VIEWPOINT

Aspirin for the Prevention of Preeclampsia and Potential Consequences for Fetal Brain Development

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Preeclampsia is a major cause of morbidity and mortality for both mother and fetus. With respect to neurodevelopment, preeclampsia has been associated with autism spectrum disorders and developmental delay.[1] Currently, professional bodies such as the American College of Obstetricians and Gynecologists (ACOG) in the United States and the National Institute for Health and Care Excellence (NICE) in the United Kingdom suggest the prophylactic administration of aspirin to pregnant women considered at high risk for preeclampsia based on maternal characteristics and medical history to reduce preeclampsia and improve both maternal and neonatal outcomes. Nevertheless, relevant studies on the prevention of preeclampsia have produced conflicting results.

The recent systematic review and meta-analysis by Roberge and colleagues[2] concluded that aspirin administration starting at or below 16 weeks of gestation at a dose of 100 mg/day or more reduces the risk of preterm preeclampsia by approximately 70%. Therefore, such a significant decrease in the incidence of preterm preeclampsia should positively affect neonatal outcomes. Moreover, the authors[2] proposed treatment of women identified as high risk by additional screening tools such as recently proposed biophysical and biochemical markers. Use of such markers will ensure inclusion and treatment of a higher percentage of women who will eventually experience preterm preeclampsia, compared with the methods advocated by ACOG and NICE.[2] Inevitably, such screening methods have low specificity and lead to a relatively high percent of false-positive results because less than 5% of women considered at high risk will actually develop preterm preeclampsia. Collectively, suggestions by Roberge and colleagues[2] will probably increase the number of pregnant women who are treated with aspirin, as well as dosage, and prolong treatment duration with respect to current recommendations by professional bodies. It is worth underlining that only perinatal adverse effects have been studied and reported in relevant publications.[2]

Aspirin is a potent inhibitor and modifier of cyclooxygenase (COX) 1 and COX2, the rate-limiting enzymes for prostanoids synthesis, including prostaglandin-E_2 (PGE_2). Aspirin administered during pregnancy is transferred across the placenta to the fetus and the developing fetal brain. Notably, the drug-eliminating pathways of the fetus (both metabolic and excretory) are immature and may intensify the concentration of aspirin and therefore the potential consequences of aspirin administration.

What are some of the recent findings on the COX2/PGE_2 pathway? Innovative experimental animal work[3] has suggested that neuronal and microglia-derived PGE_2 is a key effector of sexual differentiation of the brain, a process starting in the early-stage embryo and ending postnatally. As per the consequences of COX2/PGE_2 disruption, postnatal subcutaneous injection of the COX inhibitor indomethacin permanently and severely impairs male sexual behavior in adulthood. Importantly, aspirin in the drinking water of pregnant dams is associated with long-lasting (nevertheless, not permanent) outcomes regarding adult male-typical sex behavior in offspring. The "masculinizing" results of PGE_2 proves powerful because females treated intracerebroventricularly show sexual behavior identical to males as adults.[3] In a wider view, it has become evident that PGE_2 is one of the microenvironmental factors that drive the phenotype and the regional differences of microglia. The latter have recently emerged from their conventional innate immune cell role and are currently viewed as key regulators of brain development.[4]

Genetic and environmental abnormalities in components of the COX/PGE_2 pathway have also been implicated in clinical studies on autism spectrum disorders.[5] Additionally, it has been recently shown that COX2-deficient mice exhibit prominent autism-related behaviors and notable alterations in the expression of autism-linked genes.[5] Moreover, evidence supports an interaction between the PGE_2 and the Wnt signalling pathways, which are crucial regulators during brain development and also linked to autism.[6]

The conclusions of the recent meta-analysis by Roberge and colleagues[2] will probably lead to changes of current policy for the prevention of preeclampsia to the direction of increased and prolong maternal and fetal exposure to aspirin. Based on experimental data establishing the significant role of the COX2/PGE_2 pathway in brain development, we suggest that researchers promptly assess long-term potential outcomes of aspirin administered during pregnancy on the neurodevelopment and behavior of offspring. Families that have participated in excellent randomized clinical trials on the prophylactic use of aspirin over the last decades may be used as the study cohort.

By decreasing the incidence of preterm preeclampsia, we reduce the likelihood of complications in both mother and child. Nevertheless, we need to assess whether animal data regarding the impact of COX2/PGE_2 disruption apply to humans and ensure that potential actions of aspirin on the developing fetal brain do not lead to long-term impairments that supersede the benefits of its use.

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