Editorial

Non-obstetric surgery and later childhood development: optimal anaesthesia for the mother-infant dyad

R. J. Kearns, [1] M Shaw[2] and S. M. Nelson[3]

1 Consultant, Department of Anaesthesia, Glasgow Royal Infirmary, Glasgow, UK

2 Professor, School of Medicine, University of Glasgow, Glasgow, UK

3 Lead Clinical Scientist, Department of Medical Physics, NHS Greater Glasgow and Clyde, Glasgow, UK

Twitter: @rjharrison79; @profscottnelson

Correspondence to: R. Kearns

Email: rachel.kearns@glasgow.ac.uk

Keywords: anaesthesia; complications; pre-natal

This editorial accompanies an article by Bleeser et al. *Anaesthesia* 2022. ANAE.2022.00631

Surgery for non-obstetric issues occurs in up to 1:100 pregnancies and can be an anxiety-provoking experience for the mother and healthcare staff, with concerns for maternal and fetal well-being [1,2]. In late 2016, the American Food and Drug Administration issued a well-publicised warning, primarily based on animal models, of general anaesthesia-related neurotoxicity. They stated that repeated or prolonged use of general anaesthesia in pregnant women during the third trimester, or in children aged < 3 y, may result in impaired neurodevelopment [3]. Reassuringly, a landmark randomised trial found that general anaesthesia of short duration in otherwise healthy infants was not associated with adverse childhood neurodevelopment at ages 2 or 5 y [4,5]. Whilst these findings are encouraging, the influence of anaesthesia on the more vulnerable fetal brain is less well described and remains a research priority [6,7].

In this issue of *Anaesthesia*, Bleeser et al. are to be commended for adding valuable new information to address this clinical uncertainty. They report findings from a Belgian ambidirectional cohort study evaluating the association of pre-natal anaesthesia exposure in 129 cases and 453 matched controls with childhood neurodevelopment [8]. The primary outcome was a child's overall executive function as assessed by a postal questionnaire completed by the child's parents. Secondary outcomes were self-declared psychosocial issues; mental health diagnoses (classified by the *Diagnostic and Statistical Manual of Mental Disorders*); and learning disorders using detailed, validated questionnaires. The overall response rate was 64%, despite the extensive efforts made by the authors, with participants contacted up to eight times. Consistent with the trial by Davidson et al. in infants [4], no difference was observed in the primary outcome between fetuses exposed to maternal anaesthesia and controls (t-score of the composite score of the executive function questionnaire; weighted mean difference of t-scores: 1.9, 95%CI -0.4–4.2; p = 0.10), nor in secondary outcomes of psychosocial problems (weighted mean difference of t-scores: 1.1, 95%CI -1.2–3.3; p = 0.36), mental health diagnoses or learning disorders [4,5]. The findings were similar with alternative statistical methodology including propensity score adjustment and matching, and in sensitivity analyses with age strata, or after exclusion of fetuses exposed to important confounders such as chemo- or radiotherapy and illicit drugs. Exploratory analyses showed an increased risk with general anaesthesia, intra-abdominal, laparoscopic, or prolonged (> 1 h) surgery for executive function alone, with estimates for the weighted mean difference of t-scores in these subgroups ranging from 3.2 to 4.5, an effect size explained by the authors as being of a similar magnitude to a parental university level education [8].

This study represents the largest study in this field to date and provides useful information and reassurance to parents and healthcare staff [8]. Given that a randomised controlled trial to assess potential causality of neurotoxicity secondary to fetal exposure to general anaesthesia is not feasible, only observational studies with their inherent biases can estimate potential treatment effects. To their credit, the authors use propensity scores in an inverse probability of treatment weighting approach to try to reduce bias from 15 confounders. Despite this, it is likely that residual and unmeasured confounding remains. In the primary analyses, all operations were included, from dental procedures to complex oncological surgery, such that the mean (SD) duration of surgery was 91 (94) min. This suggests that for some procedures surgical time was only a few minutes, but for others, several hours. Similarly, all anaesthetic modalities were included. The heterogeneity of surgery and anaesthesia may lead to differences in important intra-operative variables such as blood pressure and oxygenation, though these data were not included. With respect to child development, factors such as severity of illness, recovery period and time away from the child, ability to breastfeed, presence of paternal/family support and need for subsequent therapies and maternal hospital admissions may have also contributed.

Existing literature

There are relatively few studies of contemporary practice with which to compare these findings. The authors cite an Australian observational study of 2024 children born between 1989 and 1992, only 22 of whom were exposed to anaesthesia antenatally [9]. This study reported higher externalising behavioural scores in the exposed group but is limited by its historical nature and the low number of exposed cases [9]. Other studies have examined associations of anaesthesia during delivery on childhood outcomes. A cohort of 5320 children born between 1976 and 1982 showed no difference in learning disabilities between babies born by caesarean under regional compared with general anaesthesia compared with vaginal delivery [10]. More recently, a Scottish population-based observational study of 140,866 children born between 2007 and 2016 found a weak association between general anaesthesia during delivery for caesarean birth and having ≥ 1 abnormality in childhood developmental assessment at age 2 y [11]. These studies clearly represent a different population receiving exposure to anaesthesia for only a short time during delivery and highlight the dearth of literature in this area [7]. The paucity of studies serves to emphasise that this is a challenging area to investigate, and encourages consideration of alternative study designs to mimic the target randomised controlled trial. These may include repeated longitudinal assessments to estimate developmental trajectories, multivariable approaches to account for the linked nature of the neurodevelopmental assessments and which will increase the power of analyses (e.g. a child with a concern in executive functioning may be more likely to have a psychological concern), sibling studies to reduce confounding from socio-economic or genetic factors, and the use of a negative control such as paternal surgery. Lastly, objective outcomes such as educational attainment and exam performance would add substantially to parental understanding of any potential risk.

Surgery during pregnancy

The results of the exploratory analyses reported in this study highlight the clear need to optimise peri-operative care during pregnancy. We must first ensure the accurate identification of pregnancy in patients of reproductive age, by sensitively asking whether there is any possibility they could be pregnant (and performing a test with consent if there is uncertainty) before surgery [12]. A pregnant patient should never be denied medically necessary surgery, or have that surgery delayed, regardless of trimester [13]. This decision, and any subsequent surgery and anaesthesia, should be undertaken by senior staff in consultation with obstetric, neonatology, midwifery and obstetric anaesthetic teams. Prompt maternal and fetal assessment allows for multidisciplinary decision-making regarding the optimal location for surgery. For example, where the fetus is at a potentially viable gestation, or where a pregnant uterus may impact on resuscitative efforts in the event of maternal cardiac arrest, surgery should be undertaken on a site with obstetric services. Necessary equipment (caesarean section tray, uterotonics and neonatal resuscitaire) must be immediately available on site in the event that urgent delivery is required [13]. Although anaesthetic drugs are not teratogenic, clinicians must be cognisant that the direct effects of drugs are only one aspect of anaesthesia in the parturient and that performance of anaesthesia sensitive to maternal physiology with preservation of physiological parameters, and maintenance of uteroplacental perfusion is of critical importance [14]. In our own setting, we find the checklist shown in Box 1 to be useful before embarking on non-obstetric surgery during pregnancy.

Bleeser et al. have provided much needed reassuring information for parents and healthcare providers in an under-researched area, robustly demonstrating that a single exposure to anaesthesia of short duration during pregnancy for a wide range of surgical indications is not associated with any meaningful detriment to childhood neurodevelopmental outcomes [8]. This finding is consistent with randomised controlled trials and observational data assessing childhood anaesthetic exposure and neurodevelopment [4,5,15,16]. What is less clear is whether different types of surgical operation, alternative surgical approaches, repeated or prolonged exposures of anaesthesia, or the stage and status of brain development would modify this largely reassuring conclusion. We look forward to data from future complementary studies to further our understanding of this complex and important clinical issue.

Acknowledgements

The authors hold research grant funding from Wellbeing of Women. RK holds an NHS Research Scotland Career Researcher Fellowship. SN has participated in Advisory Boards and received consultancy or speakers' fees from Access Fertility, Beckman Coulter, Ferring, Finox, Merck, Modern Fertility, MSD, Roche Diagnostics and The Fertility Partnership. None of these lead to conflict of interest for this editorial. No other competing interests declared.

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Box 1 Practical considerations for non-obstetric surgery in the pregnant patient. Adapted from [13,14,17–19]

Gestation	Establish from a valid estimated date of delivery or via ultrasound scan
Location	Centre with on-site obstetric services
Communication	Multidisciplinary discussion between anaesthetic, midwifery, neonatal, obstetric, obstetric anaesthetic and surgical teams
Additional equipment	Theatre table capable of left lateral tilt or wedge, caesarean section tray, uterotonics, neonatal resuscitaire (if fetus at viable gestation), intermittent compression stockings
Pre-operative considerations	• Abdominal lead shield during imaging • Fetal monitoring/anti-D/corticosteroids for fetal lung maturation as advised by obstetric team. • Group and save/cross match depending on surgical procedure and pre-operative full blood count • Antacid (proton pump inhibitor) and sodium citrate prophylaxis
Anaesthesia	• 15° left lateral tilt to avoid aortocaval compression • Regional anaesthesia preferable. Smaller volumes required for neuraxial techniques • Higher risk of difficult intubation • General anaesthesia, rapid sequence induction, ramped position, videolaryngoscope, down-sized tracheal tube. • Maintain $ETCO_2$ in normal pregnant range (3.7-4.2kPa) • Consider arterial line and $PaCO_2$ monitoring in laparoscopic patients ($PaCO_2$ may be significantly greater than $ETCO_2$) • Maintain placental perfusion – maintain SBP within 20% of pre-operative levels with rapid treatment of hypotension (e.g. with phenylephrine infusion) • Reversal with neostigmine and atropine (glycoprolate does not cross the placenta). • No clinical data on sugammadex use on pregnancy. Recommended only if strongly clinically indicated (e.g. 'can't intubate, can't ventilate' scenario) due to concerns about progesterone binding • Analgesia: paracetamol (weight appropriate dose), opioids and regional techniques can be used, avoid NSAIDs after 32-weeks' gestation
Postoperative	• Fetal monitoring as directed by obstetric team, with specific focus on preterm labour • Thromboprophylaxis • Breastfeeding should be encouraged as normal following surgery • There is no need to express and discard breast milk after

anaesthesia