

Project Details	
Project Code	MRC21NMHCa John
Title	To treat or not to treat: investigating the impact of antidepressant use in pregnancy.
Research Theme	Neuroscience & Mental Health
Summary	In the UK ~8% of women are prescribed antidepressants to reduce symptoms of depression in pregnancy. This project will ask whether antidepressants restore normal mood in a novel preclinical model of prenatal depression, and apply comparative bioinformatics to human placenta to examine the risks and benefits of taking antidepressants in pregnancy.
Description	<p>Project Depression and/or anxiety during pregnancy pose a significant health problem due to the impact on the mother and the host of negative outcomes including emotional and behavioural problems in children. Selective serotonin reuptake inhibitors (SSRIs) are prescribed to 8% of pregnant women in UK to reduce mood symptoms. However, SSRIs cross the placenta and may impact fetal brain development also leading to adverse outcomes. This project will combine the behavioural assessment of an animal model of prenatal depression with a comparative molecular and epigenetic study of experimental and human placenta to gain a greater understanding of the risks and benefits of treating or not treating maternal mood disorders during pregnancy. Our unique preclinical model reproduces the low levels of placental lactogen driven by abnormal expression of an imprinted gene that we have observed in human pregnancies impacted by prenatal depression and anxiety. Low placental lactogen may result in females failing to undergo the normal brain changes required for them to adopt maternal behaviour causing mood symptoms. We hypothesise that SSRIs function, at least in part, by increasing local levels of pituitary prolactin compensating for low placental lactogen. To assess the benefits of SSRI and test this original hypothesis, classic behavioural assays will be used to determine the effectiveness of SSRIs in restoring normal behaviour in our experimental model, and transcriptomics and proteomics will be used to examine hypothalamic hormone transduction pathways. To assess the risk of SSRIs to offspring, a comparative study of experimental samples and human placenta exposed to SSRIs from our unique Grown in Wales Study will be performed. The placenta is a fetally derived tissue that can be readily obtained from human pregnancies providing an exceptional tool to study the impact of drugs in pregnancy. Both classic histology and the novel, cutting-edge technique of RNAscope will be applied to determine the impact of SSRI exposure on placental development. SSRI-driven gene alterations in the placenta will be identified by comparative RNA sequencing of experimental and human placental samples exposed to SSRI. Finally, the expression status and epigenetic profile of these identified genes will be examined in the fetal brain from the experimental model to seek evidence of more widespread aberrant gene expression, with potential to contribute to neurodevelopmental dysfunction. Training The use of both experimental models (in vivo training) and human cohort samples (translation potential) is a particular strength of this study which provides training across a broad range of interdisciplinary skills</p>

	<p>(developmental biology, behavioural neuroscience, bioinformatics, population-based statistics). The student will gain wet lab and dry labs skills which can be reorganised to take into account events such as the recent Covid-19 outbreak. Work will take place across two GW4 institutions for a direct exchange of knowledge and techniques with 3 month training with Dr Sarah Bailey developing the SSRI model. Comparative bioinformatic analysis will be supported by Dr Araxi Urrutia, a current collaborator. Prof John collaborates with social scientists and epidemiologists at Bristol University on the Grown in Wales Study, providing additional cross-disciplinary exposure. Maximising impact Presentations will be made at national and international meetings (ex IFPA, British Psychological Society, MARCE society). The student will contribute to a review and at least one first author paper, but likely several. All published papers will accompanied by media and Twitter announcements (@Preg_lab). The student will contribute to Student Midwife Workshops and our annual public engagement activity at Museum of Wales to ensure the wider academic, clinical and public impact of their work.</p>
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