Rejoinder to Meta-Analysis of Twin-Twin Transfusion by Skupski et al.

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Assessment of treatment options in twin-twin transfusion should involve a detailed interrogation of the placenta and fetuses prior to treatment, stratification according to response to amnioreduction and careful analysis of quality of survival. Amnioreduction and laser coagulation are not alternative and equivalent modalities for the treatment of twin-twin transfusion. Randomized trials may not be ethical without prior therapeutic/ diagnostic amnioreduction.

The meta-analytic study by Skupski et al. (2001) shows no differences in outcome data from fetoscopic laser coagulation (FLOC) vs amnioreduction (AR) vs no therapy (control group) in the antenatal management of twin-twin transfusion (TTT). The premise is that improvements in neonatal care have steadily reduced mortality, such that date of publication is a major factor in comparing series of TTT treatment. Because there was no significant difference in fetal death rates in the eligible studies, Skupski et al. (2001) chose diagnosis-to-delivery (not procedure-to-delivery) as the only other available measure. As Skupski et al. (2001) note, a disadvantage of their appropriately careful selection criteria is that so few cases can be analysed. 140 cases in all (and only 61 cases treated with AR) is a puny number compared with the estimated 2000 new cases per annum in the USA alone. Even if there are no randomised controlled trials, it seems reasonable to propose a registry at least. Such a registry exists for AR (Mari et al., 2000; Mari et al., 2001), but the results accrue from only 6 centers. The Eurofoetus registry does not regularly publish results (Gratacos & Deprest, 2000), and the only major European comparison of FLOC and AR (Hecher et al., 1999) is not eligible by the criteria of Skupski et al. (2001).

I fully agree with Skupski et al., that trials are warranted for the management of TTT. However, much more sophisticated criteria are required before cases enter such trials, and the exit data should involve quality as well as quantity of survival. FLOC and AR may be complementary rather than alternative approaches to treatment.

Detailed Assessment of TTT

Several barriers to progress in TTT need to be overcome before reliable outcome data will be forthcoming in a quantity that allows statistical analysis. The present divided state of obstetricians regarding FLOC and AR is unfortunate. To some degree it is caused by a series of misunderstandings about TTT that may also lie at the root of the Skupski meta-analysis (2001). The point is that there are deficiencies in the documentation of the status of twins at the beginning and end of the disease, whether treated or not.

First, it is commonly assumed that TTT is a homogeneous disease for which only one treatment (or none) must be the approach to the exclusion of all others.

Secondly, inadequate data is often collected on the clinical status (including staging) of the fetuses before any therapy (or none) is given. Thus, to attribute various outcomes to treatment per se is to take no account of how advanced the disease was at the time of treatment, and the extent to which one or both fetuses may already be damaged by TTT. Allied to this are the rival views that AR causes nothing more than non-specific prolongation of pregnancy without having any specific effect on the cause of TTT, while FLOC is experimental, dangerous and not required in most cases (De Lia et al., 2000).

Thirdly, FLOC and AR are not administered uniformly (De Lia et al., 1999; De Lia et al., 2000; Feldstein et al., 2000; Quintero et al., 2000; Ville et al., 1998).

Fourthly, the diagnosis-to-delivery interval could be confounded by other disorders, including pregnancy-induced hypertension, ruptured membranes, etc that are not directly related to TTT.

Fifthly, neonatal outcomes cannot be measured simply in terms of survival. Many TTT survivors have sustained structural cerebral, renal, cardiac and limb extremity pathology during the course of their disease (Barr et al., 1998; Cincotta et al., 2000; Scott & Evans, 1995; Simpson et al., 1998). Careful, long-term assessment of these variables should be an integral part of any trial and meta-analysis. Advantages of one therapy over others may involve survival quality as well as quantity.

Much is now known about the clinical spectrum of severity of TTT. It has been proposed that there are at least 3 subtypes of TTT, each dependent on a particular monochorionic (MC) placental vascular anatomy (van Gemert et al., 1998; van Gemert et al., 2001). This anatomy can now be mapped to some degree by ultrasound prior to therapy (Denbow et al, 1998; Machin et al., 2000; Machin, 2001),

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confirmed in cases requiring FLOC (De Lia et al., 1995; Quintero et al., 1998), and studied in detail post-partum (Bajoria et al., 1995; Bajoria, 1998; Machin et al., 1996). Mild cases of TTT that require minimal or no therapy have relatively abundant inter-fetal vascular connections, which have not been quite adequate to allow balanced or compensated blood return from recipient to donor. Arterio-arterial anastomoses (AAA) largely protect that majority of MC twins (about 85%) who do not develop TTT (Denbow et al., 1998). Among those who do develop TTT, the presence of AAA usually indicates that AR will be sufficient (Bajoria, 1998; Taylor et al., 2000). In contrast, TTT cases with an unremitting course unresponsive to AR and requiring FLOC usually have no AAA, but a simple vascular pattern of uncompensated causative arterio-venous anastomosis (AVA). AVAs can also be detected by Doppler ultrasound, allowing mapping of the placental vascular equator for AAAs (Denbow et al., 1998) and AVAs (Machin et al., 2000) prior to FLOC.

Based on the different severity of TTT from cases to case, staging classifications have been suggested (Feldstein et al., 2001; Quintero et al., 1999). Only some of these include fetal brain MRI before and after treatment (Feldstein et al., 2001). Staging that involves assessment of cerebral, cardiac and urinary function before and after procedures may be the most precise way of monitoring effectiveness of treatment.

In some cases, AR has caused reversal of donor/recipient role (Bromley & Benacerraf, 1996; Mielke et al., 1997), suggesting that AR has specific effects on inter-fetal vascular anastomoses. If this is true, then AR is a bona fide treatment for cases that respond with donor micturition (Kilby et al., 1997), and could be continued in milder cases so long as they respond. In cases that do not respond to AR with donor micturition, it seems logical to proceed directly to FLOC on the assumption that there are no compensatory anastomoses that can be re-opened by AR.

There is no uniformity in the definition of an adequate AR. For example, very few studies have considered amniotic fluid pressure as well as volume (Garry et al., 1998; Meager et al., 1995). In FLOC, there is a wide spectrum of thoroughness with which vessels of varying types at varying places on the placental surface are coagulated (De Lia et al., 1999; Feldstein et al., 2000; Hecher et al., 1999; Quintero et al., 2000; Ville et al., 1998). Some authors have advocated coagulating all vessels seen close to or crossing beneath the diamniotic septal membranes. The rationale is that the vascular equator does not always coincide with the base of the septal membranes, preventing adequate coagulation of all anastomoses. The disadvantage of this approach is that it may result in the coagulation of many "innocent" A-V pairs that are both connected to a cotyledon of one twin only. For growth-restricted donors, this may prove the last event in their downward course. Other authors recommend that all anastomotic vessels be coagulated at the equator, leaving innocent A-V pairs intact. If all connecting vessels are treated, there is no risk of hypotension to the survivor if one fetus subsequently dies. Modifications to the extent of coagulation can be made if the clinical status of one twin is so poor that the objective is to save only one fetus. Finally, FLOC can even be tailored deliberately to allow blood to transfuse back from recipient to donor if the clinical status allows (Feldstein et al., 2000). These variables within FLOC cases clearly affect outcome data.

Because we can stratify the clinical subtypes of TTT, accept that AR is definitive treatment for milder cases who respond with fetal micturition, recommend FLOC for non-responders who lack AAA, and vary the objectives and extent of FLOC, it is doubtful if a fully randomised trial in TTT is even ethical. It does not seem justifiable to expose mild cases to primary FLOC before finding out if they might respond to AR. It seems unacceptable to withhold FLOC from cases who are not responding to AR.

Thus, there is a basis for a 2-stage trial. Such a trial would involve full ultrasound mapping of placental vascular anastomoses, as well as fetal brain MRI, prior to treatment. The first stage of treatment would be therapeutic/diagnostic AR for all cases. The donor would be assessed for micturition (presence of fetal bladder, not amniotic fluid volume) within 24-48 hours of AR (Kilby et al., 1997). Responders would continue with AR as necessary and as long as they responded. Non-responders would be randomised to AR or FLOC, thus approximating to the present practice in various centers. However, the caveat remains that it seems unethical to randomise non-responders to AR if the treatment has proved ineffective. Fetal brain MRI would follow each procedure. Long-term neonatal follow-up and detailed placental studies would complete the trial.

Summary

On this basis, with detailed assessment of the disease before, during and after treatment, and by enrolling large numbers, it should be possible to find the optimal way to treat the subtypes of TTT according to severity. Much would depend on the stage of the disease when it first presents. The quality of data would need to be much richer than fetal/neonatal survival or procedure-to-delivery interval. Even if first trimester diagnosis of chorionicity becomes routine for multi-fetal pregnancies (Bajoria & Kingdom, 1997), it seems unlikely that these procedures will reduce morbidity and mortality to zero.

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