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Title: Third-Trimester Fetal Sleep-Wake States predict Neonate Behavioural State Regulation following Prenatal SSRI Antidepressant Exposure

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Background: Prenatal exposure to selective serotonin reuptake inhibitor (SSRI) antidepressants alter infant and child outcome. SSRIs cross the placenta and enter the fetal brain where serotonin neurons/receptors are present from early gestation. In the 3rd trimester fetus, emergence of stable sleep-wake states reflect maturing neuronal integration. Previously, SSRIs were associated with disrupted emergence of Quiet Sleep (QS). However, acute SSRI exposure reduced Active Sleep (AS) in fetal sheep. Acute and chronic SSRI effects have yet to be distinguished, and the significance for postnatal development remains unclear.

Objective: This study investigated pre- and post-dose effects of maternal SSRIs on 3rd trimester fetal sleep-wake states, and determined if these effects predict neonate behavioural state regulation.

Methods: Three groups were assessed longitudinally: SSRI-exposed (n=40), unmedicated/depressed (n=33), and healthy control (n=33). At 36-weeks’ gestation, fetal actocardiograph was recorded over two sessions designed to assess pre- and post-SSRI dose effects. Patterns of fetal HR and movement were coded to yield proportions of time spent in QS, AS, and wakefulness. Linear mixed-effects modeling was used to test group differences in displayed states, distinguishing pre/post-dose effects. On postnatal day-6, neonates underwent the Neurobehavioural Assessment of the Preterm Infant (NAPI). Behavioural state was rated throughout the NAPI. Latent class mixed modeling was used to identify trajectories in behavioural response. Fetal sleep state for each group was then used to predict neonate latent class membership with logistic regression.
**Results:** SSRI-exposed fetuses spent less time in QS (p=0.002) and more time in AS (p=0.002), with a larger effect size pre-SSRI dose. Fetuses of unmedicated/depressed mothers also spent less time in QS (p=0.034) and more time in AS (p=0.012). Behavioural state during the NAPI was best modeled with two latent trajectories: increasing reactivity; low reactivity. Time in fetal QS for SSRI-exposed neonates predicted an increased probability of being in the ‘increasing reactivity’ trajectory (p=0.029).

**Conclusions:** Prenatal SSRI exposure reduced fetal QS time, with a proportional increase in AS. Differences were larger pre-dose, suggesting a corrective effect of daily SSRI on displayed states. This disrupted emergence of QS may point to impaired fetal regulation of sleep-wake cycles, with effects that extend postnatally as increased neurobehavioural reactivity. Future work will investigate these findings with *in vivo* brain outcomes and further address effects of maternal mood.