The availability of high resolution ultrasound imaging and aneuploidy screening programmes has made the unborn a patient sui generis. When fetal malformations, genetic diseases or in-utero acquired conditions are suspected, pregnant patients should be referred to fetal medicine units with more specialized skills, larger experience and multidisciplinary counsellors to define potential options. In some cases, intervention before birth may be desirable, often not requiring direct access to the fetus, e.g. transplacental administration of antibiotics in case of fetal infection or anti-arrhythmic drugs in case of tachy-arrhythmia. Other conditions can only be treated by invasive access to the fetus. Some conditions are amenable to surgical correction, and in the majority of cases this is best done after birth. Occasionally prenatal surgery may save the life of the fetus or prevent permanent organ damage. Because of the potential complications, risks and benefits of the intervention must be weighed against each other. A consensus, endorsed by the International Fetal Medicine and Surgery Society (IFMSS), has been reached on the criteria and indications for fetal surgery (Table 1; Harrison, 1991). The majority of procedures currently clinically offered in Europe are minimally invasive (by fetoscopy) (Deprest et al., 2006), although open fetal surgery is now increasingly practiced in the United States (Adzick, 2010). An overview of indications can be found in Table 2 (Deprest et al., 2008).
Dimensions of the ethical dilemma of fetal therapy

*General dimensions directly related to the medical community.*

Fetal therapy raises a number of ethical concerns, of which the most obvious one is the balance between potential benefit and harm for the fetus as well as for its mother. This is in essence first a scientific question, and involves aspects related to point 1 to 4 of Table 1. It is up to the medical community to provide evidence that fetal intervention can provide the claimed benefit, in the absence of harm, or only at the expense of minimal and acceptable risk. There is unfortunately no evidence of benefit for the vast majority of fetal therapeutic procedures that are offered today. Exceptions are for instance the use of steroids in the prevention of respiratory distress syndrome. Also, for endoscopic procedures there is now level I evidence that laser coagulation of placental anastomoses for twin to twin transfusion syndrome is better than amniocentesis (Senat et al., 2004). The only open fetal surgical procedure with a proven benefit is the antenatal repair of selected neural tube defects (Adzick et al., 2011). The other surgical procedures are strictly spoken *investigational*, i.e. that there is no evidence in randomized controlled trials (RCT) showing their benefit. For a number of procedures, it will be difficult to ever gather such data. For instance in the case of the administration of fetal red blood cells for Rh-sensitization, fetal transfusion has an excellent track record and there are good data on long term outcomes. Also the risks associated to it are limited, but include rupture of the membranes, infection, bleeding, and occasionally fetal death. It does not seem reasonable to conduct a trial for the simple purpose of doing a RCT: it is unlikely that such will advance our knowledge or improve outcome of this disease. For other procedures, such as reversal of urinary tract obstruction, valvuloplasty for congenital heart defects, tracheal occlusion for diaphragmatic hernia, etc… it is possible that the inherent adverse effects exceed the assumed benefit. Outcomes are also very often much less conclusive, if not poorly documented. In such situations it is a duty of the medical community to conduct appropriately designed trials that balance the claimed benefits of fetal intervention against the inherent side effects of the surgery (Rodrigues et al., 2011). In reality this turns out to be very difficult. One of the principal reasons is that fetal medicine specialists often have certain prejudices or biases towards (or against) given fetal therapies. Mediagenicity of fetal therapy also tempts many clinicians and hospitals to advocate intervention, and the lay press often overadvertises procedures of yet unproven efficacy.

An often forgotten ethical aspect of fetal surgery is that these highly specialized procedures should be offered only by teams, and individuals that are familiar with and experienced in management of the pathology involved and the execution of these procedures. For a number of fetal interventions learning curves have been described. For example numbers have been determined to achieve as well as maintain proficiency in laser surgery for twin-to-twin transfusion syndrome (Hecher et al., 2000, Van Kamp et al., 2004,). A similar learning curve effect has been shown for prenatal imaging, required to select cases for fetal surgery (Cruz-Martinez et al., 2011). Given the numbers required and the rarity of cases implicated a certain centralisation is necessary to obtain optimal results. If those are not met, the fetal therapy centre should disclose its previous experience as well as turn over to the patient, and when insufficient, refer the patient to a more experienced unit. The complexity as well as the overall rarity of indications are both limitations to the wide implementation of fetal therapy. The training and credentialing for these procedures is an issue on itself. There may be a need for a regulatory authority to determine viability and efficacy for current and new programmes. It is unclear who is entitled and qualified enough for this but in the USA the medical profession has already taken an initiative to regulate this (Chescheir, 2009; Johnson 2010). Conversely, centers not offering certain fetal therapies, should give the patient options to seek advice and eventually therapy elsewhere. This should be accompanied by information on the level of evidence for the suggested therapy. Groups that offer fetal therapy have to do so within strict protocols, and are expected to keep track of their outcomes. Indeed, long term follow-up for children that have undergone a fetal invasive surgery is lacking for numerous fetal interventions despite being an essential part of information given to parents (Harrison et al., 1982; Health

| Table 1. — Criteria for Fetal Surgery. (adapted from Harrison 1982) |
|---|
| 1. Accurate diagnosis and staging possible, with exclusion of associated anomalies  |
| 2. Natural history of the disease is documented, and prognosis established.  |
| 3. Currently no effective postnatal therapy.  |
| 4. In utero surgery proven feasible in animal models, reversing deleterious effects of the condition.  |
| 5. Interventions performed in specialised multidisciplinary fetal treatment centres within strict protocols and approval of the local Ethics Committee with informed consent of the mother or parents.  |
| Fetal Surgery: | Pathophysiology | Rationale for in Utero-therapy |
|---------------|-----------------|-----------------------------|
| 1. Congenital Diaphragmatic Hernia | Pulmonary hypoplasia and pulmonary hypertension | reversal of pulmonary hypoplasia and prevent pulmonary hypertension |
| 2. Lower Urinary Tract Obstruction | Progressive renal damage by obstruction Pulmonary hypoplasia by oligohydramnios | Urinary diversion prevents obstructive uropathy and restores amniotic fluid volume |
| 3. Sacrococcygeal Teratoma | High-output cardiac failure by arteriovenous shunting Fetal anemia by tumor growth and/or bleeding within a tumor | Cessation of steal phenomenon Reversal of cardiac failure Prevent polyhydramnios |
| 4. Thoracic Space Occupying Lesions | Pulmonary hypoplasia (space-occupying mass); hydrops by impaired venous return (mediastinal compression) | prevention of pulmonary hypoplasia and cardiac failure |
| 5. Neural Tube Defects | Damage to exposed neural tube Cerebrospinal fluid leak, leading to Chiari malformation and hydrocephalus | Covering exposed spinal cord, cessation of leakage preventing hydrocephaly and reversing cerebellar herniation |
| 6. Cardiac malformations | Critical lesions causing irreversible hypoplasia or damage | Prevention of hypoplasia or arrest of progression of damage |
| Surgery on the placenta, cord or membranes | | |
| 7. Chorioangioma | High output cardiac failure by arteriovenous shunting and polyhydramnios | prevention of cardiac failure and hydrops fetalis prevention of limb deformities and function loss |
| 8. Amniotic bands | Progressive constrictions causing irreversible neurological or vascular damage | |
| 9. Abnormal Monochorionic Twinning: Twin-to-twin Transfusion | Intertwin transfusion leads to oligo-polyhydramnios sequence, haemodynamic changes; obstetrical complications (preterm labour and rupture of the membranes) | Bichorionization stops intertwin transfusion, reverses cardiac failure Preventing neurological damage Delaying delivery (amniodrainage) |
| Fetus Acardiacus and Discordant Anomalies | Discordant anomalies: where one fetus can be a threat to the other one or to avoid termination of entire pregnancy | Fetocide to improve chances of the other fetus avoidance of termination of entire pregnancy |
Council, 2009). Last, maternal side effects as well as the potential impact on future reproduction and pregnancies should be well studied and discussed (Wilson et al., 2010).

Dimensions directly related to the individual mother and fetus and family

Thanks to prenatal diagnosis the fetus has become a patient, if not in its own right, at least with a quasi-independent consideration of interest. According to a preeminent view about the ethics of fetal surgery, in the viable period, the moral status of the fetus is typically perceived as (nearly) the same as that of a neonate. This makes the fetus a patient sui generis which can be considered more or less independent from the mother: perhaps with its own rights, including a right to therapy. One fundament of ethical clinical practice is the consideration of duty. It is often argued that the obstetrician has a duty towards the fetus who will become a born baby (Chervenak et al., 1993; Chervenak et al., 1985). When the fetus is not viable yet, it seems logic to interpret our duties towards the fetal patient differently, and one would only act if the mother confers her fetus the status of patient and beneficiary of the therapy we propose. Making a sharp distinction for fetuses that have reached viability quasi provides such fetus the status of an independent patient, to whom both the physician and the mother would have stronger moral obligations. In some countries the landmark of viability is reflected in the legislation on legal abortion for medical reasons. The fetus would in this perspective at a given timepoint (viability) be considered as a patient, irrespective of the mother’s preferences (Chervenak et al., 1993). This is tempting, but not true: the fetus – irrespective of its gestational age – is dependent on the mother and her body, and no treatment can be offered without involving the mother as well. For this reason maternal consent for any fetal therapy is necessary. It is the mother who bears the burden of fetal therapy (including its failure). She acts as the moral agent in relation to choices for the fetus (Noble et al., 2008). As a consequence, the mother has the right to refuse treatment as well, irrespective of viability borders.

In practice it will be mostly a shared decision by the mother and the father and family, after consultation with the multidisciplinary fetal care team. Given the emotional and complex nature of such a decision, it is required that the multidisciplinary professional team gives not only appropriate information about the prognosis, the impact of the condition for the future child and its family environment, the need and availability of structured medical and educational support, the benefits and harms of the intervention as well as all possible alternatives. Such counselling should in a careful and expert way offer personalised support to the pregnant couple and family. As to better understand the family’s decision process, counsellors will have to be aware of the very individual circumstances that may influence the mother’s decision, such as maternal age, previous and future fertility perspectives, the presence of other children affected by the same or other serious conditions in her own or wider family, socio-cultural and religious background, etc...

Besides that, if there is a reasonable certainty that the fetus will suffer from irreversible and serious harm without the intervention, and if there is evidence regarding the effectiveness of its treatment, with very few feto-maternal risks, relatively directive counselling of the couple can be a moral duty. But ultimately, the physician has to respect the autonomous decision of the pregnant woman (and her partner). On the other hand, when a mother or couple requests a procedure of questionable benefit or carrying a significant risk, according to the treating physician or center, it should be clear that they have not a right to an intervention that experts judge as too risky and medically not justifiable. A referral for second opinion to another expert center familiar with and offering the procedure seems to be a fair step in that case.

Fetal therapy in trials

Therapeutic procedures of uncertain benefit to the fetus must be evaluated within properly designed trials with appropriate ethics committee approval, and with maternal informed consent. Consent is only informed and voluntary if the potential harms and benefits are clearly understood by the mother. The latter are not the only aspects covered during consent; appropriate access to counselling and support is necessary to ensure that there is sufficient understanding and that support is available in the event of a poor outcome. Although in medicine, clinical research and medical ethics, the free and informed consent is considered as a very important procedural way of expressing the principle of respect for autonomy, it does in the context of fetal surgery not always give women the feeling that they are in the situation to make a real free choice. Not so much because they are poorly informed, but because such decision is not solely based on self protection or risk avoidance. Pregnant women generally want to give their child the best possible start in life, even if this leads to choices and behaviour which in other situations would be considered as not morally required (Smajor, 2011). If this altruistic attitude goes hand in hand with parallel social expectations and new
technological possibilities, caution should be taken not to cause an unpleasant feeling of “pressure”, social or other, on the mothers involved.

Another important aspect of informed consent during the recruitment of patients for a trial, is the use of the term fetal ‘therapy’. The word therapy implies an inherent benefit. This might be misleading, and at the best the term ‘investigational’ or ‘experimental’ treatment should be used. Another aspect of the consent procedure is that fetal interventions are often presented as an alternative for termination of pregnancy (TOP). The latter already presupposes that the fetal intervention is therapeutic, in other words with a sufficiently high and sustainable chance for success. In fact, its outcome might not be known until after birth, and might even be worse than expected, and at that time the option for termination no longer exists. Furthermore this way of presenting things might place undue pressure on parents to consent because they feel a moral obligation to do everything possible to avoid a termination, or, feel that they find themselves in a situation of ‘nothing to lose’. One solution to avoid such situation, would be to recruit only parents who express the intention not to opt for TOP (Rodrigues et al., 2011).

Our group has been recently involved in designing a trial, in particular on the prenatal management of fetuses with isolated congenital diaphragmatic hernia (CDH) (Deprest et al., 2009). This condition can be diagnosed in the prenatal period, and there is now reasonable evidence that the individual prognosis can be predicted based on lung size and liver position (Deprest et al., 2009). Temporary Fetoscopic Endoluminal Tracheal Occlusion (FETO) prevents egress of lung fluid, increasing pressure within the fetal airways, which triggers lung growth. The procedure can now be performed minimally invasively, with an inherent preterm prelabour membrane rupture (PPROM and prematurity rate of 20%. So far no maternal side effects were observed. When offered to fetuses with severe pulmonary hypoplasia (<20% survival chances), there is an apparent increased survival up to 50%, without evidence of an increase in morbidity.

The data are however poorly controlled and therefore unreliable and there is an urgent need for a trial. Such trial unfortunately addresses a population where the termination rate in view of the predicted outcome, is very high. Also many physicians have proposed fetal intervention as an alternative to TOP, which is not recommendable (Rodrigues et al., 2011). We received however unexpected resistance when designing this trial, in particular in relation to the randomization of cases with an over 80% predicted mortality rate. Both parents and physicians may have the perception that expectant management during pregnancy in this subset of fetuses, is an (unacceptable) attitude of “losing an opportunity for improvement” during pregnancy. Conversely, prenatal intervention is perceived as “therapy”, whereas this is exactly what such a RCT would be testing. During informative talks with ethicists, it was concluded that for an institution that offers fetal therapy for this population already more than 5 years, it would be difficult to deny this procedure to patients referred for it, except if they would participate in a trial with one expectant arm.

In other words, patients would have the possibility of being treated in utero by choice, or opt for the trial. This is a de facto “back-door”, making sufficient trial recruitment difficult if not impossible. This situation describes the dramatic situation one gets in when one waits too long to set up a trial after introduction of a novel technique. The issue has now been solved, by leaving the decision to participate in the RCT or opt for intervention outside the trial, in the hands of referring physicians or centers (Rodrigues et al., 2011). In this scenario, referring fetal medicine centers counsel patients with severe or moderate CDH and decide whether or not to offer trial participation. The fetal treatment center will in that case only offer trial participation. Already two years ago we have started a randomized trial in fetuses with moderate pulmonary hypoplasia (i.e. with predicted survival 30-60%). For those fetuses, we hypothesize that fetal intervention will reduce their morbidity (bronchopulmonary dysplasia), potentially increasing survival. At present there is evidence that in this group fetal therapy does not improve prognosis (Harrison et al., 2003). All foetuses were born preterm, but had a better than expected lung function (Keller et al., 2004). This trial was however conducted at a time that the fetal procedure was much more invasive, and carried a 100% preterm membrane rupture rate. Since techniques have improved, and our ongoing experience meanwhile showed that percutaneous surgery lowers this to around 20-25% (Jani et al., 2009).

Fetal pain relief during procedures

Pain is a subjective experience occurring parallel to a physiologic response in reaction to impeding or actual tissue damage. The subjective experience of pain requires nociception and an emotional reaction. Nociception requires an intact sensory system, while an emotional reaction requires some form of consciousness. Since the fetus cannot tell us whether it feels pain and since pain cannot be assessed using conventional objective measures, the concept of fetal pain has been questioned by some.
However there are many indirect indicators that suggest that the fetus at least can feel pain. Anand et al. and Fisk et al. demonstrated that preterm infants respectively fetuses display a number of stress responses during invasive procedures (Anand et al., 1987). There is evidence that the mid-gestational fetus can respond to potentially noxious stimuli by mounting a distinct stress response. In analogy to what has been observed in neonates, prenatal stress may be expected to affect later neurodevelopment. Consequently, means to manage fetal pain / stress response in utero during invasive fetal interventions have been explored (Fisk et al., 2001). Even if it remains yet unproven whether this results in improved neurodevelopment and improved long-term outcome, it is prudent to take pre-emptive action and manage potential “painful” procedures accordingly. Our group has therefore adhered to a policy of efficient pain relief during fetal procedures and around the time of fetocide from 18-20 weeks onwards (De Buck et al., 2008). Sufentanil 1-2 µg/kg or fentanyl 10 µg/kg can be given intramuscularly or intravenously to the fetus. In the less common scenario in which the mother undergoes general anesthesia, the fetus should be sufficiently anesthetized through transplacental passage (Van De Velde et al., 2006). Research is ongoing whether postoperative fetal pain relief should be administered for some procedures.

Manipulation of the fetal genome and use of fetal stem cells for therapeutic reasons

Progress in the field of stem cell biology and gene transfer technologies is paving the way for novel treatment strategies. Single gene defects would be the theoretical target of prenatal gene therapy. Many of them can be diagnosed early in gestation, hence treated prior to birth (Coutelle et al., 2005; Toelen et al., 2010). Cystic fibrosis (CF) is the quintessential example of a monogenetic yet lethal disease. As the disease can be diagnosed early in pregnancy and since it is caused by a single gene defect, the logic solution is to insert a copy of the wild type gene, at least into the organs that are most affected. There are several reasons to do this prior to birth. The most important one is that postnatal gene therapy so far has failed for this condition. Antenatal gene therapy would also prevent disease to develop, and most likely it is going to be technically easier – mainly because the target organ is so much smaller. There is early experimental evidence that in utero gene therapy is effective in a number of genetic diseases. Proof-of-principle of the above has been demonstrated in murine models (Waddington et al., 2004).

Fetal stem cell therapy today is already a clinical reality, with the advent of successful in utero hematopoietic stem cell transplantation for severe combined immunodeficiency (Westgren et al., 2002). However the use of stem cells may be wider. They may benefit the fetus without engrafting, through paracrine effects, which are currently the subject of intensive research (Aslam et al., 2009). During the prenatal period, it is possible to harvest amniotic fluid (AF) with limited risk. From AF, mesenchymal stem cells (AF-MSC) can now be isolated and expanded for a wide range of applications (Gucciardo et al., 2009). They could be used for tissue engineering so that congenital birth defects can be more elegantly repaired. The interval between harvesting (midtrimester) and postnatal application would leave time enough for the laboratory to engineer an appropriate construct (Fauza et al., 2001).

Another interesting aspect is that AF-MSC can be easily transduced making them an attracting source for combined autologous cell & gene therapy (Grisafi et al., 2008). Again, this may be a method of persisting exposure to growth or differentiation factors. This could then be achieved by the administration of transduced autologous AF-MSC, such that they (temporarily) over-express the factor of interest.

It is obvious that fetal gene and cell therapy are of another dimension than the temporary use of drugs, or single surgical intervention. Gene and cell therapy will cause complex and continuing interaction with the recipient. “Complex”, because of the duration of the interaction and the inability of its reversal. Continuing, because it will be difficult to anticipate when the therapeutic effect is stable, or even complete. Also certain (side) effects may only become apparent later in life, and can be as drastic as a development of a tumor (Waddington et al., 2004). Because of potential post-trial events, any such clinical trial will be a permanent project, in other words a life-long experiment (Petit-Zeman, 2001; Trommelmans, 2010). Ethical assessment of such trials is a challenge on itself. One must not only address typical issues such as minimization of the risks on an individual case but also analyze how the context of gene and cell therapy influences the concept and features of the experiment. This complexity complicates also the informed consent process (Trommelmans et al., 2008). An informed consent for trials with fetal gene and/or cell therapy should not only pay attention to the immediate effect, but also deal with the principle of regeneration, its specific benefits and risks, and with the fact that living cells or duplicating organisms are used, and what their source is.

In conclusion, the prenatal diagnosis of a condition that is eligible for fetal therapy, should prompt referral to a center familiar with management of the condition and proven expertise. When fetal therapy is justified, it should be offered with full respect for
maternal choice and perception of potential risks. For therapies of unproven benefit, the absence of evidence must be disclosed, and therapy should be undertaken within well designed and approved trials. Potential risks and eventual morbidities in case of therapeutic failure should be part of the counselling, neither should fetal therapy be presented as an alternative to termination of pregnancy.

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