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CORRESPONDENCE

Behavioural disorders after prenatal exposure to anaesthesia for maternal surgery: is it the anaesthesia or the surgery? Comment on *Br J Anaesth* 2024; 132: 899–910

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Editor—We read with interest the study by Ing and colleagues[1] on behavioural disorders after prenatal exposure to anaesthesia for maternal surgery. Evaluating the effects of prenatal exposure to maternal surgery on the developing brain is essential; however, we feel the results require more cautious interpretation, and we question the authors' conclusions.

The study reports a 31% increased risk of disruptive or internalising behavioural disorders in children with 'prenatal exposure to general anaesthesia' for maternal appendicectomy or cholecystectomy. As the title and conclusion of the study imply, the authors attribute this association specifically to the adverse effects of anaesthesia on the developing brain. We do not believe the study design and reported results support this attribution.

Inherently, it is never possible to dissociate the exposure of general anaesthesia from surgical exposure, as anaesthesia is rarely provided in isolation or without a procedural indication. There are other relevant exposures in the study cohort, specifically, inflammation, infection, sepsis, and medications such as antibiotics and analgesics (e.g. paracetamol) that could have confounded outcomes. These limitations are acknowledged by the authors, but not accounted for in the analysis, and are emphasised in the accompanying editorial by Vutskits.[2] A large body of literature supports a strong and independent association between maternal inflammation and many neurodevelopmental disorders including autism spectrum disorder and attention deficit hyperactivity disorder (ADHD).[3–6] Hospitalisation for infection (in the absence of surgery or anaesthesia) is associated with childhood ADHD with an adjusted odds ratio (aOR) 1.38 (95% confidence interval 1.31–1.46), similar to the association demonstrated by Ing and colleagues.[1,4] Evidence suggests that maternal immune activation, irrespective of the aetiology of infection, can lead to microglial activation, epigenetic alterations, and increased likelihood of neurodevelopmental disorders.[3] Maternal C-reactive protein (CRP) levels during the second trimester have been correlated to the diagnosis of ADHD with a dose–response relationship.[5] Finally, studies show the strongest association between infection and neurodevelopmental disorders with exposures in the second and third trimesters, mirroring the results of the current study, and suggesting the possibility that inflammation could be causal and explain the association between anaesthesia and disruptive or internalising behavioural disorders observed by Ing and colleagues.[1,3] Ultimately, the study design and results do not allow us to draw conclusions regarding the specific role that anaesthesia exposure might have played in the development of

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disruptive or internalising behavioural disorders after prenatal exposure to maternal surgery.

Additionally, the current study results are difficult to interpret without further delineation of anaesthesia type or duration. Using data that are up to 25 years old (with the most contemporary data over a decade old) raises concerns that anaesthesia and surgical practices in older studies might not reflect current or best practices in paediatric anaesthesia and surgery.

Perhaps our most important concern is the consequence to maternal autonomy inferred by the authors' conclusions. An American College of Obstetricians and Gynecologists Committee Opinion states that, 'a pregnant woman should never be denied medically necessary surgery or have that surgery delayed regardless of trimester'.[7] Although the authors acknowledge that 'avoidance of necessary procedures can have detrimental effects', readers are left to wonder how to extrapolate these results to their patients responsibly, without the potential of negatively impacting the clinical care of the mother because of concerns for the fetus. Clinicians might also struggle with appropriately counselling patients about the benefits of undergoing necessary and time-sensitive surgery against poorly substantiated concerns about short, and necessary, anaesthetic exposure effects on downstream childhood developmental outcomes. Although conservative management of appendicitis and cholecystitis with antibiotics is occasionally warranted, many cases require surgical treatment. Any deviation from accepted care for these conditions out of concern for fetal wellbeing could violate principles of maternal autonomy and could pose serious risk to both mother and fetus.[8]

We implore readers to interpret the results and conclusions of the study by Ing and colleagues[1] with the knowledge that short duration anaesthesia exposure is unlikely the sole putative factor in adverse neurodevelopmental outcomes. Indeed, animal studies support a role for underlying inflammation promoting the developmental toxicity of sevoflurane.[9] Future study is needed to understand more fully how exposure to anaesthetics modifies the known detrimental inflammatory effects of surgery, and how we might mitigate the potentially compounding effects of inflammation, surgery, and anaesthesia. A future human study could evaluate developmental outcomes in children born to mothers with appendicitis or cholecystitis during pregnancy who do not undergo surgery (controlling for differences in severity that might warrant differences in treatment). Although randomised controlled trials will likely never be possible or ethical, there is more work to be done to understand if and how prenatal exposure to anaesthetics affects the developing brain.

Declarations of interest

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CAW serves on the editorial board of the *British Journal of Anaesthesia*.

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All other authors declare that they have no conflicts of interest.

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