PRESS RELEASE

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Supplemental prenatal progesterone reprogrammes gene linked to brain development in males

Excessive exposure to progesterone in the womb can alter a gene in the frontal cortex in male sheep fetuses, which is needed for brain development and function, according to research presented at the 28th European Congress of Endocrinology in Prague. The finding highlights the important role hormones play in fetal development in different sexes and potentially in the predisposition to adult disease.

Progesterone – a steroid hormone that supports and maintains pregnancy, and regulates the menstrual cycle – is commonly prescribed during early pregnancy, particularly for women at an increased risk of miscarriage or during assisted reproduction. While progesterone is widely used and considered safe in the short term, not much is known about its longer-term effects on fetal development and function.

Researchers from Edinburgh Napier University, the University of Edinburgh and Aberdeen University have previously shown that increased prenatal exposure to progesterone can raise progesterone levels in male sheep fetuses and alter their pituitary and testis function, as well as their steroid profile. Now, in this study, the researchers injected pregnant ewes with 200 mg of progesterone, twice a week, from day 20 to 75 (equivalent to 15 weeks of pregnancy in humans) and found that, in male fetuses, progesterone exposure was linked to an increased accumulation of a gene called SRD5A1 in the frontal cortex – a gene whose encoded product is involved in processing sex hormones that are crucial for brain development and function. While no changes were detected in key hormone receptors or related enzymes in either sex, alterations were observed in several important biological pathways in male fetuses, such as calcium signalling.

“Our findings suggest that male and female sheep fetuses may respond differently to maternal progesterone treatment, with some effects observed only in males. As we see effects on the gene level, however, we do not know if these have any consequences – either positive or negative – on normal development, health and behaviour after birth and as the offspring age,” said lead author, Dr Katarzyna Siemienowicz of Edinburgh Napier University, UK.

She added: “Though sheep are highly valuable animal models in research due to their human-like size, organ dimensions and long lifespans, this is still an early-stage study in an animal model and further research is needed to understand whether these findings are relevant to humans.”

The researchers are now planning to investigate the precise mechanisms by which progesterone may alter brain development and whether these changes have any lasting effects later in life. “Given that the developing brain is responsive to progesterone, this exposure may influence neural development but again the fetal brain is highly plastic and changes observed during fetal life may not persist postnatally. Thus, we aim to better understand how progesterone and related hormones affect the developing brain , including measuring hormone levels directly in brain tissue,” said Dr Siemienowicz.

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Abstract
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Early pregnancy maternal progesterone supplementation alters fetal frontal cortex gene expression in male fetuses

Prenatal fetal exposure to steroids is a 'Goldilocks phenomenon', where too much or too little hormone is detrimental. Progesterone is critical to support and maintain pregnancy. Maternal progesterone supplementation is commonly used during assisted reproduction and as a treatment for increased risk of miscarriage, up to 16 weeks' gestation. Progesterone and its metabolites are neuroactive steroids necessary for brain development. Effects of increased prenatal exposure to progesterone on fetal brain development are poorly understood. We previously reported that maternal progesterone administration increased male, but not female, fetal progesterone concentrations and disturbed normal hypothalamic-pituitary function in d75 sheep male fetuses (equivalent to 15 weeks of human gestation). We hypothesised that maternal progesterone supplementation in early pregnancy would alter gene expression in the fetal male frontal cortex.

Pregnant ewes received either 200 mg of intramuscular progesterone (P) or vehicle (C) twice weekly from day 20 until sacrifice at day 75 of gestation. These doses and timings were clinically realistic. Fetal frontal cortex was collected from males (C=10; P=7), RNA extracted, and gene expression measured by RNA sequencing (RNAseq) and qPCR. Data was further contextualised using Ingenuity Pathway Analysis (IPA).

There was no difference in the expression of genes encoding steroid receptors (AR, ESR1, ESR2 and PGR) and steroid metabolising enzymes (CYP17, HSD17B, CYP19 and AKR1C2), except for increased expression of SRD5A1 ($P<0.05$), an enzyme that metabolises progesterone to 5α-dihydroprogesterone and testosterone to dihydrotestosterone, in the fetal male frontal cortex from progesterone-treated pregnancies. RNAseq revealed that there were 437 nominally differentially expressed genes (DEGs) in response to progesterone supplementation. IPA analysis indicated dysregulations of numerous pathways ($P<0.05$, absolute Z score>2), including increased iron uptake and transport, cyclophilin signalling pathway, and decreased CREB and reelin signalling in neurons, calcium signalling, FAK signalling and G-protein coupled signalling, all with potential impact on brain development.

Progesterone is known to cross the placental barrier, entering the fetal circulation, reaching the developing brain and regulating key events in neural development. Progesterone may also be metabolised to different steroid classes locally within the developing brain. There is evidence in humans for increased fetal steroidogenic activity in autism, with oestradiol, oestrone and progesterone showing the largest effects on autism likelihood. Identified pathways and individual DEGs have links to neurological disorders and cognitive impairment. Whilst we cannot predict long-term consequences of these temporal gene expression shifts during fetal life, we demonstrated perturbed gene expression during development that warrants further investigation.

Notes for Editors:

1. For press enquiries, or to arrange an interview with the study authors, please contact the ECE 2026 Press Office:

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   Mob: +44 (0) 777 2264482
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2. The study **'Early pregnancy maternal progesterone supplementation alters fetal frontal cortex gene expression in male fetuses'** will be presented on **Sunday 10 May 2026, 15:25 - 15:35 CEST,** at the European Congress of Endocrinology at the Prague Congress Centre (PCC) in the Czech Republic.

3. The 28th European Congress of Endocrinology (ECE) is held at the Prague Congress Centre (PCC) in the Czech Republic, on 9-12 May 2026. See the full scientific programme here.

4. The European Society of Endocrinology (ESE) provides a platform to develop and share leading research and best knowledge in endocrine science and medicine. By uniting and representing every part of the endocrine community, ESE works to improve the lives of patients. Through the 50 National Societies involved with the ESE Council of Affiliated Societies (ECAS) and partnership with specialist endocrine societies, ESE and its partners jointly represent a community of over 20,000 European endocrinologists. ESE informs policymakers on health decisions at the highest level through advocacy efforts across Europe.