TO THE EDITORS: Chorioamnionitis is a common complication of pregnancy with approximately 1% to 3% of pregnancies with intact membranes and 6% to 10% of pregnancies with preterm rupture of membranes.\(^1\) It is associated with potentially serious adverse maternal, fetal, and neonatal outcomes and increased long-term risks of cerebral palsy (CP) and other neurodevelopmental disabilities. Recently, Tsamantioti et al\(^2\) observed this association in a retrospective population-based cohort study in Sweden. They examined the link between chorioamnionitis and neurodevelopmental disorders in a total of 2,228,280 singleton live births and stillbirths during a 12-year period. There were 4752 cases (0.21%) of CP, 17,897 cases (0.80%) of epilepsy, 50,570 cases (2.27%) of autism, 114,087 cases (5.12%) of attention-deficit/hyperactivity disorder, and 14,574 cases (0.65%) of intellectual disability. During the study period, 5770 offspring (0.26%) were exposed to chorioamnionitis during pregnancy. After adjusting for potential confounders, exposure to chorioamnionitis increased the hazard ratios of all types of neurodevelopmental disorders except for epilepsy in offspring. However, this study raised some important issues that should be addressed.

Although the authors concluded that the associations were mainly mediated through preterm delivery and the increased risk was also observed among term infants, their study lacked some important information. For example, among the 93 cases of CP with chorioamnionitis, how many were preterm and term deliveries, respectively? Similarly, the question about the 4659 cases of CP without chorioamnionitis is the same. We can expect that in both chorioamnionitis and nonchorioamnionitis groups, the rate of CP in preterm infants would be remarkably higher than that in term infants, as preterm infants are more likely to develop CP and other adverse outcomes, including abnormalities in cognition, language development, and behavior.\(^3\) Moreover, it will be interesting to know whether the aforementioned rates are considerably different between the 2 groups (chorioamnionitis and nonchorioamnionitis).

In addition to preterm delivery, especially extremely preterm delivery, inflammatory substances induced by fetal infection or inflammation can cause cerebral ischemia and damage,\(^4\) ultimately leading to adverse neurodevelopmental consequences (Figure). However, as evidenced by this study, the number of cases with neurodevelopmental impairments associated with chorioamnionitis accounts for only a very small part of all cases (697/201,880 [0.3%]). Although efforts for timely identification and appropriate interventions to treat infections during pregnancy might have benefits in reducing the burden of neurologic complications in offspring at the individual level, the efficacy is unclear as chorioamnionitis can only be cured by delivery of the infected products of conception.

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REFERENCES
Chorioamnionitis and risk of long-term neurodevelopmental disorders in the offspring: a response

We want to thank Drs Li and Chen for their interest in our work. Our study demonstrated that chorioamnionitis increases the risk of neurodevelopmental disorders, particularly cerebral palsy (CP), autism, attention-deficit/hyperactivity disorder, and intellectual disability. Regarding the distribution of CP cases by gestational age, in our study, data on gestational age were available in 92 cases of CP exposed to chorioamnionitis, where 78 (84.78%) were born preterm and 14 (15.22%) were born at term. Among 4659 cases of CP without chorioamnionitis, 3349 infants (72.07%) were born at term, and 1298 infants (27.93%) were born preterm. Therefore, as we showed in our causal mediation analyses, chorioamnionitis leads to preterm birth, and preterm birth increases the risk of neurodevelopmental impairment (ie, CP; Figure).

We agree that the overall number of cases with neurodevelopmental impairments associated with chorioamnionitis are relatively low. However, neurodevelopmental disorders, such as CP and autism, result in substantial lifetime disability for children and their families and shorten life expectancy. Our study underlined the role of an in utero infection and the chain of events leading to neurodevelopmental disorders. Such knowledge is a prerequisite for primary prevention.

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REFERENCES


FIGURE

Simplified DAG of the relation between chorioamnionitis and neurodevelopmental disorders with preterm delivery as the mediator