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GENERAL DISCUSSION

The past two decades have led to significant advances in the fields of prenatal diagnosis and fetal intervention. The rationale behind fetal interventions is to improve fetal, neonatal and long-term outcomes. However, advances in fetal therapy also raise ethical issues. These concerns involve maternal autonomy and autonomous decision-making, concepts of innovation versus research and organizational aspects in the development of fetal care centers. Priority is the safety of both pregnant women and her fetuses. It is impossible to treat the fetus without going through the pregnant women (either physically or pharmacologically); therefore any fetal intervention has implications for the pregnant women's health.

Antenatal interventions have been offered for a variety of fetal diseases, many of which would be lethal without treatment. Nowadays, fetal surgery is standard of care for highly selected indications, such as TTTS, TAPS and TRAP. Availability of this technique is limited to approximately 100 specialized centers. Starting off with pioneers' "with their backs against the wall" attempts to prevent fetal demise, the efficacy of fetal surgery has now been validated for selected indications by well-designed, randomized controlled trials. [1, 2].

The primary problems continue to be accurately identifying which fetuses will almost certainly die or become severely injured without intervention, but still will have the capacity to recover with relatively normal function if fetal surgery is performed, and to minimize the risk for preterm delivery after fetal intervention.[3] The goal of fetal surgery is clear: to improve chances of survival and the long-term health of children by intervening before birth to correct or treat prenatally diagnosed abnormalities.

Volume issues

In this thesis we focused on treatment for TTTS, as it is currently one of the most performed fetoscopic interventions. In chapter 2 we identified that 63% of fetal therapists and 52% of centers perform < 20 procedures per year. Even though there is limited evidence concerning the ideal number of procedures that should be performed to maintain high quality results (chapter 1), many studies have investigated the relationship between hospital volume data and post-operative surgical outcomes in other fields of surgery. Better outcomes have been reported in high volume institutions for high-risk procedures.[4-6] "Learning curve" and monitoring studies on fetoscopic surgery show that approximately 20-30 procedures per year (per operator) are needed to reach and maintain a requisite skill level.[7] However, for intrauterine transfusion these numbers are higher (34-49 procedures).[8]

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One of the limitations in these studies is that the effect on an individual learning curve by first assisting a senior operator was not measured. Also not included in the analysis was the extent of the operators' experience with obstetric ultrasound, invasive fetal diagnostic and other therapeutic procedures, and endoscopy prior to starting laser therapy.

Some other considerations have to be taken into account when assessing a learning curve: Case selection, or case-mix, by either treating predominantly high-risk or low-risk cases during the learning phase, will influence learning curve results. Moreover, when operating in a low volume center or center with multiple fetal surgeons, equal division of the number of procedures performed by each operator annually should be pursued in case of rare procedures such as laser surgery in TTTS.

The learning curves in our series represented the improvement of both the operators, from experience and practice, and the performance of the entire team at managing pregnancies with TTTS. Teamwork, multidisciplinary discussion with colleagues from the neonatology department (including international audits)[9], stimulation, controllability, and continuity may be beneficial factors. Another most helpful tool, in our view, was the systematic evaluation of each treated placenta through careful placental injection of colored dye.[10]

Quality control and monitoring

To optimize surgical outcomes and to decrease medical error, we propose the implementation of a continuous audit system, allowing timely feedback at each center (chapter 1). When a limited number of surgeries are performed annually, lower volume centers will be at risk of late recognition of substandard care or the incidence of complications. Aside from medical-legal aspects arising from the public's interest and willingness to invest in healthcare, we found that doctors themselves are increasingly interested in development and maintenance of expertise. The objective measurement and understanding of surgical expertise acquisition is, not surprisingly, at the forefront of surgical education programs.

To fully assess the perinatal outcomes related to the expanding number of centers performing fetoscopic laser therapy reporting and monitoring is necessary. Each center should at least report short- and long-term maternal and pediatric outcomes and the results of placental injection. Furthermore, centers performing fetal therapy should have multidisciplinary teams that evaluate the care being offered and discuss difficult cases. Regular structural reflection on ones' own practice is essential to prevent late detection of suboptimal performance. If less favorable outcomes are noticed, a quality cycle including further education, supervision of practice and improvement of learning environment should be initiated. As stated in chapter 3, we encourage starting up centers, as well as established centers to share their performance for peer review and publish their series.

A suggestion for monitoring of performance could be implementation of a central registry. Expert centers should establish criteria for certification and periodic rectification, and review the certification process. This should include criteria to be considered competent to perform laser surgery as well as the optimal volume of cases. We believe patients and referring colleagues are entitled to obtain knowledge of at least center performance for any operative procedure, including fetoscopic surgery. Practically, in case of a period of deviating or disappointing outcomes, real-time assessment using for example CUSUM methodology should be standard practice. Awareness of underperformance alone may already improve outcomes.

Access and centralization

Balancing offering geographical access while maintaining sufficient quantity of cases is challenging. (Chapter 2). Concentration of care for this highly specialized procedure has been advocated.[11, 12] On the other hand, geographical circumstances may justify the need for low volume centers, since timely referral and treatment is associated with improved dual twin survival and decreased neurodevelopmental delay.[13]

Centers offering fetal therapy should be geographically distributed throughout a country (or province, or continent) to improve access. Patients should be allowed to receive care at the institution of their choice even when this institution is located abroad, provided that care is given without unnecessary loss of time, or unrealistic burden on health care expenses when provided by public money. Close links and ongoing education to community providers and referral centers is essential to ensure timely referral.

New fetal therapy centers

The expertise and services required to be considered a fetal center appropriately equipped to perform prenatal surgical interventions (such as fetoscopic laser therapy), involves a tremendous institutional commitment.[14] This should include: an experienced fetal care team, (with fetal surgeons, dedicated sonographers and specialized nurses), available for urgent referrals every day of the year, a level III neonatal intensive care unit, a labor and delivery unit capable of caring for perioperative complications and obstetric emergencies with around the clock availability of MFM specialist/obstetricians. Logically, neonatologists should be involved, because they will typically be the primary physicians managing the care of the neonate and dealing with the medical consequences of the antenatal intervention. Moreover, it should be an institutional commitment to track long-term pediatric neurodevelopmental outcomes. Follow-up into childhood is indispensable to determine outcome in terms of motor, cognitive and behavioral development.[15] Additionally, a center should have the capability, manpower and laboratory to perform placental injection studies to evaluate treatment.

Postoperative and delivery care may be provided at an outside perinatal center or referring secondary or tertiary care center acting in close liaison to the fetal therapy center that performed the intervention. The resources should be similar to the resources provided at the fetal therapy center in order to maintain uniform care for ongoing outcome evaluation. This includes regular of weekly contact with the fetal team coordinator with (bi) weekly review by the MFM obstetrician. The fetal therapy team must provide the opportunity of around the clock immediate contact and advice for caregivers outside the perinatal center.

It is essential to have an established functional cohesive multidisciplinary team with the individual members of the team exhibiting and maintaining a level of expertise in their respective fields. To ensure quality and safety, it is paramount that this fetal surgery team operates together with some regularity. Centers developing new fetal therapy programs must receive guidance and training from experienced centers. This should include mentoring on the process of evaluation, performing the actual procedure and perioperative and post-operative care. The optimal definition for a fetal therapy center has yet to be established. Preferably however, national professional bodies such as Boards of Obstetricians & Gynecologists should have guidelines describing optimal care for pregnancies complicated by fetal anomalies potentially treatable before birth.

Challenges for fetal surgeons

Despite the increasing number of studies that have been published the last decade increasing our knowledge, MC pregnancies complicated by TTTS still pose challenging problems. Some pregnancies are even more complicated than others.

We studied antenatal surgical interventions in spontaneous MA in chapter 4. When anomalies affect only one twin, selective feticide is frequently offered as an intervention. In case of a single intended survivor, our results suggest improved pregnancy outcomes in cases treated with cord transection. Although often performed with technical success, surgical procedures in MA pregnancies can be technically challenging. Especially, cord entanglement can be hazardous during fetoscopic interventions. Multiple loops of entanglement make identification of the correct cord difficult. Although rare, accidental coagulation of the wrong cord does occur, as presented in our series and previously reported.[16]

In summary, all surgical interventions in MA twins, despite being minimally invasive techniques, carry a high risk of complications and require highly skilled operators. To improve outcomes in these rare, high-risk pregnancies, international collaboration, sharing data on techniques and protocols, benchmarking, and setting standards for indications and interventions are achievable and still very valuable goals.

Perforation of the intertwin membrane during the laser procedure, creating an iMAT pregnancy, is a common complication, which is associated with preterm birth (chapter 5). Possible explanations for this increased risk are the intensive fetal surveillance and preterm elective Cesarean sections that are carried out in this group in order to prevent cord accidents.

Recent evidence suggests that cord entanglement and monoamnionicity in themselves (after excluding congenital abnormalities) are not associated with increased perinatal mortality or morbidity[17, 18]. Moreover, iMAT differs from spontaneous amnionicity in many respects: in our series, cord entanglement was observed in only 12% of iMAT cases after birth, while it is observed almost universally in spontaneous MA pregnancies. The placental angioarchitecture of these two groups is also quite different.[19, 20] It is likely that not only cord entanglement or monoamnionicity itself, but also technical difficulties of the laser procedure and aggressive perinatal management influence perinatal outcome in iMAT pregnancies.

Another challenging group includes the triplet pregnancies complicated by TTTS (chapter 6).

In MC triplet pregnancies the outcome was poor. Most likely, this is due to the technical difficulties of the fetoscopic treatment because of the identification and coagulation of vascular anastomoses between all 3 fetuses. Care should be taken when interpreting these results due to the limited data on perinatal outcome in triplets with TTTS, particularly MC triplets. Only 27 cases of MC triplet pregnancies with TTTS have been reported in the literature. The actual number of MC and DC triplets with TTTS may be higher due to underreporting/publication bias. Several cases in which the pregnancy was terminated or fetal demise occurred spontaneously have probably not been reported. Irrespective of zygosity, triplets are high-risk pregnancies due to the high incidence of preterm delivery, intrauterine growth restriction and congenital anomalies.[21]

However, the rarity of these conditions, the required operator and prenatal diagnostic skills, the variety of management options and the requirement of in-depth counseling of patients currently limit the availability of such interventions to referral centers for fetal medicine.

Training fetal therapy

There is a need to train and educate the next generation of fetal surgeons. Expert fetal centers need a solid program in order to prepare their trainees to take over practice. Moreover, it is expected that new centers that start to perform fetal therapy will exhibit a learning curve and require guidance in learning the procedure. To ensure that the level of expertise is maintained, an evidence-based training curriculum and continuous process of reporting and monitoring of outcomes would be highly valuable.

In the absence of standardized protocols for fetal therapy, the content of the training curriculum developed in this thesis was created with international (authority based) consensus (chapter 7). It is important to note that the existence of a consensus does not mean that the correct answer, opinion or judgement has been found.[22] However, according to our expert panel, an acceptable accuracy is created. A potential limitation of the methodology is that no significance to each step in terms of outcome could be addressed. Although consensus was reached on specific substeps of the procedure, this study does not provide information whether this correctly executing a certain substep is associated with better or worse outcomes in those that perform it.

Besides evidence on how to perform the procedure, experience with performing the procedure itself is essential. The rapid pace of innovation in surgical procedures, combined with new technologies, the need to enhance patient safety and limited operating room resources illustrate the need for simulator training.

Simulator training

Simulators provide a useful tool for the attainment and maintenance of trainees' surgical skills and for immediate or late assessment of their proficiency in those skills (Chapter 8). The process of skills acquisition may demonstrate individual differences between trainees depending on cognitive capacity, perceptual speed, and psychomotor abilities.[23] Setting a certain number of procedures performed on a simulator or actual patients to form an option for fetoscopic proficiency may cause bias. Furthermore, initial improvement in performance cannot be retained without regular repetition.[24]

Perhaps more important than the simulation equipment itself, is the creation of the simulation program or curriculum. As with any curriculum development, the educator must determine several factors to create a simulation program that will be useful.

Simulation is simply one aspect of the larger educational program, not the focus of the program.[25]

Implementation of training

Despite all positive effects of simulation in fetoscopic surgical training, there are various practical limitations to implementing simulation training programs. The most obvious obstacle is the need for instructors with available time to teach those learning on simulators (internationally). The expenses currently incurred in obtaining a simulator model adequate for fetoscopic surgical training may also be challenging for individuals of MFM centers, especially in developing countries.

In addition, validation of simulator-based fetoscopy training is required by correlating the actual surgical experience with the performance on the simulator. A significant amount of important work has been done to validate simulators as viable systems for teaching technical skills outside the operating room. The next step is to integrate simulation training into a comprehensive curriculum (Chapter 9). Randomized controlled trials from the general surgery literature have proven that simulation-based training leads to detectable benefits for learners in clinical settings.[26, 27]

International collaboration

Fetal therapy centers have developed through a variety of multi-disciplinary collaborative relationships among pediatric surgery, maternal-fetal medicine and radiology (sub) specialists. They exist within established obstetric departments of (academic) centers or freestanding centers. Cooperation between fetal therapy centers should be encouraged to establish collaborative research networks (such as www.tapsregistry.org) and training curricula.

Since fetal therapy concerns rare diseases and procedures, the establishment of centers of excellence for those procedures that are both rare and technically challenging may help to improve maternal and fetal outcome.[28]

FUTURE PERSPECTIVES

Telementoring

Supervised training is essential for safe and effective development of surgical skills. Fetoscopic procedures are performed on an infrequent basis, therefore there is a need for prolonged and expensive stay in distant fetal therapy centers to accumulate hands-on experience.

We believe that a potential new strategy, involving telementoring, could enhance the rate of trainees' supervision, making training safer. Moreover, telementoring could be used to support real "competency based" training, guiding trainees from competence under supervision to competence for unsupervised procedures in a controlled environment.

Telementoring could also be used for intraoperative consultations between colleagues and to deliver new skills to remote units without the need for the mentor to be physically present or for the surgeons to travel and attend courses in distant locations. Similarly, telementoring could be an inexpensive and efficient system to accredit specialists for advanced techniques.

Finally, versatile telementoring systems could be used as a teaching aid for groups of trainees and students gathered outside the OR (e.g. in a lecture room), thus reducing the number of observers in the room, often competing for a narrow surgical field like fetal therapy. If this technique is combined with the use of a simulator, this would allow future fetal surgeons to train new techniques at a desired moment, with guidance of a fetal expert without jeopardizing patients safety.

Technical innovations

Since relatively new, often described as 'experimental', some fetal interventions are performed within research protocols. It is important to distinguish which fetal interventions are standard or evidence based therapy and which are innovative or experimental. Especially in this field, surgeons encounter blurring boundaries between scientific research and therapeutic medicine. Although innovative practice is associated with the rapidly developing technologies used in fetal intervention, this raises concerns about the protection of pregnant women and their fetuses from the risks of unproven therapies.[14] On the other hand without these innovations fetal therapy would not even exist. Once feasibility and potential benefit have been identified; innovations should be subjected to systematic formal research as soon as feasible.

Fetoscopic surgery, as all endoscopic surgeries, has shown rapid development in recent decades, including advances in quality of imaging instruments and surgical techniques.

The fetoscope is used as a diagnostic tool to expand vision by magnifying objects inside the uterus, displaying the images on a 2D monitor. Diagnostic accuracy depends on optical resolution of the scope and the physiological ability of the operators' brain for perception. During surgery the fetoscope is moved to cover the wide area inside the uterine cavity creating a flowing image. All information produced by the endoscope, i.e. motion, color and shape, is integrated to create a spatial color map in the brain of the operator that cannot be produced in a still picture. In other words, an entire three-dimensional image is created in the mind of the surgeon that cannot be shared objectively; this may result in imprecise identification of location and size of the placental vessels after fetoscopic observation. Also, each endoscope generally has a blind spot.

In fetoscopic surgery, magnified vision enables visualization of the fine architecture of the placenta and fetuses. At the same time, the surgeon encounters several challenges due to the limitations of this technique; including incorrect accommodation of the surgeons hand and vision, loss of 3D information, and narrow field of view. These associated problems could be reduced by the use of a high dynamic range camera, computer and new software to enhance imaging. In other words, showing the operator an augmented overview of the placental surface and the vascular equator to enhance efficient en complete coagulation of the anastomoses. Optimizing the operation conditions by improving imaging will undoubtedly benefit the outcomes. Computer-based image processing of fetoscopic video images adds new functionality to conventional fetoscopy, following the development of new surgical devices, laser techniques and approaches and biological knowledge.

As a surgeon, on has a unique and best view on the operating field. No trainee will experience that same look and feel before being in charge on his own. Imagine the benefits of seeing through the surgeon's eyes at that moment. Today, the implementation of a small camera, a screen and audio capability in a spectacles' frame (Google Glass, Google Inc, Mountain View, CA) is able to do that and more. The concept of using Google glass consultation while performing an operation has recently been proven.[29]

In addition to communication with others, interaction with live information adds value to technical devices such as these glasses. Imagine the possibilities: patient charts, monitoring data, pre-operative diagnostic information, equipment warning signs or augmented reality overlays, can be presented without having to turn away from the patient. Operating under the watchful eye of a world's expert, either walking you through the procedure or as a second opinion will come within everyone's reach. The sky is the limit…

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