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van Gemert, M.J.C.; Sterenborg, H.J.C.M.

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Haemodynamic Model of Twin–Twin Transfusion Syndrome in Monochorionic Twin Pregnancies

M. J. C. van Gemert^{a,b,c} and H. J. C. M. Sterenborg^a

^a Laser Center, Academic Medical Center, Amsterdam, The Netherlands

^b Beckman Laser Institute and Medical Clinic, University of California, Irvine, California, USA

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Twin–twin transfusion syndrome in monochorionic twin pregnancies is not understood completely and is controversial which hampers development of acceptable diagnostic and rational treatment strategies. A haemodynamic model was developed that relates fetal growth with (1) fetoplacental blood flow and fetomaternal effects, and (2) net twin–twin transfusion from donor to recipient twin. Fluid balance mechanisms were neglected. Placental vascular anastomoses (arteriovenous, venoarterial, arterioarterial, venovenous) were modelled as straight blood vessels connecting the placental cord insertions that grow during pregnancy. Poiseuille's law predicts significantly decreasing anastomosing resistances, and when placental sharing is unequal it is assumed that smaller placental fractions cause smaller blood volumes and pressures. Two coupled first-order differential equations describing each twin's blood volume were determined and analysis showed that placental and anastomotic development cause anastomotic blood flow to increase faster than fetal growth. Hence, it is proposed as the syndrome's underlying pathophysiology that fetal discordance increases progressively, beyond fetal compensatory capacity. Fewer anastomoses cause larger discordance, but its onset can vary widely during pregnancy. Arteriovenous plus compensating anastomoses produce dynamic steady-state growth patterns with large, opposite, measurable anastomotic blood flows. Clinical study of fetal growth patterns may identify the syndrome's underlying placental anatomy. Predicted trends depend only weakly on implemented fetal physiology and are most likely realistic. This knowledge could improve future management of the syndrome.

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INTRODUCTION

Monochorionic twins occur in about 70 per cent of monozygotic twin pregnancies, and may be complicated by twin–twin transfusion syndrome (TTTS). This serious perinatal condition accounts for much of the perinatal morbidity and mortality associated with identical twins (Bejar et al., 1990; Blickstein, 1990; Benirschke, 1993; Baldwin, 1994; Machin, Still and Lanani, 1996). Usually, TTTS presents in the second trimester of pregnancy with discordant fetal growth and amniotic sacs (poly- and oligohydramnios), chronic malnutrition of the donor fetus, often appearing to be 'stuck' to the placenta, and high-output heart failure in the recipient caused by hypervolaemia (e.g. Lopriore et al., 1995). Without intervention, perinatal survival in pregnancies affected by severe TTTS before 28 weeks is virtually zero (e.g. Bajoria, Wigglesworth and Fisk, 1995).

Clinical symptoms associated with TTTS correlate with non-compensated transfusion of blood from one twin (the donor) to the other (the recipient) along placental vascular anastomoses which link the two fetoplacental circulations. Arteriovenous (AV) (deep) anastomoses are represented by a placental cotyledon which is shared by both twins, supplied by a chorionic artery from the donor fetus and drained by a chorionic vein to the recipient. Arterioarterial (AA) and venovenous (VV) anastomoses are direct superficial placental communications in the form of blood vessels of nearly the same diameter as the chorionic arteries or veins of the twins which they connect (e.g. Arts and Lohman, 1971). However, vascular anastomoses are described in about 75 per cent of monochorionic placentae but TTTS is observed in only 25 per cent of these (Machin, Still and Lanani, 1996). Therefore, some communications must cause the syndrome, while others are insignificant or are even beneficial to the fetuses.

Clinical study of this rare condition is difficult because TTTS has a diversity of presentations and a complex pathophysiology. In animals, a suitable model is lacking although monochorionic animal placentation is known, e.g. in the Texas armadillo (Benirschke et al., 1964) and in marmoset monkeys (Benirschke and Layton, 1969). Despite over

^cTo whom correspondence should be addressed at: Laser Center, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands. E-mail: m.j.vangemert@amc.uva.nl.

100 years of clinical research (Schatz, 1882), the underlying pathophysiology of TTTS is not understood completely and is controversial (Blickstein, 1990; Talbert et al., 1996).

In an attempt to improve understanding of the syndrome, Talbert et al. (1996) developed a model of monochorionic twin fetoplacental units at 27 weeks gestation linked by various combinations of direction and number of AV anastomoses. The present model has the same objectives as that of Talbert et al. (1996), but with a different emphasis. Dynamic growth patterns of the fetoplacental twin system were analysed as a consequence of deep and superficial anastomoses. We included unequal placental sharing but neglected fluid balance hydrodynamics.

The first objective of this study was to identify how placental and anastomotic development during pregnancy causes anastomotic blood flow to increase faster than fetal physiologic growth, virtually independent of details of implemented fetal physiology. These growth rate differences, proposed as the underlying pathophysiology of TTTS control the occurrence of progressively increasing fetal discordance beyond fetal compensatory capacity. The second objective was to show that different anastomotic patterns occurring in monochorionic placentation produce widely varying differences in moment of onset, severity, and dynamic development of fetal discordance. The final objective was to describe the numerical model.

MODEL

As twin–twin transfusion of blood volume is the cause of TTTS, the model computes the fetal blood volume of the donor and recipient twins. This parameter depends on gestational age, available fractions of their common placental mass (which is assumed to be independent of gestational age), and placental vascular resistances of the AV, VA (both from donor to recipient twin), AA and VV anastomoses involved.

The model is based on three fundamental concepts: 'natural physiologic growth' of each twin, defined as the anticipated normal physiologic increase of their blood volume per week; net twin–twin transfusion of blood from donor to recipient twin which reduces growth of the donor's blood volume but increases that of the recipient; 'overall' growth of fetal blood volume, the sum of these two growth mechanisms. For the donor and recipient twin this can be expressed as:

$$\begin{aligned} \text{(growth of donor blood volume)} = & \\ & \text{(natural physiologic growth of donor blood volume)} \\ & - \text{(net twin–twin transfusion).} \end{aligned} \quad (1a)$$

$$\begin{aligned} \text{(growth of recipient blood volume)} = & \\ & \text{(natural physiologic growth of recipient blood volume)} \\ & + \text{(net twin–twin transfusion).} \end{aligned} \quad (1b)$$

'Growth' (left-hand side) is defined as the rate of change of fetal blood volume, or

$$\frac{d}{dt} V(t) \quad (1c)$$

where t (weeks) denotes gestational age and V is volume (Table 1 lists the mathematical symbols and their units).

Mathematically, the above constitutes a set of two first-order differential equations in the blood volume of each twin, coupled to each other by net twin–twin transfusion from donor to recipient, T_{TT} (ml/week). So, using V_d , V_r for blood volume (ml), and G_d , G_r for natural physiologic growth (ml/week), respectively, where subscripts d and r refer to donor and recipient twins (Table 1), the equations can be written for each case as:

$$\frac{dV_d(t)}{dt} = G_d(t) - T_{TT}(t) \quad (2a)$$

$$\frac{dV_r(t)}{dt} = G_r(t) + T_{TT}(t) \quad (2b)$$

Initial condition is that all parameters are zero at $t=0$, the moment of embryonic twinning.

The extent of fetal discordance that will develop between donor and recipient twins during pregnancy depends on how fast T_{TT} increases relative to rates of increase in G_d , G_r . For example, if T_{TT} were to increase according to a constant fraction of the (average) G -terms, fetal discordance would remain limited (see Results). Therefore, we propose that progressively increasing fetal discordance is a requisite for TTTS to develop. In the results, we show that placental and anastomotic development causes anastomotic blood flow to increase faster than natural physiologic growth. Consequently, because details of implemented fetal physiology relate mainly to natural physiologic growth mechanism, the model predictions are not greatly affected by such details.

Numerical and analytic evaluation requires actual data for G_d , G_r and T_{TT} as a function of gestational age, placental sharing and placental anastomotic anatomy. Due to the paucity of information available on normal development of fetoplacental cardiovascular function, let alone when the development is complicated by twin–twin transfusion, such data are not available for monochorionic twin pregnancies. Hence, we were forced to introduce a simplified and, sometimes, empirical description of fetal physiology.

Numerical model

By analogy with the electrical Ohm's law, fetoplacental blood flow is obtained by dividing placental perfusion pressure by placental vascular resistance. We neglected pressure losses in fetal and umbilical blood vessels. Hence, for either fetus x ($x=d, r$) $P_{ax}(t)$ and $P_{vx}(t)$ (mmHg) are its mean arterial and venous blood pressures, respectively, and $R_{plx}(t)$ (mmHg/ml week) its placental vascular resistance. Taking 'natural physiologic growth', $G_x(t)$, of the twins empirically as being proportional to their fetoplacental blood flow, $G_d(t)$ and $G_r(t)$ are defined as

Table 1. List of abbreviations, mathematical symbols and their physical units

Symbol	Definition
<i>AA</i>	Arterioarterial placental anastomosis (donor to recipient)
<i>AV</i>	Arteriovenous placental anastomosis (donor to recipient)
<i>f</i>	Dimensionless function, expressing time behaviour of radius and length of anastomoses [equation (4k, l)] (Table 4)
<i>f_d, f_r</i>	Factors, related to <i>X_{pld}</i> , <i>X_{plr}</i> [equation (A1c)]
<i>F</i>	Proportionality factor for natural physiologic growth [equation (3) and (4h–i)]
<i>G</i>	Natural physiological growth [ml/week] (equations (3) and (4b–c))
<i>h</i>	Function expressing the effects of <i>X_{pl}</i> on blood volumes (<i>h_v</i>), [equation (4d)]
<i>H</i>	Function expressing the effect of a smaller or larger blood volume than <i>V_N(t)</i> on mean arterial and venous blood pressures during twin–twin transfusion [equation (4p–r)]
<i>I</i>	Blood flow (ml/week) (placental, anastomotic)
<i>l</i>	Length (m) of anastomosing blood vessels (AV, VA, AA, VV), [equation (4j)]
<i>P</i>	Blood pressure (mmHg) (mean arterial, venous)
<i>r</i>	Radius (m) of anastomosing blood vessels (AV, VA, AA, VV) [equation (4j)]
<i>R</i>	Vascular resistance (mmHg/ml week) (placental, anastomotic)
<i>t</i>	Gestational age (week)
<i>T_{TT}</i>	Net twin–twin transfusion (ml/week) [equation (4)]
<i>TTTS</i>	Twin–twin transfusion syndrome
<i>v</i>	Viscosity [equation (4m)]
<i>V</i>	Fetal and placental blood volume (ml)
<i>VA</i>	Venoarterial placental anastomosis (donor to recipient)
<i>VV</i>	Venovenous placental anastomosis (donor to recipient)
<i>x</i>	Donor or recipient twin (<i>d, r</i>)
<i>X</i>	Fraction of the common placental mass [equation (4a)]
<i>XY</i>	Placental anastomoses (AV, VA, AA, VV) (donor to recipient)
<i>∞</i>	Proportional to
Subscripts	
<i>a</i>	Arterial
<i>AA</i>	Arterioarterial
<i>AV</i>	Arteriovenous
<i>AVE</i>	AV-equivalent resistance [equation (A4)]
<i>d</i>	Donor twin
<i>eq</i>	Equivalent placental fractions [equation (4n)]
<i>N</i>	Normal, unconnected twins with equal placental sharing
<i>pl</i>	Placental
<i>P</i>	Pressure
<i>r</i>	Recipient twin
<i>sup</i>	Superficial equivalent resistance [equation (A6)]
<i>v</i>	Venous
<i>V</i>	Volume
<i>VA</i>	Venoarterial
<i>VV</i>	Venovenous
<i>x</i>	Donor or recipient fetus (<i>d, r</i>)
<i>XY</i>	placental anastomoses (AV, VA, AA, VV)

$$G_d(t) = \left(\frac{P_{ad}(t) - P_{vd}(t)}{R_{pld}(t)} \right) F_d(t) \quad (3a)$$

and

$$G_r(t) = \left(\frac{P_{ar}(t) - P_{vr}(t)}{R_{plr}(t)} \right) F_r(t) \quad (3b)$$

The terms between brackets denote fetoplacental blood flow. Proportionality factors $F_d(t)$, $F_r(t)$ represent the effects of all fetomaternal mechanisms that convert placental blood flow into ‘natural physiologic growth’. Net twin–twin transfusion (T_{TT}) from donor to recipient twin is defined as

$$T_{TT}(t) = \left(\frac{P_{ad}(t) - P_{vr}(t)}{R_{AV}(t)} \right) - \left(\frac{P_{ar}(t) - P_{vd}(t)}{R_{VA}(t)} \right) - \left(\frac{P_{ar}(t) - P_{ad}(t)}{R_{AA}(t)} \right) - \left(\frac{P_{vr}(t) - P_{vd}(t)}{R_{VV}(t)} \right) \quad (4)$$

where the four terms denote the *AV*, *VA*, *AA*, and *VV* anastomosing blood flows, with anastomotic vascular resistances $R_{AV}(t)$, $R_{VA}(t)$, $R_{AA}(t)$, $R_{VV}(t)$ (mmHg/ml week), respectively.

Parameter assessment between 0 and 40 weeks of $G_d(t)$, $G_r(t)$ for equal and unequal placental sharing, and $T_{TT}(t)$ for

Table 2. Assumptions used for the numerical model

1. Common placental mass fractions (X_{pld} , X_{plr}) are independent of gestational age [equation (4a)].
2. Fetal blood volume is proportional to fetal weight.
3. Natural physiologic growth (anticipated normal physiological increase of blood volume per week) is proportional to fetoplacental blood flow and fetomaternal effects [equation (3)].
4. Mean arterial blood pressures of monochorionic unconnected twins as a function of X_{plx} are proportional to those of singleton fetal lambs as a function of fetal weight.
5. Placental vascular resistance and proportionality factor for natural physiologic growth are independent of twin–twin transfusion.
6. Smaller placental mass fractions cause smaller fetal blood volumes and pressures.
7. Pulsatility component of blood flow is neglected; average values for blood pressures and (anastomosing) blood flows are used.
8. Systemic blood pressure–volume curves, derived from unconnected monochorionic twins, are used during twin–twin transfusion.
9. Placental anastomosing vascular resistances are represented by straight blood vessels that connect the two umbilical cord insertions.
10. Anastomoses grow in size as a function of gestational age: (1) using that their volume grows proportional to the placental volume (as t^3 for $t < 31$ weeks; (2) using that a constant wall shear stress drives growth of the anastomosing blood vessel radii.
11. Vascular resistance of anastomosing blood vessels is according to Poiseuille's law [equation (4m)].
12. Input parameters of the model: X_{pld} , X_{plr} , $r_{AV}(40)$, $r_{VA}(40)$, $r_{AA}(40)$, $r_{VV}(40)$.
13. Output parameters of the model: $V_d(t)$, $V_r(t)$, $P_{ad}(t)$, $P_{vd}(t)$, $P_{ar}(t)$, $P_{vr}(t)$, $I_{AV}(t)$, $I_{VA}(t)$, $I_{AA}(t)$, $I_{VV}(t)$.

Table 3. Origin of physiologic parameters used for the model

Human twin fetuses	Human singleton fetuses	Fetal singleton lambs
Fetal weight (t) ^{a–e}	Blood volume (t) ^d	MAP(t) ^{h–k}
Fetal versus placental weight (40 weeks) ^c	Fetal weight (t) ^{a–c}	MAP versus fetal weight ^k
	Fetoplacental blood flow (t) ^c	
	Placental volume (t) ^f	
	Venous blood pressure (t) ^g	

t , Gestational age; MAP, mean arterial blood pressure.

^a Bleker, Breur and Huidekoper (1979). ^b Rydström (1992); ^c Dawes (1968 p 46). ^d Brace (1993). ^e Gerson et al. (1987).

^f Wolf, Oosting and Treffers (1987). ^g Ville et al. (1994). ^h Barcroft (1946). ⁱ Iwamoto et al. (1989). ^j Jensen and Lang (1992). ^k Anderson and Faber (1984).

size and nature of the anastomoses, requires four steps as presented below. Tables 2 and 3 summarize, respectively, the assumptions and origin of physiologic parameters used in the numerical model. Table 4 summarizes the model equations (a–t).

First step: assessment of $F_d(t)/R_{pld}(t)$ and $F_r(t)/R_{plr}(t)$ in equation (3) from physiologic parameters of haemodynamically unconnected monochorionic twins ($T_{TT}=0$)

Equal placental sharing. For zero net twin–twin transfusion, natural physiologic growth is the rate of change of fetal blood volume [equation (2)]. Blood volume data [equation (4c), Table 4] are adapted from measurements in healthy singleton human fetuses (Figure 3.2 in Brace, 1993) until 31 weeks, reaching 149 ml. We used a third-degree curve fit, in accordance with general growth behaviour of mammalian fetuses (e.g. Dawes, 1968). Beyond 31 weeks, weight differences developing between human singletons and twins (Dawes, 1968; Bleker, Breur and Huidekoper, 1979; Rydström 1992), and fetal

blood volume proportional to fetal weight, assumes 225 ml blood volume at 40 weeks instead of 400 ml for singletons (Brace, 1993).

Fetal mean arterial and venous blood pressures [equation (4f), Table 4] begin at 5 weeks and grow linearly until 40 weeks reaching 60 and 7.5 mmHg, respectively. This is close to blood pressures measured in individual fetal singleton lambs at various gestational ages (Barcroft, 1946; Anderson and Faber, 1984; Iwamoto et al., 1989; Jensen and Lang, 1992). The data agree with venous pressures measured in umbilical veins of human singleton fetuses (Ville et al., 1994), average mean arterial pressure of 35 mmHg measured in a TTTS case at 27 weeks: recipient 50 mmHg, donor 20 mmHg (Benirschke and Kaufmann, 1995), and the 40 mmHg mean arterial pressure used at 27 weeks by Talbert et al. (1996).

We neglected pulsatility of blood flow and pressure, in part, because changes in fetal discordance develop over longer time scales (≈ 10 – 20 weeks) than fetal heart beats (≈ 0.4 sec).

Table 4. Summary of numerical model equations

$$X_{pld} + X_{plr} = 2 \quad (5 \leq t \leq 40 \text{ weeks}) \quad (4a)$$

$$V_{xN}(t; X_{plx}) = V_N(t) h_V(X_{plx}) \quad G_{xN}(t; X_{plx}) = G_N(t) h_V(X_{plx}) \quad (0 \leq X_{plx} \leq 2) \quad (4b)$$

$$V_N(t) = 149.0(t/31)^3 \quad (t \leq 31) \quad V_N(t) = 95.5 + 39.3\sqrt{t-29.14} \quad (t > 31) \quad G_N(t) = \frac{dV_N(t)}{dt} \quad (4c)$$

$$h_V(X_{plx}) = \sqrt[3]{X_{plx}} \quad (0 \leq X_{plx} \leq 0.236) \quad h_V(X_{plx}) = 0.5(X_{plx} + 1) \quad (0.236 < X_{plx} \leq 2) \quad (4d)$$

$$P_{axN}(t; X_{plx}) = P_{aN}(t) h_P(X_{plx}) \quad P_{vxN}(t; X_{plx}) = P_{vN}(t) h_P(X_{plx}) \quad (0 \leq X_{plx} \leq 2) \quad (4e)$$

$$P_{aN}(t) = 60(t-5)/35 \quad P_{vN}(t) = 7.5(t-5)/35 \quad (5 \leq t \leq 40 \text{ weeks}) \quad (4f)$$

$$h_P(X_{plx}) = 1.247 \sqrt[3]{X_{plx}} \quad (X_{plx} < 0.236) \quad h_P(X_{plx}) = (0.3X_{plx} + 0.7) \quad (0.236 \leq X_{plx} \leq 2) \quad (4g)$$

$$\frac{F_{xN}(t; X_{plx})}{R_{plxN}(t; X_{plx})} = \left(\frac{5G_N(t)}{P_{aN}(t) - P_{vN}(t)} \right) \left(\frac{X_{plx}}{1.247} \right) \quad (0 \leq X_{plx} < 0.236) \quad (4h)$$

$$\frac{F_{xN}(t; X_{plx})}{R_{plxN}(t; X_{plx})} = \left(\frac{5G_N(t)}{P_{aN}(t) - P_{vN}(t)} \right) \left(\frac{X_{plx} + 1}{3X_{plx} + 7} \right) \quad (0.236 \leq X_{plx} \leq 2) \quad (4i)$$

$$r_{XY}(t) = r_{XY}(40)f(t) \quad \ell_{XY}(t) = \ell_{XY}(40)f(t) = 0.15f(t) \quad (4 \leq t \leq 40 \text{ weeks}) \quad (4j)$$

$$f(t) = (t-4)/(27 \times 1.193) \quad (4 \leq t \leq 31 \text{ weeks}) \quad f(31) = 1/1.193 = 0.838 \quad (4k)$$

$$f(t) = ((1/9) + 0.7055(t-27)^{1/6})/1.193 \quad (t > 31 \text{ weeks}) \quad f(40) = 1 \quad (4l)$$

$$R_{XY}(t) = \frac{8 \times v \ell_{XY}(t)}{\pi r_{XY}(t)^4} \left(\frac{1}{1.333 \times 10^8 \times 60 \times 60 \times 24 \times 7} \right) = \frac{R_{XY}(40)}{f(t)^3} \quad (4m)$$

$$\sqrt[3]{X_{plxeq}(t)} = \frac{V_x(t)}{V_N(t)} \quad (X_{plxeq} < 0.236) \quad X_{plxeq}(t) = \left(2 \frac{V_x(t)}{V_N(t)} - 1 \right) \quad (0.236 \leq X_{plxeq} \leq 2) \quad (4n)$$

$$P_{ax}(t) = P_{aN}(t) H_P(V_x(t)/V_N(t)) \quad P_{vx}(t) = P_{vN}(t) H_P(V_x(t)/V_N(t)) \quad (4o)$$

$$H_P(V_x(t)/V_N(t)) = 1.247(V_x(t)/V_N(t)) \quad (V_x(t)/V_N(t) < 0.618) \quad (4p)$$

$$H_P(V_x(t)/V_N(t)) = 0.4 + 0.6(V_x(t)/V_N(t)) \quad (0.618 \leq V_x(t)/V_N(t) \leq 1.5) \quad (4q)$$

$$H_P(V_x(t)/V_N(t)) = (13/40)[2(V_x(t)/V_N(t)) - 1]^2 \quad (V_x(t)/V_N(t) > 1.5) \quad (4r)$$

$$I_{plN}(t) = (10/6)((t^4 - 5^4)/25^4)(60 \times 60 \times 24 \times 7) \quad (5 < t \leq 30 \text{ weeks}) \quad (4s)$$

$$I_{plN}(t) = (3.361 + 0.2914\sqrt{t-29.9})(60 \times 60 \times 24 \times 7) \quad (t > 30 \text{ weeks}) \quad (4t)$$

The constant factor in equation (4m) converts SI resistance units $[(N/m^2)/(m^3/s)]$ to $[mmHg/(ml/week)]$. Parameters $V_{xN}(t)$, $f(t)$, $I_{plN}(t)$ are smoothly continuous (continuous in function and derivative): $G(t)$, $h_V(X_{plx})$, $h_P(X_{plx})$ and $H_P(X_{plx})$ are only continuous.

Unequal placental sharing. Contrary to expectation, unequal placental sharing is quite common in TTTS (e.g. Braat et al., 1985; De Lia et al., 1993, 1995; Baldwin, 1994; Bajoria, Wigglesworth and Fisk, 1995; Machin, Still and Lanani, 1996). However, physiologic data of twins with unequally shared monochorionic placentation are lacking. To overcome this, we took the case of normal placental growth, and used that the number of available cotyledons for the twins, representing placental mass fractions, remains constant throughout pregnancy [equation (4a), Table 4].

We linked natural physiologic growth of unconnected monochorionic twins with their available placental mass fractions [equations (4b–d), Table 4], using figures for fetal versus placental weights in 834 human twin deliveries corrected for 40 weeks (McKeown and Record, 1953; Dawes, 1968 p 47). We assumed that the average weight of all 834 twins (2.81 kg)

and their placentae (0.62 kg) represented the average weights of: (1) monochorionic twins who share their common placenta equally; and (2) monochorionic twin placentae. Subsequently, we used the concepts that (1) fetal twin weight (2.0–3.1 kg) increases linearly with placental weight (0.22–0.79 kg); (2) weight is proportional to blood volume; (3) unequal placental fractions correspond to unequal placental weights with 0.62 kg as their sum (e.g. fetal weights at 0.155 and 0.465 kg placental weights represent monochorionic twins with 25:75 per cent placental sharing); (4) arbitrarily, the observed linear relationship is extended to placental weights > 0.146 kg; and (5) fetal weight tends to zero as the cube root of the placental weight $F < 0.146$ kg.

In a similar way, we linked blood pressures of unconnected monochorionic twins with their available placental mass fractions [equations (4e–g), Table 4] from mean arterial blood

pressure versus fetal weight measurements in 33 singleton sheep pregnancies at 116 ± 2 days gestation (0.773 of term; term is 150 days), using Figure 8 of Anderson and Faber (1984). Results at 140 ± 2 days (Dawes, 1968 p 179) show ≈ 50 per cent larger effects of weight on mean arterial pressures than used in our model.

Finally, ratios $F_d(t)/R_{pld}(t)$ and $F_r(t)/R_{plr}(t)$ [equation (3)] derived for unconnected monochorionic twins [equations (4h), (4i)], are also used during twin–twin transfusion. This implies that we neglected any influence of twin–twin transfusion on placental properties.

Second step: assessment of anastomotic resistances to link the two fetoplacental circulations

Radius and length of anastomosing blood vessels. Single straight blood vessels connecting the placental umbilical cord insertions represent anastomosing resistances. An essential assumption in our model is that the radius and length of anastomosing blood vessels grow during gestation. Two different mechanisms are included to assess their growth. First, the volume of anastomosing blood vessels grows commensurate with that of the placenta. Placental volume was curve-fitted to an 'S-shaped' function from serial ultrasound images of six normal singleton placentae (Wolf, Oosting and Treffers, 1987). Based upon general fetal growth behaviour (Dawes, 1968), and observations that placenta and fetus grow approximately proportionally, we assumed that placental volume increases as the third power of gestational age until 31 weeks (as t^3) followed by a slower growth curve from 31 to 40 weeks. This gave a good fit to Wolf's data. Using that anastomotic and placental volumes are both proportional to t^3 , results as $r_{XY}(t)^2 l_{XY}(t) \propto t^3$ for $t < 31$ weeks. Assuming that blood vessels become functional at 4 weeks yields that radius $r_{XY}(t)$ (m) and length $l_{XY}(t)$ (m) increase linearly proportional to $(t-4)$, until 31 weeks, followed by a reduced increase beyond 31 weeks [equations (4j), k and l), Table 4].

Second, a constant wall shear stress drives growth of anastomosing blood vessel radius (e.g. Lipowsky and Zweifach, 1974). From Poiseuille's law of laminar flow (e.g. Milnor, 1982), the ratio between anastomosing blood flow and radius to the third power must be constant throughout pregnancy. Available data for average umbilical venous blood flows (Gerson et al., 1987), showing an excellent fit to a fourth-degree function [equations (4s–t), Table 4], and average length and radius of umbilical veins, growing approximately proportional to gestational age (Figure 225 of Benirschke and Kaufmann, 1995; Oepkes, 1993 respectively), confirm equations j–l (Table 4) for growth of length and radius of umbilical veins. Because further information is lacking, we propose that if such a relationship holds for umbilical veins, it will also apply to chorionic blood vessels and, therefore, to placental anastomoses.

We assumed that all anastomotic lengths at 40 weeks are 0.15 m, representing an optimum for intertwin anastomoses (Baldwin, 1994).

Placental anastomosing resistances. We use Poiseuille's law, [equation (4m), Table 4], to represent vascular resistances $R_{XY}(t)$ [mmHg/ml week] of anastomosing blood vessels of length $l_{XY}(t)$, radius $r_{XY}(t)$, and blood viscosity 0.005 (N s/m²). Using equations (4 j–l) (Table 4) for growth of $l_{XY}(t)$ and $r_{XY}(t)$, yields that $R_{XY}(t)$ decreases significantly, proportional to $1/(t-4)^3$, $t < 31$ weeks.

A placental AV anastomosis is a single cotyledon rather than a blood vessel that connects the umbilical artery and vein at the opposite placental cord insertions. However, the haemodynamic resistances of a tube and a cotyledon are likely to behave similarly as a function of gestational age. The rationale is that the radius of a cotyledonic capillary does not vary with gestational age. Instead, the number of capillaries grows commensurate with the placental volume. This is as gestational age to the third power until about 31 weeks. Approximating the vascular resistance of a cotyledon by a parallel circuit of capillary resistances (e.g. Weibel, 1984) yields that overall cotyledonic resistance is inversely proportional to the number of capillaries and, hence, inversely proportional to the third power of gestational age until 31 weeks. This is in agreement with equation (4m) (Table 4). The anastomosing AV blood vessel used in our model is, therefore, the haemodynamic equivalent of a shared cotyledon. Approximately, we derived for all anastomoses that

$$R_{XY}(t) \propto [V_P(t)]^{-1} \propto [V_{FB}(t)]^{-1} \quad (5)$$

where V_P and V_{FB} are the placental and fetal blood volumes respectively.

Third step: defining mean arterial and venous blood pressures during twin–twin transfusion

We used systemic pressure–volume relations for discordant but unconnected twins at the same gestational age to represent those during twin–twin transfusion. This implies, first, that relating $V_d(t)/V_N(t)$ and $V_r(t)/V_N(t)$ to placental mass fractions that would cause such blood volumes under conditions of $T_{TT}=0$. These placental mass fractions, X_{pldeg} and X_{plreq} [equation (4n)] follow from equations (4b) and (4d) (Table 4). Second, substitution of X_{pldeg} and X_{plreq} for X_{plx} in equation (4e) (Table 4) produces mean arterial and venous blood pressures that are assigned to donor and recipient fetuses during twin–twin transfusion, equations (4o–p).

An important consequence is that the right-hand sides of equations (2a) and (2b) become closed form expressions in the unknown and known physiologic and haemodynamic parameters, [e.g. equation (A1)], allowing analytical analysis of dynamic steady states of fetal growth patterns (see below and Appendix A).

Fourth step: solving the set of coupled differential equations (2–4)

Numerical analysis. We used a standard predictor–corrector difference technique (e.g. Hamming, 1962) and a time step of, at most $1/10\,000$ week (1.008 min). Comparing computed with exact results for unconnected twins, [equations (4b–d), Table 4], shows a numerical inaccuracy of < 0.06 per cent at

40 weeks. We expect similar accuracy for connected twins (no analytical solutions). Oscillatory solutions noticed for small AV plus AA resistances disappeared if the time step was reduced.

Analytical analysis of dynamic steady states. In cases of AV plus compensating anastomoses, fetal discordance will be set up by the AV. However, the larger the discordance becomes, the more compensation by the other anastomoses will develop, until compensating anastomosing blood flow becomes virtually equal to that of the AV. Then, a dynamic steady state ensues where fetal growth is still weakly discordant (hence, dynamic), but where the fetoplacental system strives continuously towards minimal net anastomosing blood flow (hence, steady state). Net twin-twin transfusion is now significantly smaller than (1) the two individual natural physiologic growth terms, and (2) the two opposite anastomosing blood flows. Therefore, 'overall' growth of donor and recipient twins becomes dominated by their individual (discordant) natural physiologic growth mechanisms [equation (2)] as if there is haemodynamic disconnection. Furthermore, the rate of change of the difference between the two blood volumes will become small. It will be approximated as zero for analytical evaluation of dynamic steady states (Appendix A).

Model description

The model calculates fetal blood volume of the twins from 0 to 40 weeks by solving the set of two coupled first-order differential equations given in equations (2) and (A1). Input parameters are: (1) types of placental vascular anastomoses (any combination of AV, VA, AA, VV); (2) their vascular resistances $R_{AV}(t)$, $R_{VA}(t)$, $R_{AA}(t)$, $R_{VV}(t)$ which occur in equation (4), represented in equations (4 j-m) (Table 4) by blood vessel radii at 40 weeks, lengths taken as 0.15 m for all anastomoses; and (3) the degree of unequal placental sharing by the twins [equation (4a), Table 4].

Until about 5 weeks, before placental blood flow exists, we define donor and recipient fetal blood volumes from Figure 3.2 of Brace (1993), proportional to gestational age to the third power, corrected for future unequal placental sharing if necessary, [equations (4b-d), Table 4]. At 4 weeks, placental anastomosing blood vessels become functional. At 5 weeks, mean arterial and venous blood pressures are established [equations (4e-g), Table 4], and fetoplacental blood flow begins. This results in natural physiologic growth of both twins, as expressed in equation (3). Here, mean arterial and venous blood pressures follow from equations (4o-r), parameters $F_x(t)/R_{plx}(t)$ ($x=d,r$) from equations (4h, 4i) and anastomosing resistances from equation (4m) (Table 4). Net twin-twin transfusion of blood along the placental anastomoses starts [equation (4)]. This produces discordant fetal growth between the twins. The donor fetus, having a smaller blood volume than normal, develops smaller mean arterial and venous blood pressures. Consequently, its fetoplacental blood flow is smaller than normal and, therefore, also its natural physiologic growth [equation (3)]. The opposite occurs for the recipient fetus.

Output parameters are: blood volume and pressures of donor and recipient twins, and anastomosing and placental blood flows, as a function of gestational age.

RESULTS

Concepts: underlying pathophysiology of TTTS and general trends

We propose as the underlying pathophysiology of TTTS that fetal discordance developing between the twins increases progressively. This requires net anastomotic blood flow to increase faster than natural physiologic growth [equation (2)]. This requisite follows from placental and anastomotic development according to equation (5): placental volume increases approximately proportional to fetal blood volume, and inverse anastomotic resistance. To prove this, we use (anastomotic blood flow)=(anastomotic blood pressure difference)/(anastomotic resistance). Here, the inverse anastomotic resistance grows proportional to placental and fetal blood volumes [equation (5)], and anastomotic blood pressure difference increases with gestational age (in the numerical model proportional). So, anastomotic blood flow increases proportionately faster than fetal blood volume (in the numerical model as a fourth-degree versus a third-degree curve for blood volume). Next, natural physiologic growth is defined in terms of the rate of change of fetal blood volume, equation (1c). This means it must increase slower than fetal blood volume. Therefore, equation (5) implies that anastomotic blood flow increases faster than natural physiologic growth (in the numerical model as fourth-versus second-degree curves).

Without any further specification of fetal physiology, general patterns of discordant fetal growth can now be predicted. First, unidirectional AV anastomoses cause progressively increasing fetal discordance until the driving anastomotic pressure difference becomes small. Second, for AV plus compensating anastomoses, progressively increasing fetal discordance will develop first, set up by the AV anastomosis. This will result in more and more compensating anastomotic blood flow, so that net twin-twin transfusion will tend to zero. A dynamic steady state of fetal growth then ensues, dominated by individual natural physiologic growth mechanisms. Third, for unequal placental sharing plus compensating superficial anastomoses, anastomotic blood flow will grow faster than natural physiologic growth mechanisms, and hence will tend to compensate for the discordant growth set up by the different placental mass fractions. These general growth patterns only derived from equation (5) are illustrated below from numerical and analytic (Appendix A) analysis.

Numerical results

AV anastomoses.

Figure 1 shows results from numerical computations for two different AV anastomoses, with a factor 4.2 resistance ratio, in an equally shared placenta. Progressively increasing

discordance between the twins in blood volume [Figure 1(A)] and blood pressures [Figure 1(B), venous pressures not shown] develops, caused by predicted net twin-twin transfusion of less than 1 ml/24 h [Figure 1(C)]. However, such small anastomosing blood flows constitute a significant fraction of fetal blood volumes when integrated over time. Considerable differences in fetal discordance occur for the two cases, which may have caused clinical symptoms of TTTS or fetal death around 15 and 22 weeks, respectively. The results predict [Figure 1(B)] that at about 22 and 36 weeks for the smallest and largest AV resistances, respectively, the donor's mean arterial and the recipient's venous blood pressures become equal. Although possible in the model, this represents unrealistic fetal discordance which is incompatible with fetal survival.

The insert of Figure 1(A) shows predictions for strongly unequally shared placenta. First, if the AV is from smaller to larger placental mass (—), significant discordance occurs earlier in pregnancy than otherwise. Second, the AV anastomosis from larger to smaller placental mass (---) produces early on in pregnancy a growth accelerated donor (larger placental mass) and a growth retarded recipient (smaller placental mass). However, once the anastomotic resistance becomes small enough, it dominates fetal growth. Then, the donor becomes the smaller, the recipient the larger twin. This mechanism of fetal growth reversal is also predicted in cases of AV plus compensating anastomoses provided the donor twin has access to the larger placental mass.

These predictions explain, at least in part, why the onset of clinical symptoms in twin-twin transfusion syndrome may occur abruptly and can vary so widely during pregnancy. Furthermore, it could explain several clinical reports of fetal growth reversal. As an example, Baldwin (1994) describes this phenomenon at least in part where, indeed, the donor twin had the larger placental part and the anastomotic pattern consisted of three unidirectional AV and three superficial (two AA and one VV) anastomoses. Also, Pinette et al. (1993) described fetal growth reversal but gave no placental details.

AV plus compensating anastomoses: dynamic steady states.

Figure 2 shows the results for two sets of AV plus compensating AA anastomoses of equal resistances, with a 10 000 resistance ratio between the two sets. Although the curves are unequal early in pregnancy, they tend to coalesce later [in contrast to AV anastomoses with only a factor 4.2 resistance ratio; Figure 1(A)]. Here, the dynamic steady state of fetal growth ensues, where anastomotic AV and AA flows are virtually the same. The

underlying mechanism is that the fetoplacental units strive continuously towards maintaining minimal net twin-twin transfusion (Appendix A). Blood pressures behave correspondingly (results not shown). Anastomosing blood flows increase,

Figure 1. Numerical results of two AV anastomoses and equal placental sharing, using $r_{AV}(40) = 0.1$ and 0.07 mm, respectively (indicated). D, R, N, Donor, Recipient, Normal unconnected twin with equal placental sharing [equation (4c) Table 4]. (A) Blood volumes as a function of gestational age. Inset: Results for: 25:75 per cent (—) and 75:25 per cent (---) (donor to recipient) unequal placental sharing, $r_{AV}(40) = 0.07$ mm. (B) Mean arterial blood pressures as a function of gestational age (—). Curve N is from equation (4f). — · — and — · — · —, recipient's venous blood pressures. (r_v). (C) AV anastomotic blood flows as a function of gestational age.

Figure 2. Numerical results of equal AV and AA anastomosing resistances and equal placental sharing —, $R_{AV}(40)=r_{AA}(40)=0.07$ mm; ---, $r_{AV}(40)=r_{AA}(40)=0.7$ mm, a 10 000 times lower resistance. D, R, N, Donor, Recipient, Normal unconnected twin with equal placental sharing [equation (4c), Table 4].

reaching about 27 200 ml/24 h for the low resistance case (about 19 ml/min, comparable to normal chorionic vascular flow), versus 5 ml/24 h for the higher resistances. However, net twin-twin transfusion is for both cases as small as about 0.3 ml/24 h (results not shown). Dynamic steady states of fetal growth are also predicted to occur for AV plus any combination of compensating bi-directional deep VA, and superficial AA, VV anastomoses.

Analysis (Appendix A) shows that the extent of fetal discordance during dynamic steady states depends on the resistance ratios of AV-VA, AV-AA, and AV-VV anastomoses [equation (A9)]. Figure 3 presents the individual effects, showing that VA anastomoses compensate the discordance best, AA about 50 per cent less effective, and VV very ineffective. Also, smaller compensating anastomotic resistances (larger size anastomoses), or more of them produce smaller fetal discordance. The latter result explains why Bajoria, Wigglesworth and Fisk (1995) found TTTS in placentae with one or two anastomoses, but not in their controls with more complicated anastomotic patterns.

Unequal placental sharing plus compensating superficial anastomosis: dynamic steady state.

Here, superficial anastomosing blood flow compensates for the fetal discordance set up by the different available placental mass fractions. Although TTTS might have occurred at around 15 weeks in the example chosen (Figure 4), the discordance never becomes large. The clinical consequence is

Figure 3. Individual influence of compensating anastomoses on $V_d(t)/V_r(t)$ during dynamic steady states [equation (A9)] as functions of: $R_{VA}(40)/R_{AV}(40)$ (— using R_{sup} is infinite), $R_{AA}(40)/R_{AV}(40)$ (--- using $R_{VA}=R_{VV}$ is infinite) and $R_{VV}(40)/R_{AV}(40)$ (·····, using $R_{VA}=R_{AA}$ is infinite).

Figure 4. Numerical results of an AA anastomosis and 25:75 per cent unequal placental sharing, $r_{AA}(40)=0.06$ mm. $X_{pld}=1.5$ for the donor twin (D), $X_{plr}=0.5$ for the recipient (R). Recipient's dynamic steady state (---) follows from solving $V_r(t)$ equation (A3) and using numerical results of $V_d(t)$. The discontinuity in the predicted steady state at 31 weeks is because $G_N(t)$ is continuous (but not smoothly continuous) at $t=31$ weeks [equation (4b), Table 4].

that, if TTTS occurs in this placental anatomy, clinical symptoms will tend to disappear spontaneously, as described by e.g. Braat et al. (1985).

Figure 5. Numerical results of $[V_r(t) - V_d(t)] / (0.5)[V_r(t) + V_d(t)]$, the *Fetal Difference-Average Ratio*. Data from Figure 1 (—), Figure 2 and other (indicated) anastomotic radii at 40 weeks (·····), and from Figure (4) (— · —) were used.

Morphology of fetal growth pattern: fetal difference-average ratio.

Figure 5 shows results of the fetal difference-average ratio, defined as the ratio between difference in fetal blood volumes, $[V_r(t) - V_d(t)]$, and their average value, $(0.5)[V_r(t) + V_d(t)]$. The maximum of this parameter is 2, reached when $V_d(t)/V_r(t)$ becomes 0. Its minimum is 0, reached when $V_d(t) = V_r(t)$. For AV anastomoses [from Figure 1(A)], this parameter increases significantly until anastomosing blood pressure difference becomes small [Figure 1(B)]. For AV plus compensating anastomoses, e.g. AV plus AA of equal resistance (from Figure 2), saturation occurs once the dynamic steady state of minimal net transfusion has ensued. For the small resistance cases, this occurs early, but is around 35 weeks for the larger resistances. The case of unequal placental sharing plus AA anastomosis (from Figure 4) shows a continuously decreasing curve, as predicted in equation (A10).

Variation of model parameters.

Firstly, if $T_{TT}(t)$ is a constant fraction of natural physiologic growth, e.g. AV flow is 10 per cent of $G_N(t)$. [equation (4c)] discordance increases from 20 per cent early on to 47 per cent at 25–40 weeks [insert, Figure 6(A)]. Deviations from the expected 20 per cent discordance is because AV flow is relatively large early on.

Secondly, we use the same anastomotic radius and length at 40 weeks, but two different growth curves than otherwise [equations (4 j–l)]. We use [insert, Figure 6(B)]

Figure 6. Numerical results of 0.07 mm radius (40 weeks) anastomoses. Solid lines: (1) normal resistance [equation (4j) and (4k, table 4)]. Dashed lines: according to equation (6) with (2) $n=0.5$ and (3) $N=1.5$. D, R, N: Donor, Recipient, Normal unconnected twin with equal placental sharing, Eq. (4c) of Table 4. (A) AV anastomosis. Inset: Results for $T_{TT}=0.1G_N(t)$. (B) AV plus AA anastomoses of equal resistance. Inset: Anastomotic radius for the three cases used.

$$\frac{r_{XY}(t)}{r_{XY}(40)} = \frac{\ell_{XY}(t)}{\ell_{XY}(40)} = \left(\frac{t-4}{36} \right)^n \quad \text{and} \quad \frac{R_{XY}(t)}{R_{XY}(40)} = \left(\frac{36}{t-4} \right)^{3n}$$

($n=0.5, 1.5$) ($4 < t \leq 40$ weeks) (6)

These anastomoses are, for $n=0.5$ and 1.5 , larger, respectively, smaller early on in pregnancy than normal ($n=1$).

This choice would imply that placental volume increases as $(\text{gestational age})^{3n}$ and umbilical venous blood flow as $(\text{gestational age})^{(3n+1)}$ instead of, respectively, $(\text{gestational age})^3$ and $(\text{gestational age})^4$ used in the numerical model. We emphasize that the $n=0.5$ but not the $n=1.5$ set of growth curves fit the available clinical data (Gerson et al., 1987; Wolf, Oosting and Treffers, 1987).

For single AV anastomoses [Figure 6(A)], fetal discordance begins differently, but tends to become the same later in pregnancy when the three resistances become identical. The case of AV plus compensating AA anastomoses of equal resistances [Figure 6(B)] shows again development of similar dynamic steady states, with merging blood volumes for the three growth curves. With equation (6), different fetal discordance than normal occurs early on.

Variation of other model parameters, e.g. systemic blood pressure–volume curves as a result of (1) different mean arterial and venous pressures, (2) blood volume data, or (3) effects of unequal placental sharing, may show individual variations of the fetal growth patterns, but will not change any of the general trends predicted by the model in Figures 1–5 (see Results).

DISCUSSION

The model developed for twin–twin transfusion along vascular anastomoses proposes as underlying pathophysiology of TTTS that net anastomotic blood flow has to increase faster than natural physiologic growth. General trends identified in discordant fetal growth patterns then ensue without need to specify details of fetal physiology. Numerical and analytic results from the model illustrate how onset, severity and dynamic development of fetal discordance occurring in monochorionic twins relate to placental anastomotic patterns.

Concepts

A broader formulation of the underlying pathophysiology of TTTS than proposed may be that the situation becomes pathological when fetal discordance developing between the twins increases faster than the capacity of the twins to compensate for the discordance. Both definitions match if mechanisms of fetal compensation increase their capacity approximately commensurate with mechanisms of fetal growth.

The hypothesis that placental anastomoses grow during pregnancy originates from general observations that feeding blood vessels increase in size when the organ they perfuse grows. An example is the factor of about 10 increase in aortic diameter when a term fetus has become an adult. The only direct evidence in placentation that supports our assumptions is the observed increase in umbilical cord length and radius during pregnancy (e.g. Figure 225 in Benirschke and Kaufmann, 1995; Oepkes, 1993), which are indeed approximately linear with gestational age, as used in equations (4)–(1).

Implications and perspectives

The model predicts as its most important result that different placental anastomotic patterns occurring in monochorionic twin placentation produce significantly different patterns of haemodynamic imbalance developing between the twins. Implications include: (1) very small but strongly increasing net anastomotic blood flow causes progressively increasing fetal discordance; (2) fetal discordance can start abruptly but its moment of onset can vary widely during pregnancy [insert of Figure 1(A)]; (3) large, opposite, measurable (e.g. Hecher, Ville and Nicolaides, 1995) anastomotic blood flows can occur in cases of AV plus compensating anastomoses; (4) fewer anastomoses may cause larger discordance and vice versa [Bajoria, Wigglesworth and Fisk, 1995; and equation (A6)]; (5) VA, AA, VV anastomoses compensate fetal discordance with decreasing efficacy; and (6) not only AV anastomoses but also unequal placental sharing can be the underlying cause of discordant twins (Figure 4). Furthermore, clinical observations describing fetal growth reversal (Pinette et al., 1993; Baldwin 1994) or spontaneous disappearance of symptoms (Baat et al., 1985) can be explained easily (Figures 1 and 4).

Evaluation of the fetal difference–average ratio may allow underlying placental anastomosing patterns to be distinguished. Instead of blood volume we propose to use the size of the twins, specifically heart–thoracic ratios (Pridjian, Nugent and Barr, 1991), measured by ultrasound imaging. In this way, cases of single AV, AV plus compensating anastomoses, and unequally shared placentation plus superficial anastomoses may be distinguished (Figure 5). As these anatomical cases have progressively better fetal survival (Machin, Still and Lanani, 1996), this prediction, if true, will increase the specificity of diagnosis of the syndrome, and improve assessment of its severity, its prognosis, and choice of best treatment strategy (van Gemert, Major and Scherjon, 1998; van Gemert et al., 1997).

Limitations of the model

The implemented physiology of the fetus had to be simplified, sometimes with empirical relationships, to facilitate numerical and analytic modelling. First, in equation (2), we assumed that the rate of change of blood volume is governed by natural physiologic growth, a component taken proportional to fetoplacental blood flow and fetomaternal effects, to which net twin–twin transfusion is added as a component representing transfer of blood along placental anastomoses. Because this approximation neglects effects caused by discordant nutrient content developing between the twins, our model could underestimate the discordance developing between the twins. In addition we neglected fetal compensatory mechanisms to changing physiologic conditions, e.g. compensation of blood loss for the donor twin and compensation of hypervolaemia by excess micturition for the recipient. Consequently, our model will underestimate net anastomosing blood flows that cause significant fetal discordance. However, in view of the general

concepts identified above, expressing that placental development favours anastomotic blood flow to increase faster than fetal physiologic growth mechanisms, so that progressively increasing fetal imbalance results beyond fetal compensatory capabilities, it is unlikely that compensation mechanisms, if included, would dramatically change the general predictions of the model.

Second, our assumption that placental properties (such as resistance and conversion of fetoplacental blood flow into natural physiologic growth) are not influenced by anastomosing blood flow is probably only justified for relatively small ratios of the two fetal weights. In cases of substantial net twin-twin transfusion, the donor fetus loses blood and has a lower haematocrit and, therefore, lower blood viscosity, while the recipient has the opposite. Most likely as a consequence, the texture of donor and recipient placentae becomes different (e.g. Baldwin, 1994).

Third, growth curves used for fetal blood volume, placenta, placental anastomoses and umbilical venous blood flow are not accurately known, and subject to individual variability. For example, we stated that anastomotic blood flow starts to increase proportional to t^4 , whereas natural physiologic growth

increases proportional to t^2 . Hence, considerable flexibility is left for, say growth variation in anastomotic blood flow. For example, use of $n=0.5$ in equation (6) implies that $T_{TT}(t) \propto t^{2.5}$. Because this is still a faster growth rate than that of $G_x(t)$, progressively increasing fetal discordance results (Figure 6). Consequently, although the numerical model can only provide trends to illustrate the general concepts, these underlying concepts are expected to be realistic.

Conclusion

Progressively increasing fetal discordance, beyond fetal compensatory capacity, is proposed as underlying pathophysiology of TTTS. Most implications derived from the model depend only weakly on implemented fetal physiology but explain previously incompletely understood clinical observations. Consequently, as the predictions relate clinical presentation of the syndrome with underlying placental anastomotic patterns, verification of the model from clinical study of outcome versus placental anatomy may increase our understanding and could improve future management of TTTS.

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APPENDIX A: ANALYTICAL ANALYSIS OF DYNAMIC STEADY STATES

Combining equations (4 o-r), with (2-4), yields the final set of differential equations in $V_d(t)$ and $V_r(t)$. If $V_d(t)$ and $V_r(t)$ are both between 0.618 and 1.5 times $V_N(t)$, the results are

$$\begin{aligned} \frac{dV_d(t)}{dt} = & 2G_N(t)f_d - 0.4(P_{aN}(t) - P_{vN}(t)) \left(\frac{1}{R_{AV}(t)} - \frac{1}{R_{VA}(t)} \right) \\ & + \left(\frac{V_r(t)}{V_N(t)} \right) \left[0.6 \left(\frac{P_{vN}(t)}{R_{AV}(t)} + \frac{P_{aN}(t)}{R_{VA}(t)} + \frac{P_{aN}(t)}{R_{AA}(t)} + \frac{P_{vN}(t)}{R_{VV}(t)} \right) \right] \\ & - \left(\frac{V_d(t)}{V_N(t)} \right) \left[-3G_N(t)f_d + 0.6 \left(\frac{P_{aN}(t)}{R_{AV}(t)} + \frac{P_{vN}(t)}{R_{VA}(t)} + \frac{P_{aN}(t)}{R_{AA}(t)} \right. \right. \\ & \left. \left. + \frac{P_{vN}(t)}{R_{VV}(t)} \right) \right] (0.618 < V_d(t)/V_N(t) < 1.5) \quad (A1a) \end{aligned}$$

$$\begin{aligned} \frac{dV_r(t)}{dt} = & 2G_N(t)f_r + 0.4(P_{aN}(t) - P_{vN}(t)) \left(\frac{1}{R_{AV}(t)} - \frac{1}{R_{VA}(t)} \right) \\ & + \left(\frac{V_d(t)}{V_N(t)} \right) \left[0.6 \left(\frac{P_{vN}(t)}{R_{AV}(t)} + \frac{P_{aN}(t)}{R_{VA}(t)} + \frac{P_{aN}(t)}{R_{AA}(t)} + \frac{P_{vN}(t)}{R_{VV}(t)} \right) \right] \\ & - \left(\frac{V_r(t)}{V_N(t)} \right) \left[-3G_N(t)f_r + 0.6 \left(\frac{P_{vN}(t)}{R_{AV}(t)} + \frac{P_{aN}(t)}{R_{VA}(t)} + \frac{P_{aN}(t)}{R_{AA}(t)} \right. \right. \\ & \left. \left. + \frac{P_{vN}(t)}{R_{VV}(t)} \right) \right] (0.618 < V_r(t)/V_N(t) < 1.5) \quad (A1b) \end{aligned}$$

$$f_d = (1 + X_{pld})(7 + 3X_{pld})^{-1} \quad (A1c)$$

and

$$f_r = (1 + X_{plr})(7 + 3X_{plr})^{-1}$$

Equation (A1) represents a set of two coupled first-order linear differential equations in $V_d(t)$ and $V_r(t)$, with closed form expressions of time-dependent coefficients of known values throughout pregnancy. Similarly, a linear set of equations results when one of the fetuses has a blood volume smaller than 0.618 $V_N(t)$ and the other smaller than 1.5 $V_N(t)$. However, if one fetal blood volume becomes larger than 1.5 $V_N(t)$, the right-hand sides of equation (A1) become quadratically non-linear in that fetal blood volume. Dynamic steady-state solutions follow if

$$\frac{d}{dt} [V_r(t) - V_d(t)] = [G_r(t) - G_d(t)] + 2T_{TT}(t) \approx 0 \quad (A2)$$

requiring that $2T_{TT}(t)$, and $[G_r(t) - G_d(t)]$ are much smaller than $G_r(t)$, $G_d(t)$ and the individual anastomotic flows. Combining equations (A1) and (A2), and solving for $[V_r(t) - V_d(t)]$, yields

$$\begin{aligned} \frac{(V_r(t) - V_d(t))}{\left(V_d(t) + \frac{2}{3} V_N(t) \right)} \approx & \frac{\left(2.5G_N(t)(f_r - f_d) + (P_{aN}(t) - P_{vN}(t)) \left(\frac{1}{R_{AV}(t)} - \frac{1}{R_{VA}(t)} \right) \right)}{\left(-2.5G_N(t)f_r + \left(\frac{P_{vN}(t)}{R_{AV}(t)} + \frac{P_{aN}(t)}{R_{VA}(t)} + \frac{P_{aN}(t)}{R_{AA}(t)} + \frac{P_{vN}(t)}{R_{VV}(t)} \right) \right)} \quad (A3) \end{aligned}$$

Equation (A3) is also derived, but without the terms in $G_N(t)$, if net anastomosing blood flow is set to zero, $T_{TT}=0$ [equation (4)] and substituting equations (4o–r) in this relationship. Equation (A3) shows that an exact equivalent AV resistance, $R_{AVE}(t)$, does not exist here. However, an approximate relationship follows from the numerator of the second relation

$$\frac{1}{R_{AVE}(t)} \approx \frac{1}{R_{AV}(t)} - \frac{1}{R_{VA}(t)} \quad (A4)$$

Furthermore, from the denominator of equation (A3) (second term), VV and AA anastomoses provide equal haemodynamic compensation of AV mediated fetal discordance if

$$\frac{P_{aN}(t)}{R_{AA}(t)} = \frac{P_{vN}(t)}{R_{VV}(t)} \text{ or } R_{AA}(t) = R_{VV}(t) \frac{P_{aN}(t)}{P_{vN}(t)} \approx 8R_{VV}(t) \quad (A5)$$

Consequently, if superficial placental anastomoses include, e.g. n (identical) AA and m (identical) VV anastomoses, the equivalent superficial anastomotic resistance, $R_{sup}(t)$, follows from equation (A5) and the standard relationship of parallel resistances

$$\frac{1}{R_{sup}(t)} = \frac{n}{R_{AA}(t)} + \frac{m}{8R_{VV}(t)} \quad (A6)$$

Note that more superficial anastomoses produce a smaller equivalent superficial resistance (and vice versa).

Analytical expressions for the fetal difference–average ratio can be derived. We use that $P_{aN}(t) = 8P_{vN}(t)$, the ratio of anastomosing resistances at any gestational age equals that at, e.g. $t=40$ weeks, and neglect terms in $G_N(t)$ relative to anastomotic flow terms. Using that approximately

$$V_d(t) + \frac{2}{3}V_N(t) \approx V_N(t) \approx 0.5(V_r(t) + V_d(t)) \quad (A7)$$

yields from equation (A3)

$$\frac{(V_r(t) - V_d(t))}{0.5(V_r(t) + V_d(t))} \approx \quad (A8)$$

$$7 \left(1 - \frac{R_{AV}(40)}{R_{VA}(40)} \right) \left[1 + 8 \left(\frac{R_{AV}(40)}{R_{VA}(40)} + \frac{R_{AV}(40)}{R_{sup}(40)} \right) \right]^{-1}$$

From equation (A8), ratio $V_d(t)/V_r(t)$ during dynamic steady states follows as (Figure 3)

$$\begin{aligned} \frac{V_d(t)}{V_r(t)} \approx & \left(23 \left(\frac{R_{AV}(40)}{R_{VA}(40)} \right) \right. \\ & + 16 \left(\frac{R_{AV}(40)}{R_{sup}(40)} \right) - 5 \left. \right) \left[9 \left(\frac{R_{AV}(40)}{R_{VA}(40)} \right) \right. \\ & + 16 \left(\frac{R_{AV}(40)}{R_{sup}(40)} \right) + 9 \left. \right]^{-1} \end{aligned} \quad (A9)$$

Finally, for strongly unequal placental sharing and superficial anastomoses, equation (A3) gives

$$\begin{aligned} & \frac{(V_r(t) - V_d(t))}{0.5(V_r(t) + V_d(t))} \\ & \approx 2.5G_N(t)(f_r - f_d) \left(\frac{P_{aN}(t)}{R_{sup}(t)} \right)^{-1} \propto (f_r - f_d) \frac{t^2}{(t-4)^3(t-5)} \end{aligned} \quad (A10)$$

where equations (4b), (4c) as well as (4f), (4m) (Table 4) have been used (Figure 4).

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