Medical Xpress

Male fetal hormone could influence the making of woman as well as man

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Scientists at The University of Nottingham have shown, for the first time, that a naturally occurring hormone which plays a major role in the development of the male fetus can, in the early stages of pregnancy, transfer into a 'neighbouring' fetus and potentially influence the development of female as well as male twins.

Research led by Associate Professor Ravinder Anand-Ivell and Professor Richard Ivell in the School of Biosciences and published on Thursday March 31 2016, in the academic journal *PLOS ONE*, indicates a major breakthrough in our understanding of the male specific hormone INSL3. Secreted by the male fetus in the very early stages of pregnancy this research shows, for the first time for any species, that INSL3 can cross directly to a neighbouring fetus where it has the potential to impact on its development both during the fetal phase as well as in later postnatal and adult life.

Associate Professor Anand-Ivell said: "Until now there has been a general acceptance of the idea that the fetus is quite well sealed off from other influences inside the womb. What our paper shows is that this is far from true: a hormone can and does move from one fetus to another and potentially also to the placenta and to the mother. If we can understand more about the mechanisms of INSL3 we might also be able to translate these findings to the situation in human pregnancy and look at the probable effects of this especially on a female sibling when there are non-identical twins."

INSL3 is the only known absolutely gender-specific hormone. It is secreted by the male fetus during the very early stages of pregnancy. It is part of the primary sex determination cascade, where the Y chromosome first impacts on the fetus which until that stage is relatively sexually indeterminate.

It is made by the male fetus and, as far as we know, not at all by the female fetus and only to a negligible extent by the pregnant mother, so it can act as a natural biomarker of a major fetal process – the development of maleness - in what is otherwise a very inaccessible period of pregnancy.

Leading the way in an area of non-mainstream research

There are several groups around the world looking at INSL3. But Associate Professor Anand-Ivell and Professor Ivell's breakthrough comes as a result of the very sensitive assays they developed early on in their research to measure INSL3 in humans and different model species. Professor Ivell said: "This has certainly given us an edge. But one can see, examining the literature, that the field is growing exponentially, and we indeed have stiff competition particularly now from Asia."

Associate Professor Anand-Ivell has been invited to present her latest findings at the US Endocrine Society annual conference in Boston on Sunday April 3. The Society was established 100 years ago to celebrate the work of endocrinologists and to bridge the gap between innovative research and exceptional clinical care. ENDO2016 is one of the largest and most important international hormone conferences attended by many hundreds of international delegates.

'Maleness' could also influence 'femaleness'

The research, jointly funded by The University of Nottingham and the Leibniz Institute for Farm Animal Biology in Germany, was carried out using pigs as a model so that the scientists could study several male and female fetuses in a single pregnancy and clearly show the transfer of INSL3 from one fetus to another.

Associate Professor Anand-Ivell said: "In the male fetus testosterone is important, but what INSL3 does is to promote some of the other features of maleness, such as promoting the testes to move into the scrotum. It may do other things as well but we still know too little about this stage of pregnancy. Similarly, we still know far too little about how these hormones may act in a female fetus."

INSL3 is the first peptide hormone from any species to have such a clear biomarker property. Other hormones, such as testosterone, are less suitable, because they are also made in substantial amounts by female foetuses.

This research has a lot of relevance to human pregnancy and to pregnancy of all mammals. It shows that not just fat-soluble hormones like testosterone, but potentially many other types of hormone can and do move from one foetus to another and potentially to the mother during pregnancy.

The discovery is the result of 15 years of research

Professor Ivell and Associate Professor Anand-Ivell began looking at INSL3 as a hormone produced by the testes of adult men and animals more than 15 years ago. They showed that it is extremely useful as a biomarker for pubertal development as well as for aging in men and much of the more negative symptoms of old age in men have their origins in a decline in testis function.

Just how this happens is another theme they are currently working on. They have also shown that INSL3 is made in small amounts in the ovaries of women of reproductive age. Here it plays a crucial role in the ability of the follicles containing the egg cells to make steroid hormones, particularly androgens and consequently it is also associated with female fertility.

Professor Ivell added: "Behind all this is an evolutionary aspect which we find rather exciting. INSL3 and a small group of related hormones, which we now term 'neohormones', have evolved mostly during the relatively recent emergence of mammals from other vertebrates and have functions specifically linked to those uniquely mammalian traits such as having internal fertilization, breast-feeding, maternal behaviour etc. So far, all pharmacological developments relating to fertility and contraception have been targeting the ancient hormone systems, such as the gonadotropins or steroid hormones, which have been around since the beginning of time. We think that maybe by targeting these 'neohormone' systems we may be better and more specifically able to target special mammalian aspects of reproductive physiology."

More information: Andreas Vernunft et al. The Male Fetal Biomarker INSL3 Reveals Substantial Hormone Exchange between Fetuses in Early Pig Gestation, *PLOS ONE* (2016). DOI: 10.1371/journal.pone.0152689

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