<td>69</td>
<td>4,751</td>
<td>907</td>
<td>2,984</td>
<td>2,660</td>
<td>271</td>
<td>997</td>
<td>51.4</td>
<td>6.4</td>
<td>191</td>
<td>285</td>
<td>15.6</td>
</tr>
<tr>
<td>40</td>
<td>11</td>
<td>7,469</td>
<td>1,397</td>
<td>4,255</td>
<td>4,118</td>
<td>267</td>
<td>871</td>
<td>60.0</td>
<td>7.5</td>
<td>225</td>
<td>285</td>
<td>18.5</td>
</tr>
</tbody>
</table>

Trans; transplacental flow; L: lung fluid (50% of total flow, see text); Osm_{amn}: osmolality of amniotic fluid; P_{a} and P_{v}, arterial and venous blood pressures, respectively; V_{b}, fetal blood volume; Osm_{fet}, fetal blood osmolality.
near normal values, in agreement with clinical findings
(11, 35, 39).
Interestingly, larger size AV and AA anastomoses (Fig. 3B, inset) simulated a “stuck” twin occurring at 22 wk of gestation. Discordance in blood volumes was ~33%. However, because net fetofetal transfusion decreases and may ultimately approach zero (not shown), reaccumulation of amniotic fluid in the donor twin occurs spontaneously, here at ~27 wk. Comparison with Fig. 3B (lowest solid curve) suggests that occurrence of a stuck twin is not a unique indication of the severity of TTTS.

Twins with bidirectional AV anastomoses. If the AV anastomosis is compensated by an oppositely directed AV anastomosis, the most common types of vascular anastomoses in TTTS (9, 10, 32, 36, 37), a steady state of the smallest possible net fetofetal transfusion develops, quite similar to the case of AV plus AA anastomoses. Bidirectional AVs therefore differ in their hemodynamic effects from single or unidirectional AVs (34).
In response to various combinations of AV plus opposite AV anastomoses, our model predicts similar amniotic fluid and fetal blood volumes as shown in Fig. 3 for AV plus AA anastomoses. Twins with unequal placental sharing of their circulations. In our model unequal placental sharing of the two circulations causes discordant fetal and amniotic fluid development, because the fetus having the smaller placental circulation receives a smaller transplacental fluid flow from the mother (see dots in Fig. 4). Our model predicts that unequal placental sharing, with an AV anastomosis from the larger to the smaller placental circulations, results in later onset of TTTS than in the case of equal sharing (see bold lines in Fig. 4A) and a seemingly paradoxical reversal of the oligohydramniotic sequence in which the initially larger twin with greater amniotic fluid volume becomes the smaller twin with oligohydramnios (see bold lines in Fig. 4B). This phenomenon has been described (18) but, unfortunately, without placental analysis. Recently, late onset of TTTS has indeed been correlated with unequal circulatory sharing and two small unidirectional AV anastomoses from larger to smaller placental parts (23).

Severity of TTTS. In our present and previous (34) models, the etiology of TTTS is a stronger increase in net fetofetal transfusion (I_{net}) than fetal growth of each twin. Consequently, the ratio of fetal growth of the donor twin’s blood volume and I_{net} represents a proper model parameter to indicate the severity of the imbalance that develops between the twins’ circulations. Thus the closer this ratio remains near one when a stuck twin occurs, the milder is the TTTS. Conversely, the smaller the ratio, the more severe forms of TTTS.

Table 3. Amniotic and fetal parameters for an AV anastomosis, from Sharma et al. (29), throughout gestation as predicted by the model

<table>
<thead>
<tr>
<th>Gestation, wk</th>
<th>Trans, ml/wk</th>
<th>U, ml/wk</th>
<th>S, ml/wk</th>
<th>IM, ml/wk</th>
<th>Osm_{amn}, mosmol/kgH2O</th>
<th>P_{a}, mmHg</th>
<th>P_{v}, mmHg</th>
<th>Osm_{fet}, mosmol/kgH2O</th>
<th>COP_{fet}, mmHg</th>
<th>I_{AV}, ml/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>d</td>
<td>r</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>13</td>
<td>50</td>
<td>56</td>
<td>175</td>
<td>244</td>
<td>166</td>
<td>196</td>
<td>14</td>
<td>20</td>
<td>279</td>
<td>279</td>
</tr>
<tr>
<td>15</td>
<td>62</td>
<td>82</td>
<td>260</td>
<td>448</td>
<td>248</td>
<td>332</td>
<td>39</td>
<td>68</td>
<td>279</td>
<td>279</td>
</tr>
<tr>
<td>17</td>
<td>67</td>
<td>108</td>
<td>307</td>
<td>731</td>
<td>303</td>
<td>493</td>
<td>66</td>
<td>158</td>
<td>279</td>
<td>279</td>
</tr>
<tr>
<td>19</td>
<td>80</td>
<td>124</td>
<td>188</td>
<td>1,069</td>
<td>195</td>
<td>672</td>
<td>52</td>
<td>294</td>
<td>279</td>
<td>279</td>
</tr>
<tr>
<td>21</td>
<td>100</td>
<td>135</td>
<td>10</td>
<td>1,165</td>
<td>98</td>
<td>846</td>
<td>3</td>
<td>449</td>
<td>280</td>
<td>278</td>
</tr>
</tbody>
</table>

d, Donor; r, recipient; I_{AV}, arteriovenous anastomotic transfusion. Lung liquid production is the same as in Table 2 (see text).
develop. Figure 5A shows predicted evolution of this ratio for two different AV anastomoses (I and II) without compensation (Ia, Ila) and with compensating AA anastomoses (Ib, Ic, IIb) and for unequal placental circulatory sharing (III) with an AV anastomosis from larger to smaller placental part, again without compensation (IIIa) and with compensating AA anastomoses (IIIb, IIIc). Bold lines indicate cases resulting in a “stuck” donor and severe discordance between fetuses. Thin lines indicate cases not resulting in a stuck twin before 30 wk of gestation. Figure 5A also shows that a “stuck” twin may occur early in pregnancy (Ia, Ib) or late (IIa) depending on the placental angioarchitecture. Furthermore, a stuck twin occurring early, e.g., curves Ib and Ic, representing milder TTTS cases, does not necessarily indicate increased severity of TTTS compared with a stuck twin occurring later, e.g., curves IIa, Ib, and IIIa, representing more severe TTTS. In addition, curve Ic represents a case (also shown in Fig. 3B, inset) where the donor grows only slightly less than net fetofetal transfusion, from 14.5 to 23 wk, sufficient to become stuck at 22 wk of gestation. However, because net fetofetal transfusion started to decrease at 18 wk, the donor could accumulate amniotic fluid again at ~27 wk (Fig. 3B, inset), indicative of mild TTTS.

Figure 5B shows the corresponding curves of urine production (ml/wk) for the donor twins. Our model suggests that fetofetal transfusion from single AV anastomoses (curves Ia, IIa, IIIa) may show strongly decreasing urine production rates once the donor has become stuck, suggestive of lack of bladder filling in donor twins, whereas in cases of compensated AV anastomoses (curves Ib, Ic, IIb) urine production will not cease, possibly implying that bladder filling persists in the donor.

**DISCUSSION**

Model. To our knowledge, this mathematical model is the first to incorporate both hemodynamics and amniotic fluid dynamics in monochorionic twins throughout pregnancy. The model combines the approaches of Talbert et al. (31), Curran et al. (8), and van Gemert and Sterenborg’s previous hemodynamic model of TTTS (34). Growth of fetal total body fluid (Eq. 1) is governed by the net transplacental fluid flow (Trans). Previously (34), fetal growth was assumed proportional to the fetoplacental circulation. However, in our present model, we tacitly assumed that the fetoplacental circulations can incorporate all fluids...
transferred across the placenta, and we adapted the same relationships between fetal blood volume and blood pressures as before (34). Consequently, although the mechanisms for fetal growth may seem different in the two models, they are actually very similar.

Previously (34), we emphasized that incomplete information is available on the normal cardiovascular development of fetuses, let alone when the development is complicated by fetofetal transfusion. Equally so, incomplete information is available on the physiology of amniotic fluid dynamics. We were therefore forced to improvise using a simplified and sometimes empirical description of fetal and amniotic fluid physiology. Furthermore, we tried to limit the number of model variables to those that seemed essential in simulating clinically realistic TTTS development. Consequently, we did not include discordantly developing (patho)physiological adaptation processes that are likely to be secondary to onset of TTTS (e.g., blood viscosity, oxygenation of fetal organs, and pathological alterations in fetal, placental, and cardiac development). Including such mechanisms throughout gestation would not only be a formidable but most likely impossible task to date in view of the limited information available. Therefore, like any model, our model is a deliberate oversimplification that can serve as a point of departure for understanding a much more complicated reality (5). As a consequence, our model can only provide trends to illustrate the general concepts. However, these underlying concepts are likely realistic.

First, in Eq. 3, we assumed the total net flux of water and nutrient solutes across the placenta (Trans) is governed by the driving osmotic and hydrostatic pressure gradients. This is a simplification of the placental water and solute transfer. Solutes can diffuse through the placenta, be actively transported by the placenta, and be produced by fetal plasma. Water transfer is sensitive to the fetoplacental and also maternal blood flow, neither of which is incorporated in the model. Therefore, until these mechanisms have been fully identified, empirical description is inevitable.

Second, lack of data available for fetuses forced us to adapt empirical control mechanisms for urine production and fetal swallowing rates (i.e., control of urine production from scaled adult values for chronic arterial pressure changes and swallowed volume by fetal osmolality). Moritz et al. (19) described the association of fetal arterial blood pressure and urine output in the ovine fetus, demonstrating that a Pa-to-PaN ratio of 1.35 ± 0.08 gives a U-to-UN ratio of 3.2 ± 0.3, where N denotes normal values. Our control function (16) gives a quite similar U-to-UN ratio of 2.7 for a Pa-to-PaN ratio of 1.35. It is also acknowledged that our regulatory equations for swallowing are in agreement with data derived from the ovine fetus (22) where it was reported that a 6% decrease in osmolality causes an ~50% decrease in swallowed volumes. In our model, a 4% decrease in osmolality causes swallowed volumes to be equal to the lung fluid produced, which reduces swallowed volume to 53% of its normal value at 30 wk of gestation. Consequently, we believe that the control mechanisms used generate realistic behavior of these amniotic fluid flows.

TTTS. Preliminary clinical data suggest that bidirectional AV anastomoses cause TTTS in ~55%, whereas AV plus AA combinations cause it only in ~30% (36). Consequently, AA anastomoses have been touted to play a predictive role in onset and severity of TTTS (9, 32). The possible differential effects of polyhydramnios on AV (and opposite AV) vs. AA transfusion have recently been proposed by the authors (33) as a possible explanation.

Our model simulated a wide spectrum of TTTS presentations, all of which have been described clinically. First, the AV anastomotic transfusion responsible for TTTS causes a continuously increasing fetal discordance predicted to develop between the twins. Although the donor twin becomes growth retarded, the recipient twin’s blood volumes remain nearly normal. In our model, this is due to the recipient’s increased urine production in response to increased mean arterial blood pressure that helps to keep its total blood volume near normal values. In contrast, compensation of blood loss for the donor twin is insufficient (Fig. 3A). Although this behavior has been observed clinically (11, 35, 39), it contradicts the predictions of our previ-
ous model (34), which only shows symmetric deviations from the normal growth curve (see open circles in Fig. 3A). We emphasize, however, that the size discordance overall in TTTS has an extremely wide range and not all donors become growth retarded, depending (at least in part) on gestational age, severity of TTTS, and circulatory sharing of the placenta. Second, considering uncompensated as well as compensated anastomotic patterns, we simulated that the oligo-polyhydramnios sequence can occur early or late during pregnancy and can represent severe as well as milder forms of TTTS. Notably, milder TTTS does not necessarily present later in gestation than more severe TTTS. In addition, we simulated the occurrence of a stuck donor and a polyhydramniotic recipient with small as well as large fetal discordance in their blood volumes, varying between \( \sim 30-55\% \). Furthermore, TTTS was simulated to reverse between the donor and recipient and can even disappear spontaneously, as observed clinically (1, 7). Components in our model that are responsible for this wide spectrum of severity of TTTS are 1) size of the AV anastomoses (donor to recipient), 2) capacity of the compensating anastomoses with respect to the AV, and 3) placental circulatory sharing between the twins. This spectrum of severity included in the stuck twin-polyhydramnios sequence that defines TTTS has important clinical correlates. Varying therapies, including septal disruption (28), amnioreduction (17), and laser ablation of placental vessels (17), may each have specific TTTS anastomotic anatomies that are amenable to the therapy. However, therapies thought to be clinically efficacious may be serving only as surgical placebos in cases that would spontaneously abate. Our model suggests that measurement of urine production of the donor twin may have a predictive value in the assessment of severity (26).

In conclusion, our model simulates a wide variety of realistic manifestations of amniotic fluid and fetal growth behavior in TTTS during pregnancy related to placental angioarchitecture. We hypothesize that our model will allow an assessment of the efficacy of current therapeutic interventions for TTTS, including both hemodynamic and amniotic fluid volume interventions.

**Perspectives**

Monozygous twinning has an incidence of \( \sim 3.5 \) in 1,000 pregnancies, with 75\% of these cases sharing one
monochorionic placentas in which their fetoplacental circulations are virtually always coupled by one or more placental vascular anastomoses. TTTS complicates monochorionic twin pregnancies in 6–35% of cases by significant net fetofetal transfusion along the anastomoses, from donor to recipient. As a result of net fetofetal transfusion from imbalanced vascular anastomoses, the donor twin may become growth retarded with oligohydramnios, while polyhydramnios may occur in the normal size recipient, who often develops circulatory volume overload. If these sequelae remain untreated, high morbidity and mortality rates ensue. Despite these consequences, predictive abilities, early diagnosis, and treatment options remain markedly limited. The mathematical model developed in the present study may enable an improved understanding of TTTS pathophysiology and identify the sequence of events that determines efficacy and outcome of current and potential therapeutic interventions.

A. Umur is supported by the The Netherlands Heart Foundation Grant 99.174. M.G. Ross is supported by National Heart, Lung, and Blood Institute Grant HL-40899.

REFERENCES


32. Taylor MJO, Denbow ML, Tanawattanacharoen S, Gannon C, Cox PM, and Fisk NM. Doppler detection of arteio-


