Maternal gene therapy for placental insufficiency

Anna David

Reader and Consultant in Maternal and Fetal Medicine

Rebecca Spencer

Clinical Research Fellow in Maternal and Fetal Medicine
rebecca.spencer@ucl.ac.uk

Institute for Women's Health, University College London

Developing therapies for diseases of pregnancy is an important but challenging task. Despite maternal and perinatal conditions making up 7% of the global burden of disease, there are few or no evidence-based treatments for diseases of pregnancy such as fetal growth restriction, pre-eclampsia and preterm labour.[1] There is also a 'drought' of new therapies in development. This is partly as a result of industry underinvestment but also because there are many ethical and regulatory barriers to carrying out clinical trials in pregnant women.[2]

The EVERREST project is a multinational and multidisciplinary collaboration that aims to carry out the first trial of maternal growth factor gene therapy in pregnancies affected by placental insufficiency, a common cause of fetal growth restriction.[3] An important first step in the project was to explore the ethical and social acceptability of the proposed trial, as this would be the first use of gene therapy in pregnancy.

Placental insufficiency and fetal growth restriction

During pregnancy placental villous development and normal placental circulation are key to delivering oxygen and nutrients from the mother to the growing fetus. In placental insufficiency there is poor placental development and insufficient maternal blood supply to the uterus. This leads to restricted growth of the fetus, where the estimated fetal weight (EFW) is less than expected and commonly small for gestational age (SGA, EFW <10th centile). In placental insufficiency there may also be Doppler ultrasound changes in the uterine and umbilical arteries.

In normal pregnancy the vascular resistance in the uterine arteries falls, increasing the flow of the mother's blood to the womb. In placental insufficiency the resistance in the uterine arteries remains high, with a pre-diastolic 'notch' in the flow pattern. There may also be high resistance to blood flow in the umbilical arteries, described as an increased pulsatility index, reflecting a problem with the circulation of fetal blood through the placenta. At its most severe there can be absent, and even reversed, end-diastolic flow in the umbilical arteries.

There is currently no treatment for placental insufficiency. When it develops in mid-pregnancy the parents and healthcare professionals face a constantly changing balance of risks and benefits when deciding whether to continue monitoring a pregnancy, with the risks of stillbirth and neuro-developmental impairment from chronic *in utero* hypoxia, or to deliver a baby preterm, with all of the complications that may ensue.[4]

Developing a maternal therapy

One potential strategy to treat placental insufficiency is to increase the flow of blood through the mother's uterine arteries that supply the maternal side of the placenta. This is the approach taken by the EVERREST project. Vascular endothelial growth factor (VEGF) is important for the development of the placenta and its circulation, and reduced VEGF availability is implicated in the pathogenesis of placental insufficiency.[5] Therapeutic manipulation of VEGF and other angiogenic factors is now being studied as a method to improve fetal growth in placental insufficiency. Gene therapy results in local and short-term increases in the levels of growth factors such as VEGF, and has been safely used in other vascular beds such as the coronary artery circulation.[6] In pre-clinical studies VEGF gene therapy increases uterine artery blood flow in the short- and medium-term,[7,8] and it safely improves fetal growth in animal models of placental insufficiency.[9,10] The EVERREST project proposes to give VEGF gene therapy directly into the uterine arteries of pregnant women with early onset and severe fetal growth restriction due to placental insufficiency, using interventional radiology.

What do women and caregivers think?

As part of the EVERREST project we undertook a literature review exploring the ethics of experimental medicine research in pregnant women, particularly in relation to the use of maternal gene therapy. The findings of this review were used as the basis for semi-structured qualitative interviews with 21 women who had had a previous pregnancy affected by early onset severe fetal growth restriction due to placental insufficiency.[11] Similar interviews were performed with 34 stakeholders from national and international medical, midwifery, disability, and parental support organisations. Because of the multinational nature of the EVERREST project women and stakeholders were interviewed from Germany, Spain, Sweden and the UK.

Overall the interview studies found no fundamental or insurmountable objections to a

clinical trial of maternal gene therapy for placental insufficiency. Most respondents viewed the clinical trial in positive terms. Issues relating to informed consent were key considerations for many of the respondents; both women and stakeholders highlighted the importance of having sufficient information, support and time in which to make a decision to take part. All of the women felt that they would have been capable of freely deciding whether or not to participate, with most of the women saying that they would have wanted to participate in such a trial.

The literature review raised the issue of whether it was ethically acceptable to give an intervention which might lead to a baby surviving with severe disabilities when otherwise it would have died *in utero*. Over half of the women interviewed felt that this was acceptable, as long as the disability was not due to a complication of the trial intervention. However, a minority of women did not feel that this was acceptable, because of the long-term impact on the child and family. While most respondents were not concerned about the use of maternal gene therapy, one of the German stakeholders felt that this would be unacceptable in Germany. Interestingly this opinion was not shared by the German women interviewed.

There are still many regulatory challenges before a trial of maternal gene therapy for placental insufficiency can take place. Among these will be demonstrating an acceptable safety profile based on reproductive toxicology studies that are currently being completed. Data from previous human trials of VEGF gene therapy in cardiovascular and peripheral vascular disease show good long-term safety, and our pre-clinical studies demonstrate no fetal vector transfer. The attitudes of the women and stakeholders that were interviewed support the continuation of the EVERREST project. The views expressed by the women in our study echo the findings of other qualitative studies exploring women's experiences of obstetric research, and support the development of maternal and fetal therapies in general.

To find out more about the EVERREST project visit www.everrest-fp7.eu

Funding

Magnus Growth, a Magnus Life Science programme, is part of the EVERREST Consortium working to support the ongoing translation of maternal growth factor gene therapy. The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007–2013) under grant agreement no. 305823.

References

1. **World Health Organization.** *The Global Burden of Disease: 2004 Update.* [Online] 2008. Available from: www.who.int/healthinfo/global_burden_disease/2004_report_update/en/ [accessed 27 April 2016].
2. **David A., Thornton S., Sutcliffe A., Williams P.** *Scientific Impact Paper No. 50. Developing New Pharmaceutical Treatments for Obstetric Conditions.* London: RCOG; 2015.
3. **EVERREST Consortium.** *EVERREST: Maternal Growth Factor Therapy to Improve Fetal Growth.* [Online]. Available from: www.everrest-fp7.eu [accessed 27 April 2016].
4. **Lees C., Marlow N., Arabin B. et al.** Perinatal morbidity and mortality in early-onset fetal growth restriction: cohort outcomes of the trial of randomized umbilical and fetal flow in Europe (TRUFFLE). *Ultrasound Obstet Gynecol* 2013;42:400-08.
5. **Andraweera P.H., Dekker G.A., Roberts CT.** The vascular endothelial growth factor family in adverse pregnancy outcomes. *Hum Reprod Update* 2012;18:436-57.
6. **Hedman M., Muona K., Hedman A. et al.** Eight-year safety follow-up of coronary artery disease patients after local intracoronary VEGF gene transfer. *Gene Ther* 2009;16:629-34.
7. **David A.L., Torondel B., Zachary I. et al.** Local delivery of VEGF adenovirus to the uterine artery increases vasorelaxation and uterine blood flow in the pregnant sheep. *Gene Ther* 2008;15:1344-50.
8. **Mehta V., Abi-Nader K.N., Peebles D.M. et al.** Long-term increase in uterine blood flow is achieved by local overexpression of VEGF-A(165) in the uterine arteries of pregnant sheep. *Gene Ther* 2012;19:925-35.
9. **Carr D., Wallace J.M., Aitken R.P. et al.** Uteroplacental adenovirus VEGF gene therapy increases fetal growth velocity in growth-restricted sheep pregnancies. *Hum Gene Ther* 2014;25:375-84.
10. **Swanson A., Rossi C., Ofir K. et al.** Maternal uterine artery gene therapy with AdVEGF-A165 increases weight at term in a guinea pig model of fetal growth restriction. *Hum Gene Ther* 2015;26:A14.
11. **Sheppard M., Spencer R.N., Ashcroft R. et al.** Ethics and social acceptability of a proposed clinical trial using maternal gene therapy to treat severe early-onset fetal growth restriction. *Ultrasound Obstet Gynecol* 2016;47:484-91.