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EDITORIAL

# A closer look at the fetal programming hypothesis with obstetric ultrasound☆,☆☆

## Uma análise mais profunda da hipótese de programação fetal com ultrassom obstétrico

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Most, if not all, pregnant women in developed countries will have an ultrasound examination to time pregnancy and assess the health and development of the embryo or fetus. Nonetheless, surprisingly few cohort studies have used routine health care or research ultrasound data to test their hypotheses. Repeated ultrasound assessments during pregnancy offer the opportunity to examine the association of intra-uterine exposures with fetal growth and the association of fetal growth patterns with child outcomes. Most studies of fetal programming simply rely on a proxy measurement of fetal growth: maternal or midwife report of birth weight. Birth outcomes are only crude summary measures of fetal growth and cannot provide information on growth across different times in pregnancy. Furthermore, individuals may reach the same birth weight through different fetal growth trajectories. Pinto et al. are to be complimented for the use standardized clinical ultrasound conducted by one clinician to test an important public health question: do children of anxious or depressed mothers have a worse start to life even before they are born?[1]

Depression and anxiety during pregnancy have been associated with numerous poor child outcomes, but several important questions remain: how much of the observed association between maternal psychiatric problems and child development is due to confounding by lifestyle or background factors such as socio-economic status; how much is due to genetic effects on maternal psychopathology and child development; is the prenatal development particularly vulnerable to depression or anxiety in specific periods; and can the effects of anxiety or depression be differentiated?

In the past years, we have witnessed several approaches to address the causality of intra-uterine exposure associations; some of these cast doubt on the fetal programming hypothesis. Sibling designs suggest that many potential side-effects of antidepressant drug use during pregnancy probably reflect background risks.[2] Comparative tests of the associations of paternal and maternal exposure during pregnancy suggest that the association of maternal depression with ADHD can best be explained by confounding factors, as paternal depression was similarly associated with this outcome.[3] Sometimes, genetic variants related to an exposure can help identify whether an association of an intrauterine exposure with a child outcome is causal. However, such a Mendelian randomization approach is tricky, as pregnancy constitutes a short exposure period to maternal genes. Nonetheless, this approach provided initial evidence that even very moderate alcohol consumption during pregnancy has negative effects on child development.[4] Others

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have used frequently repeated measures of depression to identify a time during pregnancy when the offspring is particularly vulnerable – but results suggest that the vulnerability does not vary.[5] Pinto et al. address another question important to our causal understanding[1]: are the observed associations of depression and anxiety specific? Their results are in line with observations from the work of our and other groups, that anxiety during pregnancy typically has much stronger effects on child development than depression.[6] Interestingly, pregnancy-specific anxiety has been increasingly recognized as an important risk factor for neurodevelopmental outcomes. In contrast, the observed associations attributed to depressive symptoms are often better explained by confounders, comorbid anxiety symptoms, or postnatal depression. Moreover, as Pinto et al. rightly emphasize, it matters how symptoms are measured, as traits, as states, and if the same or specific instruments are used.[1]

Finally, I would like to point out that the effect size of the observed association between anxiety during pregnancy and fetal weight gain in the present study is improbable. A child born to an anxious mother in the Centro Hospitalar do Porto was more than 800 g lighter at birth than a child of a non-anxious mother.[1] Even given the wide confidence interval, this effect size is not realistic. The authors discussed selection bias – a possible explanation, but I am convinced that this effect size is more likely to reflect a chance finding or a confounding factor. Henrichs et al., in a much larger, very well controlled study in the Netherlands using repeated obstetric ultrasound assessments, observed that mothers with significant symptoms of anxiety during pregnancy had fetuses who grew at a rate that was 3.2 g/week lower.[7] This study from my group was embedded in the Generation R Study (''R'' stands for Rotterdam), a large longitudinal, population-based cohort following more than 8000 children from fetal life onwards. There have been multiple time points of data collection on that cohort, with data at age 10 years most recently completed. The repeated fetal ultrasounds, combined with detailed pregnancy questionnaires, offered Generation R researchers the most unique opportunities. Moreover, for many mothers the ultrasound assessments were the reasons to participate in the cohort in the first place; in the early 2000s, routine obstetric ultrasound was not a part of the regular healthcare system, nor was it reimbursed by the insurers. The Generation R researchers studied trajectories of fetal head growth to test whether maternal exposures during pregnancy had an impact on early neurodevelopment. Not only maternal depression and anxiety, but also smoking during pregnancy, maternal serotonin-specific reuptake inhibitor (SSRI) use, lack of folic acid supplementation, and cannabis exposure all negatively affected fetal head growth.[8] Furthermore, this data was used to address the association between intrauterine growth trajectories and child development, adopting similar statistical techniques as Pinto et al. We found support for a relation of intrauterine head growth with observed motor development, but not with behavioral or emotional problems of infants and preschool children.[9] However, more studies addressing the important question of if and how anxiety and depression of the mother during pregnancy affect the offspring are necessary. The study by Pinto et al. is a wonderful reminder that obstetric ultrasound is a tool underutilized by researchers to help answer these questions ''very relevant to public health''.

## Conflicts of interest

The author declares no conflicts of interest.

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