Length. The length of your article has been specified in your accompanying confirmatory email/letter. Please adhere to this as closely as possible. This limit is ***inclusive*** of space for illustrations and tables. As a guide for conversion, a half-page illustration or table is equivalent to 250 words of text so for every table or illustration included deduct 250 words from your total word allocation.

Presentation of manuscripts. Manuscripts must be submitted in **English** and should be typed in double-spacing. Margins of at least 25 mm should be left on all sides.

Practice Points. Where appropriate, summarise the most important points of relevance to clinical practice; these should be brief and set out as a bullet point list at the end of the main text. Some examples relating to the topic of *Arterial Embolization for Obstetric Haemorrhage* are shown here.

Self-assessment Questions
All authors are asked to submit two multiple choice questions (MCQs), extended matching questions (EMQs) or short case scenarios which will contribute to the self-assessment section of the journal. These should be based on the author's review; further guidance regarding the construction of these is given below on pages 00-00.

Further Reading
Articles should **NOT** contain any reference citations in the text. A list of **no more than 10 key sources of Further Reading** should be included at the end of the article.

Placental Gene Therapy

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Abstract 150 words

Gene therapy uses genetic material as a drug delivery vehicle to express therapeutic proteins. Placental gene therapy may be useful for correction of two important obstetric conditions, fetal growth restriction and pre-eclampsia in which there is a failure of the physiological trophoblast remodeling of the uterine spiral arteries in early pregnancy. The patient in this scenario is the fetus. Placental gene therapy might be justifiable when (a) there is reasonable certainty that the fetus will suffer irreversible and substantial harm without the intervention, (b) the intervention is safe and effective, (c) the risk to the health of the mother is negligible and (d) the mother can give informed consent to the intervention.

Key words: medical ethics; gene therapy; placenta; fetal therapy

Introduction

The practice of obstetrics is rich in ethical considerations pertaining to the fetus and the mother. In no other specialty is the clinician carrying out risky procedures on one person with the aim of benefitting a (legal) non-person contained within. Who is their patient? Where does their duty of care lie? The status of the fetus, the autonomy of the pregnant woman and the relationship between the two creates clinical, ethical and legal dilemmas. New therapies are being introduced that highlight these ethical issues, and gene therapy is one such. This review addresses the ethical issues that arise when considering gene therapy to the placenta for treatment of genetic or placental disease.

Placental gene therapy

Gene therapy uses genetic material as a drug delivery vehicle to facilitate expression of therapeutic proteins. Vectors such as manipulated viruses, are used to carry to the genes to the target cell or organ, where they use the cellular machinery to express the protein. An increasing number of clinical trials show that for certain diseases, such as severe combined immunodeficiencies for example, postnatal gene therapy is efficacious.

Pre-clinical studies in animals show that delivery of gene therapy to the fetus can provide a long term cure of single gene disorders, such as haemophilia, although clinical studies in H. Sapiens have yet to be done. Attempting to treat the fetus by giving gene therapy to the mother's circulation or into the placenta however, has so far not been shown to be successful. Only low levels of vector reach the fetus and the placenta is a highly effective barrier to vector transfer. Developments in vector design however may open the way to treat genetic disease in the fetus in the future.

Placental gene therapy may be useful for correction of two important obstetric conditions, fetal growth restriction (FGR) and pre-eclampsia, that are major causes of maternal and neonatal morbidity and death worldwide. The underlying abnormality is a failure of the physiological trophoblast remodeling of the uterine spiral arteries into low pressure, passively dilated channels conducting blood to the intervillous space that normally results in the huge increase in uterine perfusion from early pregnancy. Growth factors implicated in the pathogenesis of this uteroplacental insufficiency include Vascular Endothelial Growth Factor (VEGF), Insulin Growth Factor (IGF) and Placental Growth Factor (PlGF). Over-expressing VEGF protein using gene therapy in the uteroplacental circulation increases uterine artery blood flow, and causes vasodilatation and new vessel formation, all of which may ameliorate the underlying abnormality in FGR and pre-eclampsia. In this situation the aim is to treat the mother in order to benefit the fetus. It is the uterine arteries and the maternal side of the placental circulation that is the target in placental gene therapy. This is different to the more usual case in which the fetus is directly given treatment to cure a fetal condition via the mother's uterus, although the ethical issues are very similar.

Justification for placental gene therapy

The 1992 report of the Clothier committee recommended that gene therapy should be limited to life-threatening diseases or disorders for which no current alternative effective treatments are available. The Gene Therapy Advisory Committee (GTAC) was established in 1993 to oversee and implement gene therapy clinical research. In its 1998 report GTAC took account of ethical and safety issues relating to the potential use of gene therapy in the fetus *in utero*, and concluded that it was unlikely to be acceptable for the foreseeable future. Gene therapy directed to the placenta however, was not specifically considered.

Complications of growth restriction are concentrated in fetuses weighing around 500 gms or less, where growth velocity is reduced from an early gestation, and the fetus is sufficiently small to be nonviable if delivered, or associated with high postnatal mortality (>50%) and morbidity rates. When there is documented evidence from serial ultrasound scans that fetal growth has ceased completely and the weight remains below 500 gms the only management options currently available are to terminate the pregnancy, await inevitable fetal death *in utero*, or, if the fetus is between 450 and 500 gms, perform a caesarean section with a high chance of postnatal death or disability, and the usual risks to the mother associated with caesarean section. It is clear that even for normally grown fetuses born very premature, small increases in fetal growth and gestation at birth, such as a birthweight of 700g, or reaching 28 weeks of gestation, are associated with major improvements in survival and morbidity. It is in this extreme, but not uncommon, scenario (approx 2:1000 pregnancies), where no other therapies are available, that placental gene therapy to improve uterine blood flow might be both ethically acceptable and clinically relevant.

Fetal issues

Intuitively, the patient in the placental gene therapy scenario is the fetus. This is because the primary intention of the therapy is to promote growth of the fetus by improving placental function, in the hope of improving postnatal outcomes for the fetus. Considering the fetus as a patient, and the potential conflict that presents to the mother and her clinician, is at the very core of the ethical issues in placental gene therapy. Advances in fetal medicine, ultrasound and neonatal care in particular have supported a changing view of the fetus. When a neonate born at 23 weeks may survive and enjoy a good quality of life, then it may be argued that there is little

difference in moral status between a late-gestation fetus and a newborn baby. The obstetrician has a duty of care to the mother, and it has been argued, a duty to the fetus because it is potentially a born baby. Key to this concept of obligation to the fetus is the concept of viability, which states that there is a distinction between the 'pre-viable' fetus and the 'viable' fetus. The argument continues that the pre-viable fetus can only be considered a patient if the mother confers such a status on it whereas the 'viable' fetus is always regarded as a patient.

This concept of viability has several problems. Viability is not fixed during gestation but depends on a number of factors such as the technological skill available, gestational age, birthweight and the presence of fetal abnormalities and indeed, placental gene therapy would aim to alter the viability status of the fetus. The fetus at any stage of gestation is dependent on its mother and only becomes an independent person when it is separated from the materno-placental unit at birth.

The 'fetus-as-a-patient' concept can create ethical conflict between the clinician and the mother, should she refuse a diagnostic or therapeutic intervention that the clinician considers to be beneficial to the fetus. Further, the duty of the clinician is firstly to 'do no harm' (principle of non-maleficence) and secondly 'do the best for their patient' (principle of beneficence). It is ultimately the mother who must decide what is in the best interests of her fetus, to give informed consent to any proposed intervention, and to also refuse treatment if she so wishes.

English law gives absolute priority to the mother's rights over that of the fetus she carries. The mother's decision is likely to depend on concerns for her family and other children, financial, psychosocial or religious factors. The autonomy of the mother is particularly important when the outcome of placental gene therapy can be uncertain. It is possible that an intervention might be of partial benefit to the fetus, by

saving its life, but result in the birth of a baby with a severe condition leading to its suffering and death within a few months. This arguably is a worse outcome than if the baby had not been born alive. The choice of termination of pregnancy to prevent suffering in the offspring remains available to parents before birth even if treatment fails, but not after birth.

Gene transfer to the germline is a potential risk of placental gene therapy. The GTAC subgroup on New and Emerging Technologies (NETS) considered that germline interventions are 'off limits at present' in agreement with the Clothier committee principles. Germline gene transfer has been observed after pre-clinical studies in large animals and depends on the gestational age and route of injection. It is unlikely that placental gene therapy would pose a risk to the germline because compartmentalization of the primordial germ cells would already have occurred by the time of the intervention, and the fetus would be exposed to very low levels of vector. Nevertheless it is an issue that will need careful study including transgenerational pre-clinical animal studies before translating therapy into man.

Maternal issues

The argument that the fetus, viable or otherwise, should be considered as the, or a, patient is controversial, and as noted above is not the position taken in English law. Nevertheless, obstetricians and pregnant women alike frequently do proceed on the assumption that the fetus is a patient, and one whose interests are of central concern. It is also possible, and perhaps desirable, to argue that it is the woman herself who is the primary, if not sole, patient. Certainly the law and research ethics principles assume that it is her consent which is crucial (and in passing, we may note that the father's consent is not relevant in law, even if it may be important in practice). Two issues are central here: the need for the autonomous consent of the woman as

someone under going a risky (and at this stage experimental) procedure. Second, we need to consider whether the woman's interests are promoted (as required by the principle of beneficence) by the treatment. Many many women have a strong interest in maintaining the pregnancy. Where they do so, they have an interest in increasing the chances that the baby when born will be healthy. The decision to seek to maintain a pregnancy in the situation where placental gene therapy may be considered will necessarily be a difficult and highly personal one.

A core principle governing gene therapy recommended by the Clothier committee, was that patients should take part in gene therapy research trials only after a full explanation of the procedures, risks and benefits and after they have given their informed consent, if they are capable of doing so. The time available to parents to consider an intervention for FGR is likely to be short, because of the rapidly increasing demands that the fetus places on the uteroplacental circulation, and the difficulty in predicting early in pregnancy which fetuses are likely to be affected. Counseling should be independent and non-directive. This is difficult when the alternatives are termination of pregnancy or almost certain neonatal death. Nevertheless, care must be taken to ensure that a placental gene therapy intervention is not presented coercively as an option to avoid a termination of pregnancy. The range of possible outcomes for the pregnancy should be understood by the parents. A team of consulting professionals is needed to consider the justification for intervention and to ensure the best outcome for the fetus and the mother's immediate and long term health including any future children.

Delivering placental gene therapy

There must be a balance between the safety and the risk to the mother for delivery of placental gene therapy. In some ways the intervention needs to be as safe

as the alternatives, namely letting the fetus demise *in utero* or terminating the pregnancy, both of which carry a low risk of harm. Allowing the pregnancy to continue might be harmful if the mother has also developed co-existing pre-eclampsia, and the intervention failed to treat this. The uteroplacental circulation could be targeted using minimally invasive interventional radiology techniques, such as those used to place catheters in the uterine arteries prior to Caesarean section in the presence of major placenta previa. It would be critical to maintain sufficient uterine artery blood flow to the fetus during delivery of the gene therapy since a small, compromised fetus may be easily harmed by small reductions in substrate and oxygen supply. It is clear that much pre-clinical work is needed in this area.

Ethical issues in translating research into the clinic

Regulatory procedures will need to be satisfied before human application could be attempted. This will involve lengthy toxicological animal studies including trans-generational experiments. Phase I human trials might also face hurdles because of difficulties in testing pregnant women where toxicological studies are usually contraindicated. Lifelong follow up of the mother and fetus is advocated in the context of prenatal gene transfer.

A hypothetical treatment

Assuming that a safe and effective placental gene therapy approach was to be possible, how might it work in practice for treatment of FGR? Uteroplacental insufficiency can be suspected in the first trimester of pregnancy but more commonly is picked up at the anomaly scan that is commonly performed at 20 -22 weeks of gestation. Other causes of FGR would need to be sought and excluded, and the diagnosis of uteroplacental insufficiency confirmed two weeks later. After the

intervention, sonography could be used to monitor fetal wellbeing and growth according to usual fetal medicine practices. There remain the options of terminating the pregnancy or awaiting fetal demise should the placental gene therapy fail.

Practice Points

- Delivering genes to the placenta may be useful for correction of obstetric conditions such as severe fetal growth restriction or pre-eclampsia that affect the uteroplacental circulation.
- The patient in the placental gene therapy scenario is the fetus.
- Placental gene therapy might be justifiable when there is reasonable certainty that the fetus will suffer irreversible and substantial harm without the intervention
- The intervention will need to be safe and effective, with negligible risk to the health of the mother and where the mother can give informed consent.

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