Models of twin-twin transfusion syndrome

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Chapter 6

Discordant Fetal Growth Patterns in Monochorionic Twin Pregnancies Described by Simple Mathematical Relations

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ABSTRACT
Our objective was to assess the validity of previously derived simple mathematical relations representing trends of discordant fetal growth of twin-twin transfusion syndrome (TTTS) and cases that were suspect but not confirmatory for developing the syndrome (pseudo-TTTS). In 25 monochorionic twin pregnancies, fetal growth was determined by standard ultrasonography. The difference between estimated fetal weights (dEFW) as well as the difference divided by the average of the two weights, the difference average ratio of fetal weights (DAR), were fitted to the predicted TTTS and pseudo-TTTS trends of discordant fetal growth, derived from our hemodynamic model. The best fits were compared with the clinical data of the model equations. The results were as follows. Out of 13 TTTS cases, dEFW correctly predicted eight (67%) and DAR correctly predicted 10 (77%). Out of 12 pseudo-TTTS cases, dEFW correctly predicted seven (58%) and DAR correctly predicted nine (75%). If pseudo-TTTS was predicted, dEFW was correct in 7/9 (78%), and DAR in 9/12 (75%) cases. If TTTS was predicted, dEFW was correct in 8/12 (67%), and DAR in 10/11 (91%) cases. In conclusion, the difference average ratio has a greater predictive power for prognosis than the difference between the estimated fetal weights. The simple mathematical relations derived to identify trends of fetal discordant growth seem to describe the clinical growth patterns well, which shows evidence that some clinical TTTS and pseudo-TTTS manifestations are actually predictable and quantifiable.

Key words: monochorionic twin pregnancy, discordant fetal development, model predictions, twin-twin transfusion syndrome (TTTS), pseudo-TTTS.
INTRODUCTION

Twin-twin transfusion syndrome (TTTS) is a serious complication of monochorionic twinning that occurs in about 10-25% of monochorionic placentaion. The syndrome presents as the oligo-polyhydramnios sequence with a hypotensive, oliguric, often small for gestational age donor twin, which frequently becomes stuck in its membranes, and a hypertensive, polyuric, normal size recipient twin, which may develop cardiomegaly, forward heart failure and hydrops as additional complications, representing increased TTTS severity (Quintero et al., 1999). The syndrome is associated with significant mortality and morbidity (van Gemert et al., 2001).

Our group has developed hemodynamic and amniotic fluid dynamics computer models of two monochorionic feto-placental circulations connected by placental anastomoses (van Gemert and Sterenborg, 1998; Umur et al., 2001). With these models the etiology of TTTS was proposed to be as follows: during gestation, the net feto-fetal transfusion from donor to recipient increases to a greater degree than each twin’s increase in blood volumetric growth. Furthermore, we showed that the imbalance that develops between the two feto-placental circulations as a consequence of net feto-fetal transfusion can vary widely. Therefore, clinical symptoms caused by the circulatory imbalance can also evolve mildly. This may result in milder forms of TTTS, i.e., the oligo-polyhydramnios sequence without or with fewer additional complications, in pseudo-TTTS (Mari et al., 1998; van Gemert et al., 2000a), i.e., clinical manifestations that are suspect although not confirmatory for TTTS, or in uncomplicated non-TTTS monochorionic twin pregnancies.

Despite the complexity of the hemodynamic model (van Gemert and Sterenborg, 1998), it turned out to be possible to approximate the model equations analytically, and derive simple mathematical relations representing trends of fetal discordant development of TTTS and pseudo-TTTS pregnancies (van Gemert and Umur, 2000a). Unexpectedly, the agreement with biometry data from four selected clinical cases was remarkably good. Because simple mathematical relations characterizing fetal discordant growth could have clinical relevance, e.g., by showing evidence that fetal growth patterns of monochorionic twins may follow simple rules, we sought to assess the validity of the predicted trends by comparing the predictions with clinical growth patterns in a larger number of TTTS and pseudo-TTTS pregnancies than before.

METHODS

TTTS was defined according to current criteria as severe oligohydramnios (deepest pool less than 2 cm) or anhydramnios in one twin’s sac (stuck twin), in combination with gross polyhydramnios in the other sac (deepest pool more than 8 cm) (Zikulnig et al., 1998). Pseudo-TTTS was defined as previously (van Gemert et al., 2000a), i.e., either oligohydramnios in one twin’s sac, or polyhydramnios in the other, or at least a difference in estimated fetal weight of 35%, but not simultaneously the oligo-polyhydramnios sequence.

Estimated fetal weights were determined from measurements of the biparietal diameter, head circumference, abdominal circumference, and femur length, as described by Hadlock et al. (1985). For each pregnancy, the difference between estimated fetal weights (dEFW) and the difference average ratio (DAR), defined as the dEFW divided by the average weight of both twins, were calculated.

Hemodynamic model

The hemodynamic model (van Gemert and Sterenborg, 1998) relates fetal growth of its blood volume with (a) natural physiologic growth, defined as the anticipated normal physiologic
increase of blood volume per week, and (b) net feto-fetal transfusion of blood from donor to recipient through placental anastomoses. In words, the equations read

\[
growth \text{ of recipient/donor blood volume} = (natural \text{ physiologic growth of recipient/donor blood volume}) \pm (net \text{ feto-fetal transfusion}) \tag{1}
\]

Here, the "plus" sign refers to the recipient, and the "minus" sign to the donor. The full numerical solution of the equations has been described previously (van Gemert and Sterenborg, 1998), based on growth of the anastomoses proportional to placental growth as the proposed etiology of TTTS. This mechanism causes irreversibly increasing fetal discordance in response to unidirectional arterio-venous anastomoses, but steady state discordant growth if these anastomoses are adequately compensated by other deep (i.e. opposite arterio-venous), or superficial (i.e. arterio-arterial, veno-venous) anastomoses.

In a previous paper (van Gemert and Umur, 2000a) we derived approximate analytical solutions of the hemodynamic model as follows. First, we took the difference between the two growth equations (Eqn.1). This gives an equation expressing the growth difference between recipient and donor, Eqn.2a below. Second, we took the sum of the two growth equations (Eqn.1), where the net feto-fetal transfusion terms cancel, which gives an equation for the sum of their growths, Eqn.2b below. The two results become

\[
growth \text{ difference between recipient and donor} = (difference \text{ between natural physiologic growths}) + 2(net \text{ feto-fetal transfusion}) \tag{2a}
\]

\[
sum \text{ of their growths} = (sum \text{ of natural physiologic growths}) \tag{2b}
\]

For TTTS we used Eqn.2a and assumed that twice the net feto-fetal transfusion is much larger than the difference between natural physiologic growths of both twins. For pseudo-TTTS, i.e., adequately compensated arterio-venous anastomoses, implying virtually zero net feto-fetal transfusion, we assumed that the net feto-fetal transfusion becomes insignificant, i.e., twice the net feto-fetal transfusion is much smaller than the difference between the natural physiologic growths. Finally, we used the following approximations. First, natural physiologic growth increases proportional to the second power of gestational age and, second, net feto-fetal transfusion during TTTS increases proportional to gestational age minus 5 to the fourth power (Table 1), where we assumed that the feto-placental circulations started at 5 weeks gestation.

Therefore, for TTTS

\[
growth \text{ difference between recipient and donor} \approx 2 (net \text{ feto-fetal transfusion}) \propto (t-5)^4 \tag{3a}
\]

\[
sum \text{ of growths} \propto t^2 \tag{3b}
\]

where symbol \( \propto \) denotes "proportional to", and \( t \) denotes gestational age in weeks.

Similarly, for pseudo TTTS

\[
growth \text{ difference between recipient and donor} \approx \frac{(difference \text{ between natural physiologic growth})}{sum \text{ of growths}} \propto t^2 \tag{4a}
\]

\[
(t) \tag{4b}
\]
Straightforward integration (van Gemert and Umur, 2000a) resulted in the following trends (Table 1).

<table>
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<th>dEFW</th>
<th>DAR</th>
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<tr>
<td>TTTS</td>
<td>(\propto (t-5)^5)</td>
<td>(\propto \frac{(t-5)^5}{t^3})</td>
</tr>
<tr>
<td>Pseudo TTTS</td>
<td>(\propto t^3)</td>
<td>(\approx \text{constant})</td>
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Table 1. Approximate relations representing trends of discordant fetal development for TTTS and pseudo-TTTS cases. dEFW: difference between estimated fetal weights. DAR: difference average ratio of fetal weights, defined as the difference between the two weights divided by the average of the weights. \(t\): gestational age in weeks, symbol \(\propto\) denotes "proportional to".

First, for TTTS

\[
dEFW = \text{difference between estimated fetal weights} \propto (t-5)^5
\]

\[
DAR = \text{difference between estimated fetal weights/average of the two weights} \propto \frac{(t-5)^5}{t^3}
\]

Second, for pseudo-TTTS

\[
dEFW \propto t^3
\]

\[
DAR \approx \text{constant}
\]

Data analysis

The clinical data of estimated fetal weights, excluding the birth weights, were fitted to the two predicted trends of Table 1, TTTS and pseudo-TTTS, using a polynomial fit program written in MATLAB, in a least squares sense. Parameters dEFW and DAR of the TTTS fits (Eqn.5) and dEFW of the pseudo-TTTS fit (Eqn.6a) were forced to pass through zero at five weeks gestation. The best fit, i.e., the fit with the smallest 95% confidence interval, was designated as the prediction of the model equations. These predictions, either development of TTTS or pseudo-TTTS, were compared with the clinical outcomes.

RESULTS

All monochorionic twin pregnancies available between December 1998 and July 2001 that developed TTTS or pseudo-TTTS with at least four data points of estimated fetal weights were included in the study. Twenty-five pregnancies were available for analysis. Three cases (9, 15, 19) were from the literature (Braat et al, 1985; Sharma et al, 1995; Suzuki et al, 1999). Cases 2 (Zondervan et al, 1999), 16 (Nikkels et al, 2002) and 18 (Nikkels et al, 2001) were analyzed in detail elsewhere. Cases 1, 13, 15 and 19 were used in our previous paper (van
<table>
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<th>Case</th>
<th>Model</th>
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**Table 2.** Clinical data and model analysis of 25 monochorionic pregnancies. US: Ultrasound examination. AR: Amnioreduction. CS: Cesarian section. Sept: Septostomy. Before laser treatment. After thrombosis of a major chorionic vein. Numbers used in the second column (Prev) represent the cases of our earlier manuscript (van Gemernt et al, 2000b). Gemernt and Umur, 2000). In four cases (13, 14, 21, 22) fetoscopic laser therapy was performed (Dr. K Hecher, Hamburg) and the gestational period before the treatment was used for analysis. The clinical cases are summarized in Table 2. Results of the statistical analysis are given in Table 3. Out of the 25 cases the dEFW analysis correctly predicted 15 (60%) and the DAR analysis correctly predicted 19 (76%) cases. In 4 of the 25 cases (16%) dEFW analysis fitted both trends equally well, versus 2 (8%) for the DAR analysis. Out of 12 pseudo-TTTS cases (1-12, Table 2), dEFW analysis correctly predicted seven (58%), and DAR analysis correctly predicted nine (75%) cases. Out of 13 TTTS cases (13-25), dEFW analysis correctly predicted eight (62%) and DAR analysis correctly predicted 10 (77%) cases. If pseudo-TTTS was predicted, dEFW analysis was correct in 7/9 (78%) and DAR analysis in 9/12 (75%) cases. If TTTS was predicted, dEFW analysis was correct in 8/12 (67%) and DAR analysis in 10/11 (91%) cases.

**Fig.1a**) Difference Average Ratio (DAR) analysis for a typical TTTS case (Case 17 in Table 2). Bold lines are the model fits using the two trends given in Table 1. Thin lines are the 95% confidence interval given by MATLAB for the two fits. Circles: DAR values calculated from the estimated fetal weights. Birth: DAR value
calculated from birth weights.

Fig.1b) Difference Average Ratio (DAR) analysis for a typical pseudo-TTTS case (Case 2 in Table 2). Bold lines are the model fits using the two trends given in Table 1. The thin lines are the 95% confidence interval given by MATLAB for the two fits. Circles: DAR values calculated from the estimated fetal weights. Birth: DAR value calculated from birth weights.

Fig.2) Difference Average Ratio (DAR) analysis for a pseudo TTTS case (Case 10 in Table 2) in which the analysis was unable to differentiate between TTTS and pseudo-TTTS (equal 95% confidence intervals). Bold lines are the model fits using the two trends given in Table 1. Thin lines are the 95% confidence interval given by MATLAB for the two fits. Circles: DAR values calculated from the estimated fetal weights. Birth: DAR value calculated from birth weights.

Figs.1a,b show examples of DAR analysis for typical TTTS and pseudo-TTTS growth patterns respectively. The bold lines are the model fits using the two trends given in Table 1. The thin lines denote the 95% confidence interval estimate given by MATLAB for the best fit, and the poorer fit. TTTS was the best fitted trend for Fig.1a (case 17 in Table 2), and
pseudo-TTTS was the best fitted trend for Fig. 1b (case 2 in Table 2). Fig. 2 shows an example where the analysis fitted both trends equally well. Although this was a pseudo-TTTS case clinically (case 10 in Table 2) our analysis until 31 weeks gestation was unable to predict this behaviour.

DISCUSSION

In a larger number of cases than previously (van Gemert and Umur, 2000a), our results confirm that fetal discordant development in TTTS and pseudo-TTTS monochorionic twin pregnancies may follow simple rules. It seems extraordinary that the complex hemodynamic problem of two coupled feto-placental circulations, which also includes fetal and placental growth, is amenable to simple analytical analysis. The results confirm that TTTS is associated with significantly stronger discordant growth than pseudo-TTTS (van Gemert et al, 2000a). The analysis also suggests that the DAR is an effective parameter to identify cases that likely develop TTTS, which may be of clinical relevance, particularly when it is impossible to use the normal oligo-polyhydramnios sequence diagnostic criteria, e.g. after septostomy (Suzuki et al, 1999; Pistorius and Howard, 1999).

The DAR analysis incorrectly predicted 3 (22, 24, 25) out of the 13 TTTS cases as being pseudo-TTTS. Interestingly, cases 24 and 25 were mild forms of TTTS, first, because in each case amnioreduction resulted in two survivors (van Gemert et al, 2001) and, second, in case 24 the TTTS stuck twin-polyhydramnios sequence developed at 19 weeks, but after one amnioreduction the pregnancy became completely normal. Here, no biometry data were available before 19 weeks, which suggests that the analyzed data, ranging between 19 and 32 weeks, correctly fitted a pseudo-TTTS pregnancy.

The DAR analysis incorrectly predicted 1 (case 12) out of 12 pseudo-TTTS cases as TTTS, although the stuck twin-polyhydramnios sequence never developed. This case was dominated by placental insufficiency for both twins, and anastomoses could not be identified within the cluster of tiny vessels located in the membrane separating the two small kidney-shaped placentas of similar size and histology. No explanation was found for the unusual hemoglobin concentrations found at birth (32 weeks), i.e., 11.3 mmol/l for the smaller twin (740 gr) and 6.5 mmol/l for the larger twin (1140 gr).

The DAR analysis failed to depict 2 (cases 10 and 11) out of 12 pseudo-TTTS cases as either TTTS or pseudo-TTTS. In case 10 (Fig. 2), fetal discordance remained small, with one point of largest discordance at 28 weeks. Interestingly, this point was measured by a different sonographer than the other data, and without this point the best fit would have been for pseudo-TTTS. Case 11 indeed showed variable discordant growth, without additional pathological development.

Several of the clinical cases used in this paper were included in previous work (van Gemert et al, 2000b) for a classification of discordant fetal growth. However, in the present paper our main goal was to assess the validity of our predicted trends of discordant fetal development.

In conclusion, the simple mathematical relations derived to identify trends of fetal discordant growth seem to describe the clinical growth patterns well, which shows evidence that some clinical TTTS and pseudo-TTTS manifestations may be predictable and quantifiable.
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Prob(TTTS|TTTS) = 0.67
Prob(TTTS|Pseudo) = 0.22
Prob(TTTS|ND) = 0.75
Prob(Pseudo|Pseudo) = 0.78

LR(TTTS) = 1.85
LR(Pseudo) = 0.26
LR(ND) = 2.77

Prob(TTTS|TTTS) = 0.91
Prob(TTTS|Pseudo) = 0.25
Prob(TTTS|ND) = 0
Prob(Pseudo|Pseudo) = 0.75

LR(TTTS) = 9.23
LR(Pseudo) = 0.31
LR(ND) = 0.00

Table 3 Statistical analysis. Prob(A|B): Probability of A given a B test result. LR(A): Likelihood ratio=Prob(Test result A|TTTS)/Prob(Test result A|Pseudo). ND: No-diagnosis.
REFERENCES


