On 14 December 2016, the US Food and Drug Administration (FDA) issued a warning that the repeated or lengthy use of general anaesthetic and sedative drugs in children under 3 years old and in pregnant women in their third trimester may affect the development of children's brains. Warning labels were required to be added to general anaesthetic and sedative drugs.1

Data from published studies in pregnant and young animals have shown that the use of general anaesthetics increases the chance of apoptosis and neurodegeneration in the developing brain. Persistent memory and learning disabilities have been demonstrated2,3 as well as increased severity with increasing duration of anaesthesia.4 Certain human studies suggest an association between anaesthesia and subsequent behaviour or learning issues such as autism, attention-deficit disorder, and language deficits.5-7 Some researchers postulate that even relatively simple anaesthesia of babies and young children can pose a risk of neurotoxicity. The question is whether or not we can translate such animal data to humans and to what extent we should question is whether or not we can translate such data from published studies in pregnant and young animals have shown that the use of general anaesthetics increases the chance of apoptosis and neurodegeneration in the developing brain.

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For many years well-designed human studies were lacking. Data were mainly observational and retrospective, and with too many confounding factors. There were often conflicting results in different studies.9,10 Recently, however, more robust human studies have been published such as General Anaesthesia compared to Spinal anaesthesia (GAS) study11 and Pediatric Anesthesia NeuroDevelopment Assessment (PANDA).12,13 The GAS study, which compares children less than 60 weeks’ post-gestational age (but older than 26 weeks’ post gestation) undergoing hernia surgery under either general anaesthesia or awake regional anaesthesia, has shown that at the 2-year mark (secondary outcome), there is no increase in risk of learning disability. This study is ongoing with its primary outcome being the Wechsler Preschool and Primary Scale of Intelligence Third Edition Full Scale Intelligence Quotient score at 5 years old. The PANDA study was a sibling-matched cohort observational study that examined whether anaesthesia exposure in healthy children younger than 3 years old is associated with an increased risk of impaired global cognitive function as the primary outcome. Their secondary outcome was abnormal domain-specific neurocognitive function and behaviour at the ages of 8 to 15 years. The study found no significant difference between the exposed and unexposed in terms of both primary and secondary outcomes. Both studies point towards a slightly more reassuring outlook for short-duration exposure to anaesthesia in children.

Moreover, the FDA uses a cut-off age of 3 years old. This age limit is highly debatable since there is currently no evidence to support the use of 3 years as a cut-off or that anaesthesia in infants older than 3 years will not be harmful; and vice versa. Some use 3 years as a cut-off for the period of rapid neurodevelopment in a child; nonetheless a few retrospective cohort studies point towards anaesthesia affecting children of an older age group.14,15 Many of these concerns are likely to be applicable to all patients undergoing surgery with those at the extremes of age being more vulnerable.

Duration of surgery and the extent of tissue trauma, need for blood transfusion, and the choice of anaesthetic agent are also important variables. Data from the American Society of Anesthesiologists (ASA) Closed Claims Project were analysed and revealed that children under 1 year of age with associated disease were at increased risk of major and minor morbidity.16 Cardiac arrests related to anaesthesia most often occurred in infants who were ASA status 3 to 5 and undergoing emergency procedures. Paediatric anaesthesiologists should therefore collaborate with surgeons to determine the best time for surgery in a child.17 Often, children need anaesthesia for operations or procedures that should not be delayed. In these cases, it is easier to balance the detrimental effects of not having the surgery against the potential risk of anaesthesia. In
non-urgent surgeries that will not affect the child or the outcome of the operation if postponed until later in life, it is reasonable to discuss with all parties involved, including their parents or guardians, as to whether deferring the surgery can be considered in very young children. Given that perioperative complications are more common in the very young,\textsuperscript{18} this is a good general principle that has always been advocated by those involved in perioperative paediatric care, notwithstanding this FDA warning.

References