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EDITORIAL

Fetal therapy: progress made and lessons learnt

Kypros H. Nicolaides[1,2]* and Lyn S. Chitty[2,3]

[1]*Harris Birthright Research Centre of Fetal Medicine, King's College Hospital, London, UK*
[2]*Department of Fetal Medicine, University College London NHS Foundation Trust, London, UK*
[3]*Clinical and Molecular Genetics Unit, UCL Institute of Child Health, London, UK*

Fetal therapy began more than half a century ago when Liley reported the first intraperitoneal transfusion for the treatment of fetal anaemia in Rhesus disease (Liley, 1963). This was to be replaced with intravascular transfusion, initially by fetoscopy and subsequently by ultrasound-guided cordocentesis. This is now a well-established therapy and one which was never subjected to rigorous evaluation. In this issue of *Prenatal Diagnosis*, we focus on fetal therapy, exploring how far it has developed since these early reports and discuss how new approaches might further change management, highlighting the need for rigorous evaluation of any new technology prior to clinical implementation.

The widespread use of ultrasound scanning in the 1980s and the prenatal detection of fetal defects stimulated the development of a wide range of techniques for intrauterine interventions. The aim was to improve the outcome for conditions that were traditionally treated by postnatal surgery because it was thought that prenatal surgery could reduce irreversible damage to the developing organs. However, for the large part the absolute benefit in terms of improved longer term outcome for affected fetuses remains unknown. It is only in the last few decades or so that we have realised that the only way to properly assess many of these therapies is with randomised trials, which must include structured long-term follow-up to determine the true benefits and costs. A good example is the management of lower urinary tract obstruction where shunting initially seemed to improve outcome as more babies survived the neonatal period. However, most studies were small and had no control group, thus making it impossible to define any benefit resulting from the intervention and longer term follow-up was patchy and inconsistently collected (Ruano, 2011). Furthermore, because of the rarity of many of these conditions, much of this research must be multicentre and multinational, raising an issue in itself as these techniques will be concentrated in centres of excellence, thereby limiting equity of access and focussing expertise in a few centres (Ville, 2011).

*Correspondence to: Kypros H. Nicolaides, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK.
E-mail: kypros@fetalmedicine.com

The inadequacy of the research done to date has dawned and with it we are beginning to see a more scientific approach to the development of fetal therapy with randomised trials being established to determine the optimum management for twin–twin transfusion syndrome (Chalouhi *et al*., 2011) and *in utero* repair of meningomyelocele (Bebbington *et al*., 2011). Gradually, we are gaining information on the natural history of some conditions to enable better case selection (Gucciardo *et al*., 2011) and developing better standards upon which to assess the severity of disease (Cannie *et al*., 2011). Others now have well-documented cohorts of survivors of fetal therapy who they are following up to determine long-term outcome (Maschke *et al*., 2011). The problem here is not only the need to maintain contact with the family, but the changing standards of neonatal and prenatal care complicate data interpretation. Attempts are also being made to understand the underlying pathology of potential iatrogenic disease caused by the therapy itself; for example, the tracheal changes associated with fetal tracheal occlusion in the management of congenital diaphragmatic hernia (Jani *et al*., 2011). Hopefully, lessons have been learnt from experiences over the last few decades, and as we gain the technical expertise to treat ever more conditions, we will focus expertise in a few centres, and collaborate broadly to enable a common policy and increased numbers for randomisation across continents (Artz and Tulzer, 2011).

In the main, we have seen surgical therapy move from more to less invasive, from open surgery to endoscopic or percutaneous therapy under ultrasound guidance as with the management of cystic lung lesions (Witlox and Oepkes, 2011) and sacrococcygeal teratomas (Gucciardo *et al*., 2011). Indeed, for some conditions we have seen the development of medical therapies for the mother, thereby indirectly treating the fetus; for example, the treatment of fetal and neonatal alloimmune thrombocytopaenia by administration of immunoglobulin to the mother (Kamphuis and Oepkes, 2011) or the administration of drugs to suppress production of maternal antibodies or hormones that may harm the developing fetus (Hui and Bianchi, 2011). The exception is the return to open fetal therapy in the recently reported trial of open fetal surgery for myelomeningocele (Bebbington *et al*., 2010). While this trial did address some of the previous omissions in that it was randomised, multicentre, used highly

skilled operators and included long-term follow-up, the seemingly good results must be weighed against the significant maternal morbidity that ensued and the persistent neonatal and childhood morbidity, albeit reduced when compared with cases treated postnatally.

One of the major problems associated with any invasive therapy, be it via a needle, fetoscopically or performed through a hysterotomy, is prelabour, preterm rupture of the membranes. There are a variety of strategies which can be used to treat this situation (Deprest *et al*., 2011; Haller *et al*., 2011), but whether the most effective is the platelet plug or mussel glue remains to be seen.

What will future fetal therapy bring? David's group describe some of the advances in fetal gene therapy that may see an effective treatment for a wide variety of genetic and non-genetic fetal conditions (Mehta *et al*., 2011). Will this lead the way for effective treatment of ruptured membranes? Will the use of stem cells allow early and less invasive repair of spinabifida and other structural malformations? Whether it does or not, we would do well to remember the lessons of the past and ensure that these techniques do not continue to 'creep' into practice, but are properly evaluated in a randomised way and with a good, structured follow-up to enable assessment of longer term morbidity as well as early mortality.

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