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Reducing the risks of prenatal opioid exposure in children

Exposure to low doses for short periods outside the first trimester appears not associated with adverse neurodevelopmental outcomes

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According to 2019 data from the Centers for Disease Control and Prevention, approximately 7% of women in the United States were prescribed opioids during pregnancy.[1] Prescription opioid use among pregnant women with private insurance or Medicaid coverage in the US is prevalent.[2 3] In particular, the incidence of neonatal abstinence syndrome, as a result of drug withdrawal, increased by 83% from 2010 to 2017, albeit while declining by 18% between 2016 and 2020.[4 5] However, the risk of neurodevelopmental disorders in children with prenatal opioid exposure remains unclear because previous studies had small sample sizes and limited follow-up periods.[6 7] The linked study by Kang and colleagues (doi:10.1136/bmj-2023-077664) addressed this research gap using data from the National Health Insurance Service of South Korea.[8] Their study cohort included 3 128 571 children and 2 299 664 mothers, further categorised into subgroups according to prescription opioid dose, duration, and exposure periods as well as the frequency of prescriptions. The authors adjusted for many confounding factors, conducted stratification analyses, examined dose responses, and performed interaction analyses between opioid use and corresponding medical indications.

Kang and colleagues identified a small increased risk of neuropsychiatric disorders among children with prenatal exposure to prescription opioids during any trimester of pregnancy, compared with infants not exposed to opioids (hazard ratio 1.06 (95% confidence interval 1.04 to 1.09)), which they interpreted as clinically insignificant. However, longer durations, more prescription days, and higher doses of prenatal opioid exposure were associated with higher risk of neuropsychiatric disorders. Additionally, the increased risk of neuropsychiatric disorders was confined to prescription opioid exposure in the first trimester. This South Korean study benefits from a large sample size, an extensive follow-up period (an average follow-up period of approximately six years in the 1:5 propensity score matched cohort), and informative data to facilitate subgroup analyses.

Previous studies have also suggested an increased risk of neurodevelopmental disorders among children exposed to higher dosages of opioids and for longer durations during the prenatal period.[6 7 9] Kang and colleagues' study provides additional evidence to inform clinical decision making for pregnant women requiring pain management. While prenatal exposure to low doses of opioids for short periods outside of the first trimester was not found to be associated with an increased risk of neurodevelopmental disorders, caution is warranted when prescribing opioids for longer durations or at higher dosages.

The opioid epidemic remains a public health crisis globally, particularly in the US and Canada. Numerous national and state level initiatives have been used in the US to curb both illicit use and overprescribing of opioids. Key strategies included the establishment of statewide prescription drug monitoring programme and modifying the federal controlled substance scheduling of hydrocodone containing products to a more restrictive classification.[10 11] Guidelines by the American College of Obstetricians and Gynecologists recommend the use of alternative non-opioid pain management strategies to avoid or minimise opioid use in pregnancy.[12] When opioids are necessary for treating acute pain, the guidelines advise using the lowest effective dose and duration.[13]

Strict adherence to and enforcement of these guidelines would likely reduce unnecessary opioid related risks to women and children. However, 25% of pregnant women who received opioids had a prescription for more than seven days, and 10% received a supply of opioids lasting longer than 30 days.[14] Such findings suggest that increased efforts are needed to ensure that opioids are only prescribed for pregnant women when absolutely necessary, and that minimal effective doses are prescribed for the shortest duration necessary to manage severity of pain, especially in the first trimester.[15 16]

Another notable aspect of Kang and colleagues' study, from a methodological standpoint, was their assessment of the interaction between prescription opioid use and the medical indications associated with prescribing opioids. Results of the interaction analysis demonstrated that opioid use for pain was significantly associated with development of neuropsychiatric outcomes. This finding suggests that rather than opioid exposure, pain and underlying diseases causing pain cannot be dismissed as risk factors for increased likelihood of neuropsychiatric disorders among children. Uncontrolled or poorly managed pain during pregnancy may result in maternal stress, depression, and hypertension, thereby leading to adverse pregnancy and neonatal outcomes.[17 18]

Additionally, the consideration of ethnic group and pharmacogenomic differences among patients is crucial when prescribing opioids to diverse populations. Cytochrome P450 2D6 enzyme genetic polymorphisms affect the metabolism of many opioids, including codeine and tramadol.[19] Notably, up to 10% of white individuals lack this enzyme, leading to decreased metabolism and ineffectiveness of these opioids in comparison to other ethnic groups.[20 21]

In conclusion, given the unique clinical value of opioids for managing severe pain, additional research is needed to fully characterise the degree of risk and thoroughly disentangle the association among pain, pain management, and various pregnancy outcomes.

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