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# Opinion

## Twin–twin transfusion syndrome: don't rely on fluids and bladders to catch it early

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Prospective studies suggest that twin–twin transfusion syndrome (TTTS) complicates approximately 10% of all monochorionic pregnancies[1]. If left untreated, TTTS is associated with mortality rates above 80%[2]. In 1999, Quintero *et al.* proposed a staging system for TTTS based on a theoretical sequence of events: (1) presence of oligo-/polyhydramnios sequence; (2) absent bladder filling in the donor; (3) abnormal Doppler findings in one or both fetuses; (4) hydrops in one or both fetuses; and (5) single or double fetal demise[3]. It is well-recognized that, particularly before 20 weeks of gestation, Quintero stages may not correspond to the chronological evolution of TTTS (i.e. stages may be skipped) or the criteria for each stage may not be met fully, even in the presence of severe TTTS. Furthermore, these events were defined using absolute values, for example amniotic-fluid depth[4], rather than considering relative intertwin differences, which we discuss later in this Opinion.

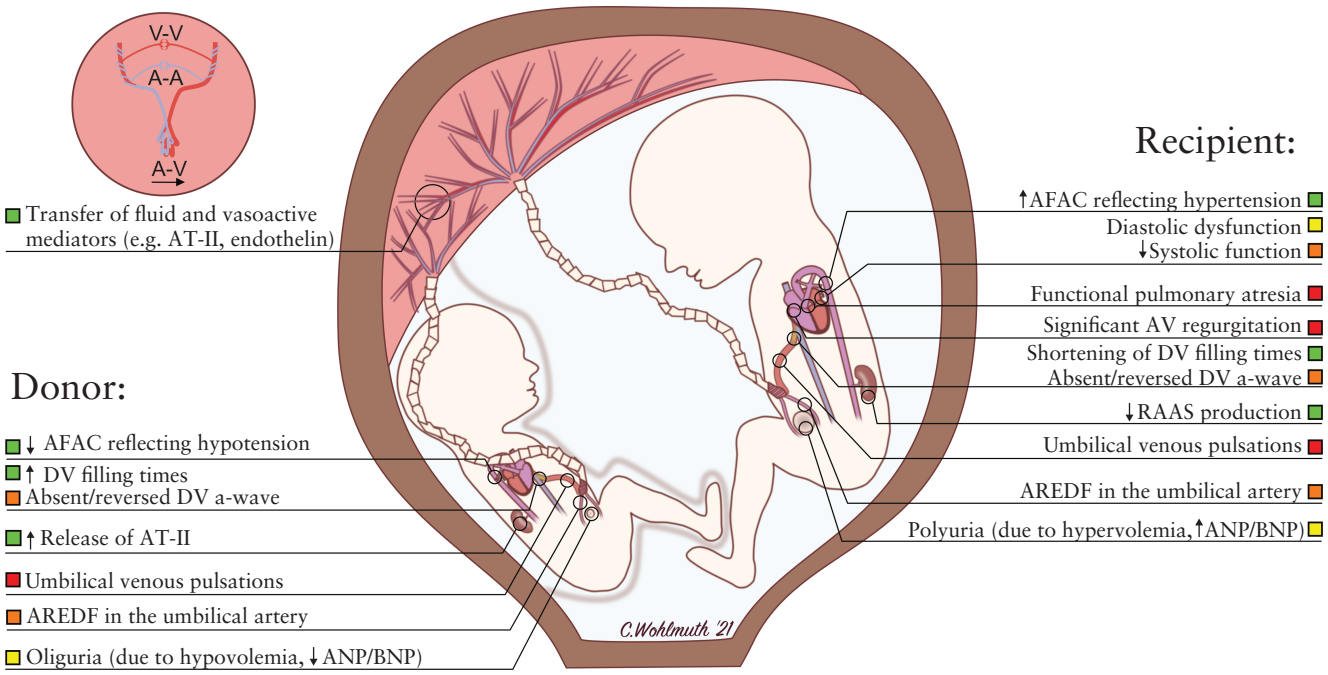
Prior to advances in fetoscopy, TTTS was treated by serial amnioreduction, which reduced maternal discomfort from excessive polyhydramnios, decreased premature contractions and the resultant transient Doppler changes suggested an improvement in placental circulation[5]. In 2004, a randomized controlled trial showed that fetoscopic laser coagulation (FLC) of placental vascular anastomoses was a superior treatment approach which improved significantly fetal survival and neurologic outcomes at 6 months of age compared with serial amnioreduction[6]. In contrast to serial amnioreduction, FLC is a causal treatment approach that leads to rapid normalization of the cardiovascular pathophysiology[7] and has become the first-line treatment for TTTS Stage II and higher. Although FLC comes at the cost of potential complications, including preterm prelabor rupture of membranes and miscarriage or premature delivery, survival of at least one fetus can be as high as 90% and of both fetuses as high as 70%, if performed in high-volume centers[8].

Improved TTTS survival rates have shifted the research focus towards assessment of the long-term outcomes, particularly neurologic impairment[9], but it remains difficult to separate the impact of TTTS itself from the consequences of premature delivery. Currently, the general recommendations suggest offering FLC only after the criteria for Quintero Stage II or above are met[4]. The question of whether this is truly the optimal timing of FLC, however, remains unanswered. Recently, a multicenter, randomized controlled trial comparing FLC with expectant management in pregnancies with Stage-I TTTS between 16 and 26 weeks' gestation and cervical length > 15 mm was stopped after 7 years due to slow recruitment. Although almost 60% of the 58 pregnancies randomized to expectant management progressed to higher stages of TTTS, the study could not demonstrate benefit from early intervention[10]. Based on recent publications on early changes in TTTS, it is reasonable to speculate that assessing more specialized early cardiovascular parameters rather than depending on 'preserved *vs* absent bladder filling' may form a more robust basis on which to offer FLC earlier than currently recommended in these pregnancies.

### Pathophysiology of twin–twin transfusion syndrome

Although the exact initiating mechanisms of TTTS remain uncertain, it is universally accepted that unbalanced unidirectional placental vascular anastomoses permit the net transfer of fluid from one fetus (donor) to its cotwin (recipient)[11]. This results in volume-depletion in the donor that triggers downstream compensatory mechanisms including the activation of the renin–angiotensin–aldosterone system (RAAS)[5,12–14]. Transfer of vasoactive substances from the donor to the recipient fetus results in increased afterload, thus reducing the recipient fetus' ability to compensate for the imbalance[15]. Fluid overload ensues from unbalanced intertwin transfusion and this triggers the secretion of natriuretic peptides resulting in polyuria and subsequently polyhydramnios, followed by inhibition of the RAAS system in the recipient. Studies supporting this sequence of events have documented that vasoactive mediators are equally elevated in recipients and donors, even though mRNA expression of renin is virtually absent in recipients[5,12–14]. In addition, the placenta itself may serve as a source of vasoactive mediators. Placental tissue has been shown to express RAAS components and differences in RAAS expression have been proposed between the donor and recipient placental portion[16,17].

The ongoing shift of fluid and vasoactive mediators results in deterioration of the recipient's cardiovascular system with increasing intracardiac filling pressures and diastolic dysfunction, followed by the more readily appreciated findings of decreasing cardiac contractility, systolic dysfunction, atrioventricular valve regurgitation




| Timing of cardiovascular manifestation: | | | |
|---|---|---|---|
| Early | Intermediate | Advanced | Late |
| - Increased release of vasoactive mediators in the donor<br>- Transfer of fluid and vasoactive mediators to the recipient<br>- Intertwin Δ in DV filling times and AFAC | - Oligo-/polyhydramnios sequence<br>- Recipient diastolic dysfunction | - Recipient systolic dysfunction<br>- AREDF in the umbilical artery in both twins<br>- Absent/reversed DV a-wave in both twins | - Functional pulmonary atresia in the recipient<br>- Significant AV regurgitation in the recipient<br>- Umbilical venous pulsations in both twins<br>- Cardiac failure and hydrops in the recipient |

**Figure 1** Cardiovascular pathophysiology of twin–twin transfusion syndrome. Δ, difference; A-A, arterioarterial anastomoses; A-V, arteriovenous anastomoses; AFAC, aortic fractional area change; ANP, atrial natriuretic peptide; AREDF, absent or reversed end-diastolic flow; AT-II, angiotensin-II; AV, atrioventricular valve; BNP, B-type natriuretic peptide; DV, ductus venosus; RAAS, renin–angiotensin–aldosterone system; V-V, venovenous anastomoses.

and, ultimately, cardiac failure[5,7]. A summary of the proposed cardiovascular pathophysiology of TTTS is shown in Figure 1.

## Cardiovascular assessment in twin–twin transfusion syndrome

Several groups have proposed the use of cardiovascular parameters to guide surveillance and treatment in evolving TTTS. A cardiovascular scoring system was developed by the group at the Children's Hospital of Philadelphia (CHOP) to grade the severity of cardiovascular involvement in TTTS[18]. However, the CHOP score mainly incorporated findings that occur relatively late in TTTS and/or are already included in the Quintero staging system for TTTS (abnormal umbilical artery Doppler, umbilical venous pulsations, absent or reversed ductus venosus (DV) a-wave, ventricular hypertrophy, atrioventricular valve regurgitation or fusion of E and A waves)[18]. In subsequent studies, the CHOP score has not been proven to be predictive of outcome in TTTS[19]. Similarly, the modification of the Quintero staging system proposed by the group at the University of Cincinnati in Ohio included only parameters that are typically observed in advanced TTTS, which may again explain why it has not been incorporated into routine practice[20].

A number of potentially more useful cardiovascular parameters have been investigated, including measures of preload (DV time intervals)[21,22], afterload (aortic distension)[7,23] and cardiac function (long-axis function and strain)[7]. Results suggest that discordance in twin-pair measurements may be a practical indicator of intertwin cardiovascular imbalance and emerging TTTS.

### *Preload*

While an absent or negative a-wave of the DV is seen in Stage-III TTTS and reflects imminent cardiac failure, it occurs relatively late in the disease process. However, measurement of time intervals of the DV waveform permit a much more refined assessment of the cardiovascular system and are relatively straightforward to obtain using standard ultrasound Doppler equipment

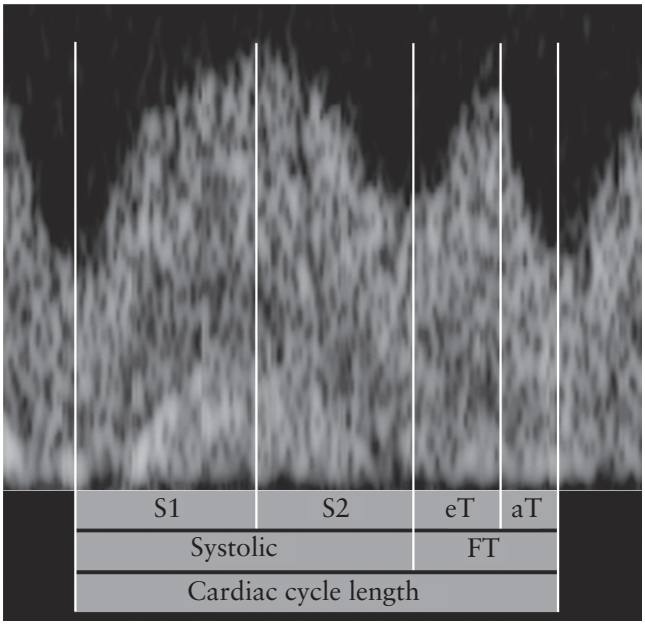



**Figure 2** Ductus venosus Doppler waveforms showing acquisition of time intervals. S1, acceleration time during ventricular systole, measured from the nadir of the a-wave to the peak of systole; S2, deceleration time during end-systolic ventricular relaxation, measured from the peak of systole to the nadir between systole and diastole; Systolic, sum of S1 and S2; eT, early diastolic filling time, measured from the onset of diastolic filling to the beginning of the fast deceleration caused by atrial contraction; FT, total diastolic filling time, measured from the onset of diastolic filling to the nadir during atrial contraction; aT, late diastolic filling time, obtained by subtracting eT from FT. Relative time intervals are calculated by dividing the time interval by the total cardiac cycle length: S1 (%) = S1 (ms)/cardiac cycle length (ms); S2 (%) = S2 (ms)/cardiac cycle length (ms); eT (%) = eT (ms)/cardiac cycle length (ms); aT (%) = aT (ms)/cardiac cycle length (ms); FT (%) = FT (ms)/cardiac cycle length (ms); Systolic (%) = Systolic (ms)/cardiac cycle length (ms). Reproduced from Wohlmuth *et al.*[21] with permission.

(Figure 2)[21]. The unique DV waveform reflects four distinct phases of the cardiac cycle: S1, acceleration time during ventricular systole; S2, deceleration time during end-systolic ventricular relaxation; eT, early diastolic filling time, from the onset of diastolic filling to the beginning of fast deceleration caused by atrial contraction; and aT, late diastolic filling time. These time intervals are normalized to the cardiac cycle length. In a study of 149 monochorionic pregnancies seen in our center, we showed that intertwin differences in DV time intervals preceded the development of TTTS on average $12 \pm 6$ days before the diagnosis was made based on the Quintero criteria[21]. An important practical finding was that intertwin pair discordance of time intervals, especially of eT normalized to the cardiac cycle (eT (%)), could predict progression to TTTS, a finding that was recently confirmed in an independent study[22].

### *Afterload*

Estimation of systolic blood pressure in the human fetus applies the modified Bernoulli equation to the peak velocity (Vmax) of an atrioventricular valve regurgitant jet ($4\,\text{mmHg} + 4 \times \text{Vmax}\,\hat{}\,2$)[7,24]. Using this method, we and others have recorded systolic pressures higher than expected for gestational age in recipient fetuses[7]. However, this method is applicable only if there is atrioventricular valve regurgitation, which is a variable finding in TTTS. An alternative approach is to use the aortic distension waveform as a surrogate for the pressure waveform. In an animal model using cannulated fetal lambs, our group has confirmed that acute changes in fetal blood pressure translate into changes in aortic distensibility, measured using tissue tracking of the short axis of the descending aorta in the transverse abdominal view[25]. In a separate study of human monochorionic pregnancies complicated by TTTS, intertwin differences in aortic distensibility were present even in the early stages of TTTS, supporting the hypothesis that recipient hypertension is present in early TTTS[23]. Neonatal hypertension in ex-recipients has also been observed in a small series of TTTS pregnancies managed by serial amnioreduction[24]. Postnatal studies evaluating vascular stiffness in donor twins, whose vascular territories are generally smaller, have shown that ex-donors treated by serial amnioreduction, in comparison to those treated by FLC, had higher arterial stiffness during infancy which, however, did not translate into increased blood pressure at the age of 10 years[26–28].

### *Cardiac function*

Measurements of cardiac contractility and systolic function, including long-axis function, appear to change later in the disease process and systolic function tends to diminish only in more advanced disease stages[1,7]. In a prospective study evaluating global longitudinal ventricular strain in monochorionic pregnancies undergoing routine biweekly surveillance, with the observer blinded to twin pairing and outcome, intertwin discordance in ventricular strain values was seen in those that developed TTTS. Unlike Doppler recordings of the DV waveform, which are easier to obtain and more reproducible, a shortcoming of strain is lack of reproducibility due to technical difficulties with its measurement; hence, although strain is an interesting parameter to increase knowledge of the pathophysiology of TTTS, it is difficult to support its adoption into routine clinical practice[1].

## Conclusions

Effective therapy is available for TTTS but there is considerable morbidity and mortality if treatment is delayed. The Quintero criteria have enabled implementation of universal screening for TTTS outside dedicated fetal treatment centers and will, therefore, continue to form the basis of screening of monochorionic pregnancies. However, there is sufficient evidence base to refine the diagnostic tools we use to screen pregnancies at high risk for progression of TTTS, thereby enabling earlier referral, diagnosis and

therapy. To achieve this goal, intertwin differences in cardiovascular parameters as early signs of cardiovascular imbalance (e.g. DV time intervals) could be assessed. Only when we systematically incorporate cardiovascular parameters that show discordance early in the disease process into screening programs and subsequent management decisions, will we be able to identify pregnancies that may benefit from early FLC in future randomized controlled trials. We propose to include these parameters into ongoing multi-institutional efforts for core TTTS parameters. As Mark Twain once said: 'The secret of getting ahead is getting started'.

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