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Future Directions in the Management of Twin-to-Twin Transfusion Syndrome

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Twin-to-twin transfusion syndrome (TTTS) is the major complication of monochorionic (MC) pregnancy. The outcomes of this condition have been significantly improved after the introduction and widespread uptake of fetoscopic laser ablation over the last decade. However, there is still a significant fetal loss rate and morbidity associated with this condition. Improvements in the management of TTTS will require improvements in many areas. They are likely to involve refinements in the prediction of the disease and clarification of the optimum frequency of surveillance and monitoring. Improvements in training for fetoscopic surgery as well as in the technique of fetoscopic laser ablation may lead to better outcomes. New technologies as well as a better understanding of the pathophysiology of TTTS may lead to adjuvant medical therapies that may also improve short- and long-term results.

■ **Keywords:** Twin-to-twin transfusion syndrome, monochorionic twins, laser therapy, review

TTTS complicates approximately 10% of all MC pregnancies due to placental vascular anastomoses between the two fetal circulations. It is a major determinant of perinatal outcomes and is associated with a significant risk of single or double fetal demise, preterm birth, and neurological injury in survivors (Lewi et al., 2010). It appears to be more prevalent in spontaneously conceived MC pregnancies compared to those conceived after assisted reproductive techniques (Ben-Ami et al., 2015). After the pioneering development of fetoscopic laser ablation of the placenta (FLAP) for the treatment of TTTS more than two decades ago (de Lia et al., 1990; Ville et al., 1995), it was not until 2004 following the publication of the Eurofetus randomized control trial that it became the treatment of choice and indeed standard of care for this condition (Senat et al., 2004). Combining all published series, perinatal survival of at least one twin after laser therapy is in the region of 81–88%, and survival of both twins occurs in 52–54% of pregnancies (Akkermans et al., 2015).

Future directions in the management of TTTS are likely to involve refinements in the prediction of the disease, clarification of the optimum frequency of surveillance, technique of FLAP, prediction of adverse outcome after treatment, and development of other vascular ablative techniques. This review will therefore focus on these areas.

Prediction and Monitoring of TTTS

Prediction

Accurate prediction of those MC twins who will go on to develop TTTS is important to allow appropriate targeted monitoring as well as for developing potentially preventative treatments. At present, no useful predictor with a high enough sensitivity or specificity is available. Discordant nuchal translucencies were shown to increase the risk of subsequently developing TTTS (Kagan et al., 2007; Sebire et al., 2000), but this association has not always been confirmed (Memmo et al., 2012). Abnormal ductus venosus waveforms have also been shown to be predictive of the later development of TTTS but functions poorly as a predictive test (Maiz et al., 2009).

Monitoring

TTTS frequently develops between 16 and 28 weeks but occasionally can occur either earlier or later in gestation.

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Severe untreated TTTS has a very high loss rate and likelihood of very premature delivery (Fisk et al., 2009). With all MC twins, there is a high loss rate, particularly before 24 weeks (Lewi et al., 2008; Sebire et al.,1997), with most of this due to TTTS. The introduction of fetoscopic laser ablation dramatically changed the outcomes for this condition. Because of the potential of rapid disease progression, close surveillance of all MC twins is advised to allow for the opportunity for early intervention.

However, the optimal regime for ultrasound MC surveillance is not known. Most international guidelines now recommend 2–3 weekly ultrasound assessment from 16 weeks (Emery et al., 2015; Fisk et al., 2009; Morin & Lim, 2011; Royal College of Obstetricians and Gynaecologists, 2008). Nevertheless, there is little data on the speed of development of TTTS or the efficacy of the frequency of monitoring in MC twins. Sueters concluded that two-weekly scans with clinical instructions regarding early presentation for rapid abdominal girth was optimal monitoring for MC twins (Sueters et al., 2006). Thorson found that a scan interval of greater than 2 weeks resulted in detection of a higher stage TTTS and potentially later intervention (Thorson et al., 2011).

The introduction of a policy of two-weekly ultrasounds for every MC twin has significant resource and cost implications. As the monitoring includes growth and Doppler assessment as well as potentially cardiac and other specialized assessments, it may require specialized fetal medicine services to properly monitor for the complications of MC twins. In many centers, monitoring of MC twins are now performed in specialized fetal medicine units or by obstetric sonographers with advanced training who are able to recognize early features of TTTS (or indeed other complications specific to MC pregnancies).

The evolution of management protocols for complicated MC pregnancies appears to have resulted in improved outcomes. The STORK study (D'Antonio et al., 2013) suggested that there has been an improvement in the early loss rate (<24 weeks) in MC twins over the past decade. They noted that the fetal losses <24 weeks had decreased from 8.9% to 4.9% and while there was a smaller reduction in losses after 24 weeks over the same time period, it had not reached statistical significance. In a series of MC twins followed from the first trimester, Lewi et al. (2008) found that while the loss rates were similar to those of Sebire et al. (1997) in an earlier era, there was the suggestion that there were fewer double losses, suggesting that laser/fetal therapy was potentially having a beneficial impact.

Future developments in monitoring and prediction of TTTS may help in better targeting of who should be monitored improving resource allocation and potentially allowing earlier intervention and improving outcomes.

Prediction of Adverse Outcome After Treatment

The main adverse outcomes after invasive therapy include miscarriage or preterm birth secondary to the procedure, single or double fetal demise, neurological injury, development of twin anemia polycythemia sequence (TAPS), or recurrent TTTS. A short cervix is an important predictor of preterm birth and loss in singletons and twins. It is also a major determinant of preterm delivery in MC pregnancies complicated by TTTS (Robyr et al., 2005). The presence of polyhydramnios compounds the risk of preterm labor or preterm pre-mature rupture of membranes (PPROM). However, a short cervix is not a contraindication to fetoscopy, as good results have been reported and alternatives such as amnioreduction are less effective (Chavira et al., 2009). There is evidence that cervical length assessment prior to FLAP helps stratify the risk of either PPROM or preterm birth. Spontaneous preterm birth at <34-weeks gestation is associated with a pre-operative cervical length of <28 mm (Papanna et al., 2015). Preventive strategies should therefore focus on this high-risk group. While progesterone has been shown to be effective in decreasing the risk for preterm delivery in singletons, it has not been shown to have any effect in preventing preterm birth in twin pregnancies (Rode & Tabor, 2014). However, in twins with a short cervix, an individual participant data meta-analysis has suggested a benefit for the use of vaginal progesterone (Schuit et al., 2015), although the numbers analyzed were small. The efficacy of cervical sutures in preventing preterm birth in twins with a short cervix is also unclear. A Cochrane review of the use of cervical suture for preventing preterm birth in twins shows no benefits in all types of twins (Rafael et al., 2014). A more recent cohort study suggested that there was a significant prolongation of pregnancy in those with a cervix less than 15 mm (Roman et al., 2015). Cervical pessary was not effective in twins with or without a short cervix (Nicolaides et al., 2015).

There is considerable scope for more research to find effective treatments for cervical shortening in multiple pregnancy and in TTTS. In addition, there is increasing evidence that abnormalities in impedance in the donor's umbilical artery or middle cerebral artery helps predict the risk of fetal demise post-procedure (Eschbach et al., 2015).

Major neurodevelopmental handicap is a significant problem affecting twins who survive TTTS. In the era of amnioreduction, the incidence of major neurodevelopmental disability was reported to be up to 25% (Cincotta et al., 2000). With FLAP, the incidence of cerebral palsy and developmental delay is reported at 5–10% (Gray et al., 2011; van Klink et al., 2013; van Klink et al., 2014). Cerebral injury is mostly due to hypoxic-ischemic injury resulting in cystic periventricular leukomalacia, middle cerebral artery infarction, or injury to the basal ganglia, thalamus, and/or cortex. Risk factors associated with severe cerebral injury include advanced gestational age at the occurrence of single fetal demise (OR 1.14, 95% CI: 1.01–1.29) for each week

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of gestation, TTTS (OR 5.0, 95% CI: 1.30–19.13), and a lower gestational age at birth (OR 0.83, 95% CI: 0.69–0.99) for each week of gestation (Van Klink et al., 2015). Careful monitoring and appropriate treatment may reduce the risk of this devastating complication.

Training for Fetal Therapy

A recent systematic review (Akkermans et al., 2015) of almost 4,000 cases of TTTS treated with FLAP showed that the mean gestation at the time of treatment was 20.9 ± 1.9 weeks. The mean perinatal survival of both twins and at least one twin was 52 ± 14.8% and 81 ± 8.3%, respectively. The overall survival was 69.1%. In smaller center specific series, outcome figures are even more impressive. With increasing experience with fetoscopic treatment there are now increasing numbers of centers developing around the world, leading to improvement in access to laser ablation. Currently, fetoscopic laser surgery for TTTS is a procedure for which no objective tools exist to assess technical skills. To ensure that future fetal surgeons reach competence prior to performing the procedure unsupervised, it is important that appropriate training programs are developed to ensure competency. This is already happening in some European centers with proficiency-based simulator training resulting in improved performance (Peeters et al., 2015). Ideally, new surgeons and centers can be trained by existing units. Telemedicine has been used by new centers to allow surgeons to remotely observe fetoscopic procedures being performed to improve training. This has been helpful and can even be done internationally (Chan et al., 2003).

Nevertheless, a major disadvantage of increasing the number of centers to improve access is the potential to decrease the workload of existing centers, thereby simultaneously decreasing operator experience. This may affect the outcomes by increasing complication rates. However, as indicated earlier in this review, the use of simulators may improve training and outcomes (Peeters et al., 2015). The use of cumulative sum analysis can identify a learning curve and be used to monitor performance and be used for ongoing quality assurance (Peeters et al., 2014).

In Australia, laser ablation was pioneered in a few centers after key personnel trained in overseas centers. Once the initial results were seen to be effective and the Eurofetus RCT showed that it was the optimal treatment, the number of centers increased. While this is of major benefit to patients in reducing the vast distances pregnant women would have to travel to access treatment in a country the size of Australia, it has the downside that no center can achieve the very large numbers some international centers have achieved. In spite of this, Australian outcomes have been as good as those reported from international centers (Cincotta et al 2009; Meriki et al., 2010; Teoh et al., 2013). Learning curve and workloads are important issues when deciding whether a city or region should establish a laser ablation service. The balance between access for patients, distances for them to travel, and workload and experience of operators is often difficult to achieve. The benefits of concentrating services leading to increased experience should lead to better results and fewer complications (Gratacós, 2012). However, good training, preparation, audit, and collaboration can optimize results even with relatively small numbers of cases (Morris et al., 2010; Papanna et al., 2011).

Improvements in Current Techniques and Development of New Techniques

The overall management of TTTS will benefit from developments in other areas such as the management of PPROM, preterm labor, as well as interventions for the prevention of neurodevelopmental problems.

One of the major complications of fetoscopy is PPROM. The incidence of PPROM after fetoscopic laser ablation is thought to be about 27% (Maggio et al., 2014). PPROM leads to delivery and a reduction in the median interval from surgery to delivery of about 4 weeks. There is a suggestion that there is a higher incidence of PPROM with larger ports at fetoscopy (Beck et al., 2012). It is suggested that using a smaller port may result in a decreased risk of PPROM. The disadvantage is the decreased visualization of the placenta and the potential to increase the operative time and increase the risk of missing vessels, and so other complications may develop (Gratacós, 2012). Given the advances in fiberoptics, lens technology, and miniaturization of fetoscopic instruments, there is significant potential of reduction in the procedure-related complication rates.

Improvements May Come From New Technologies

Computer-assisted surgical planning using 3D volume reconstruction, either with ultrasound or magnetic resonance imaging, may allow mapping of the uteroplacental architecture and could help optimize surgical technique and therefore outcomes (Pratt et al., 2015). A more recent development is high intensity focused ultrasound (HIFU), which uses high energy ultrasound to ablate tissues. There has been research into using this technique to ablate vessels and potentially to use it as a non-invasive method to ablate placental anastomoses (Aoki et al., 2009). It has been successfully used to occlude flow to an acardiac twin (Okai et al., 2013). This non-invasive technique is potentially very exciting and there has already been work using this technique to ablate vessels ex vivo. It potentially could be used to ablate placental vessels if accurate mapping of chorionic plate vessels was possible without direct visualization. With evidence of the effectiveness of the Solomon technique in treatment of TTTS, it may be sufficient to identify the vascular equator and use a non-invasive technique to occlude any vessels that may cross over the equator. Much work needs to be done before this could be trialed.

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Medical Treatments in TTTS

The concept of potential medical therapies for TTTS has a long history. Digoxin was first suggested for hydropic babies with severe TTTS before any effective ablative therapies were available. While placental anastomoses are essential to the development of TTTS, there are multiple endocrine and vasoactive disturbances that are found and that are thought to contribute significantly to the pathophysiology (Fisk et al., 2009). Discordant activation of the renin angiotensin system has been demonstrated, and elevations of endothelin, ANP, and BNP have been documented. Cardiomyopathy is thought to be an important contributing component to morbidity and mortality in recipient twins (Crombleholme et al., 2010). While laser ablation stops the transmission of volume and vasoactive and endocrine factors across the placenta, there is the potential for medical treatments to improve outcomes if the pathophysiology is better understood.

Optimization of Fetal Status Pre-Therapy

There is clear evidence of the benefits of maternal steroids and magnesium sulphate to ameliorate some of the complications associated with pre-maturity. The data relating to these interventions are derived from singleton pregnancies, and there is a paucity of similar data in the multiple pregnancy literature, let alone in the general MC cohort or more specifically, that relating to TTTS. Most practitioners extrapolate evidence from the singleton literature to the multiple pregnancy cohort. While this may not be unreasonable, more research is clearly required to identify precise indications as well as the sub-group of women who may benefit from these interventions, given the significant cardiovascular and circulatory perturbations present in MC pregnancies complicated by TTTS.

Crombleholme performed a case control cohort study of the use of nifedipine given pre-laser for women with TTTS and found that there was a significantly improved survival in the treated group compared to untreated controls (Crombleholme et al., 2010). Whilst these results would need to be confirmed in a RCT, this raises the potential for adjuvant medical treatments to assist or improve current treatment.

Neuroprotective agents have been shown to decrease incidence of cerebral palsy in preterm delivery. While women at risk of preterm delivery after laser may currently receive this, there is the potential for agents to be given at other critical times. Would prophylactic administration of such agents benefit all women with TTTS regardless of severity or if prenatal therapy was required even if preterm delivery was not thought to be an immediate risk? The incidence of cerebral palsy and neurodevelopmental delay is not entirely related to the degree of pre-maturity in MC twins. Van Klink et al. (2014) noted that the incidence of cases of cerebral palsy decreased even with a decrease in mean gestation of delivery in their series over a decade. Magnesium has been shown to decrease the incidence of CP if given for neuroprotection in preterm deliveries (Chang, 2015). It is also considered a neuroprotective agent experimentally as it is being trialed for stroke intervention in adults (Saver et al., 2014). The potential of giving magnesium or other potential neuroprotective agents at the time of laser ablation has not been explored.

Acute TTTS

Chronic TTTS develops in the second trimester and has been extensively studied with clear diagnostic criteria, and laser ablation is clearly the optimal current treatment. However, acute transfusion of blood can also occur and is a distinct entity (Skupski et al., 2012). Acute peripartum transfusion is described as typically occurring in labor and its incidence is thought to be about 2–5%. It is characterized by large discordance in hemoglobin. There are also acute perimortem TTTS and placenta-fetal and feto-placental transfusions. While these are uncommon and occur later in pregnancy, monitoring and predicting or preventing these events are difficult. These conditions are not well characterized, and while they share some characteristics with typical chronic TTTS, they usually do not have the oligo/polyhydramnios seen in chronic TTTS. Clearly, there is much research required as to the causes of these acute transfusions and what monitoring can be done to identify and potentially prevent this from occurring.

TAPS is another condition that is less well described. Although it is more commonly seen after incomplete laser ablation, it can occur spontaneously. The optimal management for this condition is still unclear, and greater recognition and further research into frequency of surveillance, treatment, as well as indications for intervention is required.

Distant Developments

Robotically assisted surgery is associated with less trauma to tissues. Its potential use in fetal surgery may be decreasing complications such as PPROM. Potentially robotic technology may allow insertion of fully articulated instruments into the uterus (Flake, 2003). Other technological developments further into the future include micromachines, further developments in computational sciences, imaging, molecular science, biomedical engineering, and nanotechnologies (Apuzzo & Liu, 2001). Work continues on the development of nanoparticles, particularly in their potential use for drug delivery for treatment of conditions such as cancer. Some are able to cross the placenta and there is potential scope for the development of nanoparticle-based drug therapy for the treatment of placental or fetal conditions (Keelan et al., 2015), including TTTS.

Conclusion

Currently, FLAP is the only proven treatment option for the more severe stages of TTTS. Further research into

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optimum techniques for surveillance of at-risk pregnancies, prediction of treatment complications, as well technical advances, is critical to improve the already impressive outcome figures for this disease. Concurrently, long-term outcome data (particularly cardiovascular and neurodevelopment) of children who were born after in utero treatment is vital to ensure that there is appropriate correlation with pre-natal therapy. Registry-based research would be important in this regard.

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