Best Practice & Research Clinical Anaesthesiology 37 (2023) 73–86

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

7

Neuraxial analgesia in labour and the foetus

R.J. Kearns, Dr [a, *], D.N. Lucas, Professor [b]

[a] School of Medicine, University of Glasgow, UK
[b] London North-West Healthcare NHS Trust, London, UK

Keywords:
labour analgesia
neuraxial analgesia
epidural analgesia
combined spinal epidural
LA
neonatal outcomes
childhood outcomes

Providing pain relief during labour is a fundamental human right and can benefit both mother and foetus. Epidural analgesia remains the 'gold standard', providing excellent pain relief, as well as the facility to convert to anaesthesia should operative intervention be required. While maternal well-being remains the primary focus, epidural analgesia may also have implications for the foetus. Data from meta-analyses finds that epidural compared with systemic opioids in labour is associated with reduced neonatal respiratory depression. Clinically relevant neonatal outcomes such as Apgar score <7 at 5 min, neonatal resuscitation and need for admission to a neonatal unit are reassuring, with the benefits of epidural analgesia for both mother and neonate outweighing any potential risks. Recent concerns regarding an association of epidural with the development of autism spectrum disorder in childhood appear to be unfounded, with several large observational studies refuting this association. This review discusses the evidence relating to maternal neuraxial analgesia in labour, implications for the foetus *in utero*, and childhood outcomes both in the immediate peripartum period and longer term.

Introduction

Labour is likely to be one of the most painful events a person will experience in their lifetime and adequate pain relief is a fundamental human right [1]. Epidural analgesia for labour is safe and effective and is recommended by the World Health Organization [2]. The rate of epidural use in labour varies

* Corresponding author. School of Medicine, University of Glasgow, 2nd Floor, Lister Building, Glasgow Royal Infirmary, 10-16 Alexandra Parade, Glasgow, G31 2ER, UK.
E-mail address: rachel.kearns@glasgow.ac.uk (R.J. Kearns).

https://doi.org/10.1016/j.bpa.2023.02.005

globally and was reported as between 10 and 83% in a survey of thirteen high-income countries, though rates in low and middle-income countries are lower [3,4].

Epidural safety and efficacy have been highlighted as key quality indicators by a UK national Delphi process [5,6]. The use of lower concentration LAs (LA) [7], the safe use of adjuvants in epidural infusions [8], guidance on the use of lipid emulsion for LA toxicity [9], optimisation of epidural maintenance techniques [10] and clear standards for post-epidural neurological monitoring [11] have all contributed to improvements in labour and delivery outcomes. Rigorous research and ongoing quality improvement are vital to ensure continued advances in epidural practice.

Whilst the mother remains the focus for anaesthetic interventions during labour and delivery, any intervention may also have implications for the baby [12–14]. However, these are less frequently discussed during the consent process [15]. As maternal and neonatal well-being are inextricably linked, ensuring that analgesia is safe for the neonate is also a clear priority for both parents and clinicians [16]. This review presents the evidence relating to neuraxial analgesia and neonatal and childhood outcomes.

Labour pain and the foetus *in utero*

Although labour and birth are physiological processes, labour without pain relief is not without potential adverse consequences. Poorly controlled pain can lead to the development of maternal physiological stress resulting in cortisol and catecholamine release, hyperventilation, increased oxygen consumption, respiratory alkalosis with left shift of the oxygen dissociation curve, and consequent impaired foetal oxygen transfer. This results in compensatory maternal metabolic acidosis with uterine vasoconstriction and subsequent foetal acidosis [17]. As well as cortisol and catecholamine release, uncontrolled pain in labour activates the release of β lipotropin and β endorphin. The increased sympathetic response can lead to incoordinate uterine action and reduced uteroplacental perfusion, hyperglycaemia, lipolysis, ketosis and increased production of lactate [15]. These acids, together with catecholamines, can cross the placenta, increasing foetal oxygen requirement and compounding maternal and foetal metabolic acidosis [15].

Uncontrolled pain may have longer-term adverse consequences for both mother (and indirectly to the neonate), such as in the development of post-traumatic stress disorder and post-natal depression [18,19]. The provision of analgesia in labour may mitigate these effects and hence benefit both mother and foetus. Whilst pain relief can ameliorate the maternal stress response, any analgesic technique used can directly affect the foetus via placental transfer of drugs and indirect effects via changes to maternal physiology.

Choice of analgesia in labour

The experience of pain in labour is complex and highly variable, incorporating physical, psychosocial, emotional, and environmental factors [20]. Consequently, requirements for analgesia differ substantially between patients, and in some cases, fear of labour is such that an elective caesarean section is requested [21]. Options for pain relief can be broadly divided in to non-pharmacological, pharmacological and neuraxial techniques, and ensuring adequate and timely information regarding the options for pain relief in labour is important to ensure fully informed decision making [22]. This information has traditionally been limited to maternal risks and benefits with little information on foetal and neonatal factors, though these are likely to be important to most parents. A summary of commonly used analgesic techniques and evidence from meta-analyses relating to associations with neonatal outcomes is included in Table 1.

Neuraxial analgesia

Neuraxial analgesic techniques (lumbar epidural analgesia or combined spinal-epidural) are commonly used, safe and effective, and have the advantage of avoiding systemic drug administration. Lumbar epidural is performed by identifying the epidural space using a loss of resistance technique, before threading a catheter, and incrementally administering LA, usually combined with an opioid. For combined spinal-epidural analgesia (CSE), the intrathecal space is entered with a spinal needle after

Table 1
Commonly used analgesic techniques and neonatal outcomes; findings from meta-analyses.

Analgesic technique	Associations with neonatal outcomes
Nitrous oxide	No difference in Apgar score or neonatal asphyxia when compared with controls [27] No difference in neonatal outcomes when compared with neuraxial analgesia [28]
Systemic opioids	No clear evidence of neonatal adverse effects but evidence of low quality and of very low certainty [29] Neonate more likely to require naloxone administration when compared with epidural analgesia [28]
PCA remifentanil	No differences in Apgar score <7 at 5 min with remifentanil PCA compared with neuraxial analgesia [30]
Epidural	No clear differences between epidural and systemic opioid groups for neonatal outcomes, admission to neonatal unit, and Apgar score <7 at 5 min [28] Neonate less likely to receive naloxone than with systemic opioids [28] No difference in Apgar scores or neonatal unit admission when neuraxial opioids compared to LA only neuraxial technique [31]
Combined spinal epidural	No significant difference in umbilical pH, Apgar score, or neonatal unit admission compared with low dose epidural [23] Increased incidence of non-reassuring FHR compared with conventional lumbar epidural [32]

identifying the epidural space. Intrathecal drugs are administered, and the epidural catheter subsequently threaded. Potential advantages of CSE in labour include a more rapid onset of pain relief, and reduced need for rescue analgesia [23]. A CSE may also be advantageous when the foetus is in the occiput-posterior position, or for conversion to anaesthesia in the high-risk parturient (e.g. cardiac disease) where gradual and incremental onset of sympathetic block may be desirable. However, CSE is more technically challenging than standard lumbar epidural and in the Royal College of Anaesthetists' Third National Audit Project, was associated with a higher incidence of permanent neurological complications (3.9/100 000 [95% CI 1–22] vs. 0.62/100 000 [95% CI 0–3.4] [24].

Before deciding on a method of pain relief, a thorough discussion to support informed consent, should take place between the mother and anaesthetist discussing risks, benefits, and alternatives [22]. Lower epidural use in ethnic minority and socioeconomically disadvantaged groups has been reported and such inequities must be recognised and addressed [25]. Effective pain control in labour attenuates the maternal stress response with both maternal and foetal benefits; however, the foetal stress response is not attenuated. This is advantageous given that a foetal catecholamine surge is essential for adaptation to life *ex utero*. In addition to relieving pain and its associated benefits, an effective labour epidural can be 'topped-up' to provide anaesthesia for operative delivery thereby potentially negating the need for general anaesthesia and its attendant risks to both mother and neonate [26]. This is particularly prescient in parturients at higher risk of general anaesthesia, such as those with obesity, a difficult airway, or preeclampsia.

Epidural analgesia in labour and implications for the foetus *in utero*

Labour epidural analgesia is usually established with a combination of LA and lipid-soluble opioids which work synergistically to reduce the required dose of each, minimising adverse effects. Whilst any direct foetal effects of epidurally administered agents are minimal with longer-acting LA drugs and fentanyl, the foetus may be affected indirectly via changes to maternal physiology, such as maternal hypotension and fever. Foetal heart rate (FHR) abnormalities may also be observed [32,34], however it should be emphasised that such maternal physiological changes, whilst important to recognise and act upon appropriately, do not necessarily translate into adverse neonatal outcomes. Furthermore, the attenuation of the maternal stress and sympathetic response has beneficial effects on both maternal and foetal acid-base status as previously described.

Intrapartum hyperthermia

Intrapartum hyperthermia is defined as '*a core temperature during labour of* $\geq 38^{\circ}C$ *on one occasion or* $\geq 37.5^{\circ}C$ *on two consecutive occasions 2 h apart*' [35]. This may occur with intrapartum infection, or in

association with epidural analgesia. The incidence of intrapartum hyperthermia is around 20% in patients with epidural analgesia compared to 5% in those without (where hyperthermia is almost exclusively secondary to infection) [28,36]. Epidural-related hyperthermia remains incompletely understood but is thought to be secondary to sympathetic blockade and/or immunomodulation [37]. In the first proposed mechanism, blockade of sympathetic nerves prevents vasodilatation and sweating, thus reducing heat loss. The immunomodulation theory suggests that hyperthermia is driven by proinflammatory mediators creating a 'sterile febrile response' [38]. Whilst epidural-related hyperthermia does not increase the risk of infection, it is frequently misdiagnosed as such, resulting in changes in obstetric management, and antibiotic treatment [38].

Infections, such as chorioamnionitis, are associated with neonatal brain injury but it is not clear if this increased risk is specific to patients with infection, or if intrapartum hyperthermia of any cause (including that related to epidural analgesia) is detrimental to the neonatal brain. Given the serious consequences of untreated maternal infection for both mother and foetus, treatment with blood cultures, paracetamol, antibiotics, and supportive measures is mandatory in the absence of a means of differentiating between these aetiologies [35]. The neonate should also be evaluated for sepsis with blood cultures and C-reactive protein measurement and treated empirically with intravenous antibiotics [39].

The issue of whether epidural-related hyperthermia causes neonatal brain injury remains unresolved. A meta-analysis of 41 studies reported a causal link between epidural analgesia and intrapartum hyperthermia (OR: 4.21; 95% CI: 3.48−5.09), and an association between intrapartum hyperthermia (of any cause) and neonatal brain injury (OR: 2.79; 95% CI: 2.54−2.3.06), but could not quantify any independent association between epidural-related hyperthermia and neonatal brain injury [37]. As there were only two eligible studies for the association of epidural-related hyperthermia and neonatal brain injury, and the evidence was judged to be of very low quality according to GRADE criteria, further work is required to investigate this potential association. An absence of adverse neonatal outcomes in large population-based studies [13], in meta-analyses of studies comparing epidural analgesia to non-epidural analgesia [28], and in comparisons of different concentrations of LA in epidural regimes provide some reassurance [40,41].

Foetal assessment

The cardiotocograph is ubiquitous in labour ward, becomes mandatory with the onset of neuraxial analgesia, and is used to guide obstetric decision making. The use of neuraxial analgesia has traditionally been associated with changes in FHR, a phenomenon proposed to be secondary to a reduction in maternal stress hormones and consequent uterine hypertonus/foetal hypoxaemia, or due to aortocaval compression and hypotension [42,43]. The likely reality is that any underlying process behind FHR change is complex and multifactorial.

Data from meta-analyses have led to the following conclusions:

(i) Epidural is not associated with increased incidence of FHR abnormalities when compared with parenteral opioids [44]. Although FHR abnormalities were not included in a more recent Cochrane review, there was no difference in neonatal outcomes of Apgar score, neonatal acid-base status, and neonatal unit admission between epidural and systemic opioid groups [28].
(ii) CSE when compared with epidural is associated with an increased risk of non-reassuring FHR tracings [32], however a Cochrane review found no difference between the two techniques in the need for caesarean section, Apgar scores, neonatal acid base status, or neonatal unit admission [23].
(iii) In a multivariable analysis from a prospective study comparing epidural with CSE, oxytocin was associated with an increased risk of non-reassuring FHR tracings, whilst hypotension, parity, and efficacy of analgesia were not [42].
(iv) Thus, even where an increased risk of FHR abnormalities was detected, this did not translate into poorer neonatal outcomes.

Associations of epidural with mode of delivery

Before further evaluating any association of labour epidural analgesia on the neonate following delivery, rather than foetal (*in utero*) outcomes, it is important to consider the long-standing contention that epidural analgesia increases the risk of operative delivery. This relationship is complex and prone to confounding by indication in that mothers who request epidural analgesia are more likely to have been induced, have had a more prolonged or painful labour, and have a higher baseline risk of requiring assisted or operative delivery. Despite historical evidence and dogma to the contrary, contemporary studies refute causal associations of epidural with prolonged labour and increased risk of assisted vaginal or caesarean birth [28,40,41,45]. A Cochrane review of forty randomised trials comparing epidural with non-epidural in labour found no differences in caesarean rates, nor in assisted vaginal delivery rates when trials were restricted to those performed after 2005 [28]. This finding is likely to relate to the use of lower concentrations of LA following publication of the COMET trial in 2001 [7]. This landmark study found increased rates of spontaneous vaginal delivery with low ($\leq$0.1% levobupivacaine) compared with high dose LA and substantially influenced obstetric anaesthetic practice [7]. Further meta-analyses of different concentrations of LA have found that low or ultra-low concentrations of LA are unlikely to increase rates of operative delivery compared with non-epidural analgesia [41,45]. The use of CSE may reduce the need for instrumental delivery but does not alter the caesarean section rate when compared to standard epidural [23].

Epidural analgesia in labour and neonatal outcomes

Given the potential influence of neuraxial analgesia on foetal parameters, it follows that neonatal outcomes may also be affected. These outcomes are of clear clinical importance, are impactful to parents who may be separated from their baby during a resuscitation event or admission to the neonatal unit, and who are concerned about the future development of their child.

Neonatal acid-base status

The acid-base balance status of the umbilical artery blood reflects the recent intrauterine environment and is considered a valid and robust marker of foetal and neonatal well-being. Arterial pH is indicative of both respiratory and metabolic status. Given the influence of maternal hyperventilation during labour on pH, the base excess is a more accurate measure of metabolic acidosis and hence hypoxia. Following birth, the neonate's acid-base status is dependent on its own respiration and may be depressed following maternal systemic opioid analgesia [46].

In a meta-analysis of over 2000 mothers, epidural analgesia was associated with improved neonatal acid–base status. The authors concluded that any adverse maternal physiological changes such as hypotension or fever, were likely to be outweighed by the beneficial effects on acid-base status [46]. More recent meta-analyses have found no difference in neonatal acid-base status when epidural is compared to non-epidural analgesia [28], when low dose and high dose epidurals are compared [41,45], when epidural is compared to CSE [23], and when neuraxial opioids are compared with controls [31].

Immediate neonatal outcomes

Immediate neonatal well-being following delivery is commonly measured using clinical endpoints such as the need for resuscitation at birth, Apgar score, and admission to a neonatal intensive care unit. The relationship between analgesia in labour and neonatal outcomes has been the subject of many, mainly observational studies. These have reported varying findings with some reporting an association between epidural and adverse neonatal outcomes [47,48] and others finding no such association [49,50]. A Scotland-wide population-based study of over 435 281 mother–infant pairs presenting in labour found that epidural was associated with reduced risk of requiring neonatal resuscitation, Apgar score <7 at 5-min, and admission to neonatal unit when accounting for mediation by mode of delivery [13]. Findings from meta-analyses support these results, finding no difference in neonatal outcomes of

Apgar score <7 at 5-mins or neonatal unit admission in patients receiving epidural compared with non-epidural analgesia, though the use of systemic opioids was associated with an increased risk of the neonate requiring naloxone compared with epidural [28]. Similarly, when patients receiving neuraxial opioids were compared with those who did not, and when epidural was compared with CSE, no difference in Apgar score <7 at 5-mins was seen [23,31].

Although these data are generally reassuring, there is contradictory evidence about the influence of epidural on the 1-min Apgar score. In a meta-analysis of high-versus low-concentration LA, 1-min Apgar scores were more favourable in the high concentration group [40]. This was postulated to be due to the addition of epidural fentanyl to lower concentrations of LA. These findings were partially replicated in a meta-analysis comparing high, low and ultra-low concentrations of LA, finding a higher risk of Apgar score <7 at 1-min in the low compared with the high concentration group, though no difference between ultra-low (where epidural opioid was equally likely to have been given) and high concentration groups [41]. In a meta-analysis specifically examining the influence of neuraxial opioids, no significant differences in 1- or 5-min Apgar scores were found in patients receiving neuraxial opioids compared to those who did not [31]. Unlike the 5-min Apgar score, a 1-min Apgar score <7 is not associated with poorer long-term developmental outcomes and is considered of less clinical relevance [51].

Non-opioid epidural adjuvants and neonatal outcomes

Evidence relating to epidural adjuvants other than opioids is limited. Clonidine and dexmedetomidine are alpha-2 receptor agonists which have a LA sparing effect while increasing the duration of analgesia, making them attractive for use in labour. A randomised trial of 98 term parturients comparing epidurally administered fentanyl with clonidine to treat breakthrough labour pain found similar analgesic efficacy, without an increase in maternal or neonatal adverse effects, with clonidine [52]. A meta-analysis of nine randomised trials found no detrimental effect on Apgar scores, umbilical artery pH/partial pressure of oxygen, or foetal heart rate when epidural dexmedetomidine was compared with epidural opioids or plain LA epidural infusion [53].

Neostigmine stimulates the production of nitric oxide in the spinal cord resulting in analgesia and may counteract some of the hypotensive effects of alpha-2 receptor agonists. The combination of epidural clonidine and neostigmine to epidural LA infusions was investigated in a meta-analysis of four case–control studies finding prolonged duration of analgesia and less anaesthetic and opioid administration without any negative impact on Apgar scores [54]. The authors acknowledged that additional evidence from larger studies is required to further assess both outcomes and safety of this combination of adjuvant drugs.

Epidural compared with PCA remifentanil

Remifentanil has become increasingly popular over the last two decades. Its short onset and time to peak effect, rapid metabolism by plasma and tissue esterases, and short context-sensitive half-life make it suitable for use over a long period without fear of accumulation. Remifentanil rapidly crosses the placenta but is rapidly metabolised and redistributed by the foetus making it an appealing option for analgesia in labour [55]. Despite its favourable characteristics and superiority to other systemic opioids in labour [56], remifentanil does not provide superior analgesia to epidural and associations with maternal respiratory depression are well described [57,58]. Two meta-analyses comparing remifentanil to epidural in labour found no differences in Apgar score <7 at 5-min [57], nor umbilical artery pH, though confidence intervals were wide and further evidence is required to confirm this conclusion [58]. Use of remifentanil mandates adequate staff training, and close maternal and neonatal respiratory monitoring.

Epidural and breastfeeding

The World Health Organisation and the United Nations Children's Fund recommend exclusive breastfeeding during the first 6-months of life [59]. Despite these recommendations, only 35% of

infants worldwide are exclusively breastfed [59], with lack of breastfeeding a significant risk factor for childhood morbidity and mortality and an important public health concern [60,61]. Whether epidural analgesia has any impact on breastfeeding remains uncertain and evidence is conflicting. A systematic review of 23 observational and randomised studies showed a mixture of positive, negative, and no association though studies were limited by small size, heterogeneity and inability to control for confounding factors [62]. Concerns regarding epidural opioids appear unfounded with a randomised controlled trial finding that epidural infusions containing up to 2 μg/ml fentanyl did not reduce rates of successful breastfeeding 6-weeks after delivery [63]. It is likely that other factors such as social support, cultural values, and early maternal-infant bonding experience influence breastfeeding success to a greater extent.

Epidural and post-partum depression

Uncontrolled pain is a risk factor for the development of post-partum depression and well-managed pain in labour may protect against the development of adverse psychological sequelae for the mother [64]. The development of post-natal depression may have adverse consequences for the offspring; hence labour epidural analgesia may provide an indirect protective effect. Two meta-analyses of prospective, observational studies found no difference in the incidence of post-natal depression between parturients who had received an epidural compared with those who had not [65,66]. Concerns surrounding high study heterogeneity, low study quality, and residual confounding are likely to mean that this association will undergo further study before definitive conclusions are drawn.

Association of epidural with childhood outcomes

The early years of life are essential for the health, development and well-being of a child throughout their life-course. It is therefore important to consider any influence of the choice of analgesia in labour not only with immediate neonatal outcomes but with longer-term childhood development. Unfortunately, this is an area where evidence is relatively scarce, though it has received greater attention in recent years.

In a cohort study of 4684 children born vaginally between 1976 and 1982, the use of an epidural in labour was not associated with an increased risk of learning difficulties by age 19-years when compared with controls [67]. Whilst reassuring, the findings of this study are limited by its age and the substantial changes in anaesthetic, obstetric and neonatal practice since this time. More recently a population-based study of Scottish births comparing epidural with non-epidural analgesia in labour found that epidural analgesia was associated with a reduced risk of having developmental concerns in any domain at 2-years of age, with specifically fewer concerns regarding communication and fine motor skills [13]. Furthermore, a prospective Chinese study of 508 mother–infant pairs found no association between epidural analgesia in labour and impaired neurodevelopment [68].

Epidural analgesia and autism

Further to an interest in longer-term childhood neurodevelopmental outcomes, there has been much interest in the possible association of labour epidural analgesia with autism spectrum disorder (ASD) both in the medical literature and mainstream media [69]. The widespread publicity such hypotheses attract has the potential to influence maternal decision-making, and may have unintended and potentially detrimental consequences. Robust study of this issue is of evident importance.

ASD is a heterogeneous collection of neurodevelopmental conditions characterised by behavioural differences such as repetitive behaviours, impaired communication, and social interactions. Delays in speech development, learning difficulties, impaired executive function and organisational skills often co-occur. ASD typically manifests in early childhood, with most patients continuing to have symptoms into adulthood, and is likely to have both genetic and non-genetic aetiological components, though this remains incompletely understood [70]. Possible aetiological environmental factors of parental age, maternal nutritional status, toxins or heavy metal exposure, certain drugs (e.g. anti-epileptics and antidepressants), infection during pregnancy, and adverse perinatal factors (e.g. preeclampsia, birth

asphyxia, malpresentation) have been proposed [71]. Pathophysiological mechanisms include abnormalities in brain architecture, brain connectivity, synaptic function, and the brain-gut microbiome [72–74].

Given the potential influence of perinatal factors on the development of ASD in children, placental transfer of LA as a possible mechanism for foetal neurotoxicity has been proposed. Due to their low molecular weight, epidurally administered LA can cross the placenta thereby exposing the foetus to a potential risk of neurotoxic effects such as altered synaptogenesis and apoptosis [75,76]. In a study of female, pregnant rhesus monkeys, epidural with 0.6 mg/kg bupivacaine ($n = 11$) was compared with epidural saline ($n = 8$), finding no differences in neonatal neurobehavior, early cognitive abilities, or performance of cognitive tasks by older infants, though some between group differences in behavioural assessments were reported [77]. Doses of bupivacaine were significantly higher than those used in obstetric anaesthetic practice, and as this study included only 19 monkeys and included multiple tests and comparisons, it is at high risk of a type 1 error. To our knowledge, these findings have not been repeated. In a study of epidural bupivacaine administered to pregnant guinea pigs, LA concentrations in the hearts and brains of the foetal guinea pigs were lower than the minimal amounts seen in their blood samples, suggesting low levels of LA exposure in these tissues [78]. Studies of epidurally administered LA in humans report minimal systemic absorption, low concentrations in the neonatal bloodstream [79,80], and evidence of foetal LA metabolism [81]. Contemporary doses of epidural bupivacaine and fentanyl appear to have a negligible effect on neonatal condition in human studies [33]. Despite this, concerns regarding foetal neurotoxicity secondary to placental transfer of LA persist and have been investigated in large observational studies.

In an observational, retrospective cohort study of 147 895 live births in California, Qui et al. reported a 37% relative increase in the risk of ASD in offspring of mothers who had received epidural analgesia in labour [82]. These findings were widely reported, stimulating debate in social media, the lay press, and in academic literature. The study was heavily criticised in statements from professional societies regarding the likelihood of residual confounding (including the duration of labour, presence of foetal distress, and foetal malposition), the exclusion of patients delivered by caesarean section, and the lack of causal analysis [83]. Furthermore, important characteristics of women who did and did not receive epidural analgesia were different, increasing the likelihood of residual confounding. Interestingly, there was no identified association between intrapartum fever and ASD [82]. Since the publication of this paper, four large, population-based studies from Denmark and Canada have found insufficient evidence to support an association between epidural and ASD in childhood [84–87]. Three of these papers used sibling matching to control for shared genetic and environmental factors to minimise residual confounding [85–87]. These findings add further evidence to support the role of genetic factors in the development of ASD. Characteristics and findings of these studies are presented in Table 2.

The widespread publicity surrounding the Qiu article and the inference of a causal relationship between labour epidural and ASD is a cause for concern. Such information may increase maternal anxiety and guilt over receiving pain relief in the form of labour epidural, potentially resulting in unintended consequences such as increasing the rate of emergency GA for caesarean section. Clinicians should discuss the risks and benefits of epidural analgesia with patients, highlighting that the current evidence base does not support a causal association between an epidural in labour and ASD. As randomisation to an epidural in labour is ethically questionable, the performance of a randomised trial in this area is unlikely to be feasible and observational studies are likely to prevail. There is a growing, reassuring evidence base with which to support the assertion that there is no association between epidural analgesia and adverse neurodevelopmental outcomes, including ASD [69]. However, future studies must strive to limit the influence of bias by identifying and accounting for known (and attempting to account for unknown) confounding factors as far as possible.

Summary

The provision of safe and effective epidural analgesia in labour underpins obstetric anaesthetic practice. Ensuring equity of access is a priority. Epidural analgesia provides optimal analgesia, allows for rapid conversion to anaesthesia, avoiding the risks associated with general anaesthesia, and is associated with favourable maternal, foetal and neonatal outcomes. Growing numbers of studies

Table 2
Summary of studies investigating associations between neuraxial analgesia in labour and autism spectrum disorder.

	Qiu et al. [82]	Wall-Wieler et al. [85]	Mikkelson et al. [84]	Hanley et al. [86]	Ren et al. [87]
Publication date	October 2020	April 2021	September 2021	September 2021	December 2021
Study design	Retrospective population-based birth cohort	Retrospective population-based birth cohort	Retrospective population-based birth cohort	Retrospective population-based birth cohor	Retrospective population-based birth cohort
Study period	Births from 2008 to 2015 Follow up; from age 1 year until clinical diagnosis of ASD, last date of health plan enrolment, death, or study end date (December 31, 2018)	Births from 2005 to 2016 Follow-up; from birth until 2019 or censored by death or emigration	Births from 2006 to 2013 Follow-up; from first birthday until an event of ASD, death, emigration, diagnosis of a disorder inherently linked to autism, or last day of follow-up (December 31, 2017)	Births from 2000 to 2014 Follow-up; clinical diagnosis of ASD, death, move outwith British Columbia and lost to follow-up, or last day of follow-up (December 31, 2016)	Births from 2005 to 2016 Follow-up; date of first diagnosis of neurodevelopmental disorder, death, emigration, or last day of follow-up (December 31, 2018)
Study population	147 895 singleton vaginal deliveries between 28 and 42 weeks gestation (Kaiser, Southern California)	123 175 singleton vaginal deliveries (Manitoba, Canada)	479 178 livebirths (Denmark)	388 254 term, singleton vaginal deliveries (British Columbia, Canada)	624 952 liveborn singletons born vaginally or via intrapartum caesarean section
Exposure	Use of labour epidural analgesia (n = 109 719 [74.2%]) Duration of labour epidural use	Use of labour epidural analgesia (n = 47 011 [38.2%])	Use of labour epidural analgesia (n = 92 900 [19.4%])	Use of labour epidural analgesia (n = 111 480 [28.7%])	Use of labour epidural analgesia (n = 116 296 [18.6%])
Control	No epidural	No epidural	No epidural	No epidural	No epidural
Outcome (OR HR) for ASD	Adjusted HR 1.37 (1.23−1.53)	Adjusted HR 1.08 (0.97−1.20)	Adjusted HR 1.05 (0.98−1.11)	Adjusted HR 1.09 (1.00−1.15)	Adjusted HR 1.11 (1.04−1.18)
With 95% confidence interval	Increased risk with increasing duration	Sibling matched analysis Adjusted HR = 0.97 (0.78−1.22)		Sibling matched analysis Adjusted HR 1.10 (0.99−1.15)	Sibling matched analysis Adjusted HR 1.03 (0.84−1.27)

(*continued on next page*)

Table 2 (*continued*)

	Qiu et al. [82]	Wall-Wieler et al. [85]	Mikkelson et al. [84]	Hanley et al. [86]	Ren et al. [87]
Comments	• Baseline differences between exposed patients and controls • Lack of data on pregnancy and delivery complications • Exclusion of patients undergoing caesarean section • Likelihood of residual confounding	• Large number of covariates including pregnancy and delivery complications to reduce risk of residual confounding • Relatively low epidural rate (38.2%) • Several sensitivity analyses with similar findings to main result	• Large study size • No difference in ASD diagnosis in within-mother analysis (mothers exposed to epidural in one pregnancy but not in another) • Large number of covariates including pregnancy and delivery complications to reduce risk of residual confounding • Multiple sensitivity analyses with similar findings to main result	• Large study size • Baseline differences between exposed patients and controls • Just meets threshold of statistical significance in non-sibling matched analysis but likelihood of residual confounding • No difference seen between groups in sibling analysis	• Associations between labour epidural and ASD or developmental disorders, evident in the full cohort, disappeared in sibling-matched analyses • No relationship between duration of epidural analgesia and outcome • No association between epidural and other neurodevelopmental disorders (e.g. epilepsy, ADHD)

evaluating the influence of epidural during labour with longer-term childhood outcomes have provided reassurance that epidural is neither detrimental to childhood development outcomes, nor associated with autism spectrum disorder. Greater understanding of the mechanisms underpinning epidural-related hyperthermia, how this can be differentiated from sepsis, and its clinical implications is a research priority.

Practice points

- Uncontrolled labour pain may be associated with maternal and foetal metabolic acidosis
- Epidural provides highly effective analgesia in labour
- The use of epidural for analgesia in labour is increasing
- Epidural is not associated with increased incidence of Fetal Heart Rate abnormalities when compared with parenteral opioids
- Epidural is not associated with adverse neonatal outcomes of resuscitation at birth, Apgar score <7 at 5 min, and neonatal unit admission
- Epidural is not associated with adverse childhood developmental outcomes, nor with the development of Autism Spectrum Disorder
- Epidural is associated with maternal hyperthermia but not with adverse neonatal outcomes
- No independent, causal relationship between epidural-related hyperthermia and neonatal brain injury has been established

Research agenda

- What factors are associated with receiving epidural analgesia in labour?
- What is the optimal epidural maintenance technique for both maternal and neonatal outcomes?
- Is there an association between epidural analgesia in labour and postnatal depression?
- Is there an association between epidural-related hyperthermia and neonatal brain injury?
- How can we differentiate hyperthermia secondary to infection from epidural-related hyperthermia?

Role of the funding source

The funders played no role in study design, data collection, data analysis and interpretation, in the writing of the report, nor in the decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of competing interest

DNL is President-elect of the Obstetric Anaesthetists' Association. The authors declare no other conflicts of interest.

Acknowledgements

This work was supported by Wellbeing of Women / Chief Scientist Office, Scotland (RGS2301 - grant to RK), and an NHS Research Scotland Career Researcher Fellowship (RK).

References

[1] Thomson G, Feeley C, Moran VH, et al. Women's experiences of pharmacological and non-pharmacological pain relief methods for labour and childbirth: a qualitative systematic review. Reprod Health 2019;16(1):71.

*[2] World Health Organisation. WHO recommendation on epidural analgesia for pain relief during labour. 2018. https://apps.who.int/iris/bitstream/handle/10665/272447/WHO-RHR-18.12-eng.pdf?sequence=1 [Accessed 2 September 2022].

[3] Seijmonsbergen-Schermers AE, van den Akker T, Rydahl E, et al. Variations in use of childbirth interventions in 13 high-income countries: a multinational cross-sectional study. Plos Med 2020;17(5):e1003103.

[4] Kodali BS, Jagannathan DK, Owen MD. Establishing an obstetric neuraxial service in low-resource areas. Int J Obstet Anesth 2014;23(3):267–73.

*[5] Bamber JH, Lucas DN, Plaat F, et al. The identification of key indicators to drive quality improvement in obstetric anaesthesia: results of the Obstetric Anaesthetists' Association/National Perinatal Epidemiology Unit collaborative Delphi project. Anaesthesia 2020;75(5):617–25.

[6] Lucas DN, Bamber JH. UK Confidential Enquiry into Maternal Deaths - still learning to save mothers' lives. Anaesthesia 2018;73(4):416–20.

[7] Comparative Obstetric Mobile Epidural Tial (COMET) Study Group UK. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. Lancet 2001;358(9275):19–23.

[8] Cavens L, Roofthooft E. Neuraxial labor analgesia: is there a place for neuraxial adjuvants beyond opioids. Best Pract Res Clin Anaesthesiol 2022;36(1):31–6.

[9] The Association of Anaesthetists. Guidelines for the management of severe LA toxicity. 2010. https://anaesthetists.org/Home/Resources-publications/Guidelines/Management-of-severe-local-anaesthetic-toxicity. [Accessed 2 September 2022]. Accessed.

[10] Liu X, Zhang H, Zhang H, et al. Intermittent epidural bolus versus continuous epidural infusions for labor analgesia: a meta-analysis of randomized controlled trials. PLoS One 2020;15(6):e0234353.

[11] The Association of Anaesthetists. Safety guideline: neurological monitoring associated with obstetric neuraxial block. 2020. https://anaesthetists.org/Home/Resources-publications/Guidelines/Safety-guideline-neurological-monitoring-associated-with-obstetric-neuraxial-block-2020. [Accessed 2 September 2022]. Accessed.

[12] Kearns RJ, Shaw M, Gromski PS, et al. Neonatal and early childhood outcomes following maternal anesthesia for cesarean section: a population-based cohort study. Reg Anesth Pain Med 2021;46(6):482–9.

*[13] Kearns RJ, Shaw M, Gromski PS, et al. Association of epidural analgesia in women in labor with neonatal and childhood outcomes in a population cohort. JAMA Netw Open 2021;4(10):e2131683.

[14] Palmer E, Ciechanowicz S, Reeve A, et al. Operating room-to-incision interval and neonatal outcome in emergency caesarean section: a retrospective 5-year cohort study. Anaesthesia 2018;73(7):825–31.

[15] Reynolds F. Labour analgesia and the baby: good news is no news. Int J Obstet Anesth 2011;20(1):38–50.

[16] Boney O, Bell M, Bell N, et al. Identifying research priorities in anaesthesia and perioperative care: final report of the joint national institute of academic anaesthesia/james lind alliance research priority setting partnership. BMJ Open 2015;5(12).

[17] Reynolds F. The effects of maternal labour analgesia on the fetus. Best Pract Res Clin Obstet Gynaecol 2010;24(3):289–302.

[18] Andersen LB, Melvaer LB, Videbech P, et al. Risk factors for developing post-traumatic stress disorder following childbirth: a systematic review. Acta Obstet Gynecol Scand 2012;91:1261–72.

[19] Lim G, Farrell LM, Facco FL, et al. Labor analgesia as a predictor for reduced postpartum depression scores: a retrospective observational study. Anesth Analg 2018;126(5):1598–605.

[20] Whitburn LY, Jones LE, Davey M-A, et al. The meaning of labour pain: how the social environment and other contextual factors shape women's experiences. BMC Pregnancy and Childbirth 2017;17(1):157.

[21] Ryding EL, Lukasse M, Kristjansdottir H, et al. Pregnant women's preference for cesarean section and subsequent mode of birth - a six-country cohort study. J Psychosom Obstet Gynaecol 2016;37(3):75–83.

*[22] Labour Pains. Pain relief in labour. https://www.labourpains.com/UI/Content/content.aspx?ID=46. Accessed September 4 2022.

[23] Simmons SW, Taghizadeh N, Dennis AT, et al. Combined spinal-epidural versus epidural analgesia in labour. Cochrane Database Syst Rev 2012;10(10):CD003401.

[24] Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third national Audit project of the royal College of anaesthetists. Br J Anaesth 2009;102(2):179–90.

[25] Butwick AJ, Blumenfeld YJ, Brookfield KF, et al. Racial and ethnic disparities in mode of anesthesia for cesarean delivery. Anesth Analg 2016;122(2):472–9.

[26] Guglielminotti J, Landau R, Li G. Adverse events and factors associated with potentially avoidable use of general anesthesia in cesarean deliveries. Anesthesiology (Hagerst) 2019;130(6):912–22.

[27] Klomp T, van Poppel M, Jones L, et al. Inhaled analgesia for pain management in labour. Cochrane Database Syst Rev 2012;9:CD009351.

*[28] Anim-Somuah M, Smyth RMD, Cyna AM, et al. Epidural versus non-epidural or no analgesia for pain management in labour. Cochrane Database Syst Rev 2018;21:CD000331.

[29] Smith LA, Burns E, Cuthbert A. Parenteral opioids for maternal pain management in labour. Cochrane Database Syst Rev 2018;6(6):CD007396.

[30] Weibel S, Jelting Y, Afshari A, et al. Patient-controlled analgesia with remifentanil versus alternative parenteral methods for pain management in labour. Cochrane Database Syst Rev 2017;4(4):CD011989.

[31] Wang K, Cao L, Deng Q, et al. The effects of epidural/spinal opioids in labour analgesia on neonatal outcomes: a meta-analysis of randomized controlled trials. Can J Anesth 2014;61(8):695–709.

*[32] Hattler J, Klimek M, Rossaint R, et al. The effect of combined spinal-epidural versus epidural analgesia in laboring women on nonreassuring fetal heart rate tracings: systematic review and meta-analysis. Anesth Analg 2016;123(4):955–64.

[33] Fernando R, Bonello E, Gill P, et al. Neonatal welfare and placental transfer of fentanyl and bupivacaine during ambulatory combined spinal epidural analgesia for labour. Anaesthesia 1997;52:517–24.

[34] Abrão KFR, Miyadahira S, Cicarelli DS, et al. Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. Obstet Gynecol 2009;113(1):41–7.
[35] Royal College of Obstetricians and Gynaecologists Green top guideline 64a. Bacterial sepsis in pregnancy. R Coll Obstetricians Gynaecologists. 2012; No. 64a: 1-14. https://www.rcog.org.uk/media/ea1p1r4h/gtg_64a.pdf [Accessed 4 September 2022].
[36] Jansen S, Lopriore E, Naaktgeboren C, et al. Epidural-related fever and maternal and neonatal morbidity: a systematic review and meta-analysis. Neonatology 2020;117(3):259–70.
*[37] Morton S, Kua J, Mullington CJ. Epidural analgesia, intrapartum hyperthermia, and neonatal brain injury: a systematic review and meta-analysis. Br J Anaesth 2021;126(2):500–15.
[38] Mullington CJ, Malhotra S. Hyperthermia after epidural analgesia in obstetrics. BJA Educ 2021;21(1):26–31.
[39] National Collaborating Centre for Women's and Children's Health (UK). Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection. London: RCOG Press; 2012.
[40] Sultan P, Murphy C, Halpern S, et al. The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis. Can J Anaesth 2013;60(9):840–54.
[41] Halliday L, Kinsella M, Shaw M, et al. Comparison of ultra-low, low and high concentration LA for labour epidural analgesia: a systematic review and network meta-analysis. Anaesthesia 2022;77(8):910–8.
[42] Patel NP, El-Wahab N, Fernando R, et al. Fetal effects of combined spinal-epidural vs epidural labour analgesia: a prospective, randomised double-blind study. Anaesthesia 2014;69(5):458–67.
[43] Segal S, Wang SY. The effect of maternal catecholamines on the caliber of gravid uterine microvessels. Anesth Analg 2008;106(3):888–92.
[44] Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. Am J Obstet Gynecol 2002;186(5):S69–77.
[45] Wang TT, Sun S, SQ H. Effects of epidural labor analgesia with low concentrations of local anesthetics on obstetric outcomes: a systematic review and meta-analysis of randomized controlled trials. Anesth Analg 2017;124(5):1571–80.
[46] Reynolds F, Seed PT. Anaesthesia for Caesarean section and neonatal acid-base status: a meta-analysis. Anaesthesia 2005;60(7):636–53.
[47] Ravelli ACJ, Eskes M, de Groot CJM, et al. Intrapartum epidural analgesia and low Apgar score among singleton infants born at term: a propensity score matched study. Acta Obstet Gynecol Scand 2020 Sep;99(9):1155–62.
[48] Törnell S, Ekéus C, Hultin, et al. Low Apgar score, neonatal encephalopathy and epidural analgesia during labour: a Swedish registry-based study. Acta Anaesthesiol Scand 2015;59(4):486–95.
[49] Turner J, Flatley C, Kumar S. Epidural use in labour is not associated with an increased risk of maternal or neonatal morbidity when the second stage is prolonged. Aust N Z J Obstet Gynaecol 2020;60(3):336–43.
*[50] Butwick AJ, Wong CA, Lee HC, et al. Association between neuraxial labor analgesia and neonatal morbidity after operative vaginal delivery: a retrospective cross-sectional study. Anesthesiology (Hagerst) 2021;134(1):52–60.
[51] Iliodromiti S, Mackay DF, Smith GCS, et al. Apgar score and the risk of cause-specific infant mortality: a population-based cohort study. Lancet 2014;384(9956):1749–55.
[52] Lee A, Landau R, Lavin T, et al. Comparative efficacy of epidural clonidine versus epidural fentanyl for treating breakthrough pain during labor: a randomized double-blind clinical trial. Int J Obstet Anesth 2020;42:26–33.
[53] Li N, Hu L, Li C, et al. Effect of epidural dexmedetomidine as an adjuvant to local anesthetics for labor analgesia: a meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2021;2021:4886970.
[54] Zhang N, Xu MJ. Effects of epidural neostigmine and clonidine in labor analgesia: a systematic review and meta-analysis. J Obstet Gynaecol Res 2015;41(2):214–21.
[55] Kan RE, Hughes SC, Rosen MA, et al. Intravenous remifentanil: placental transfer, maternal and neonatal effects. Anesthesiology 1998;88(6):1467–74.
[56] Wilson MJA, MacArthur C, Hewitt CA, et al. Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): an open-label, multicentre, randomised controlled trial. Lancet 2018;392(10148):662–72.
[57] Lu G, Yao W, Chen X, et al. Remifentanil patient-controlled versus epidural analgesia on intrapartum maternal fever: a systematic review and meta-analysis. BMC Pregnancy Childbirth 2020;20(1):151.
[58] Liu ZQ, Chen XB, Li HB, et al. A comparison of remifentanil parturient-controlled intravenous analgesia with epidural analgesia: a meta-analysis of randomized controlled trials. Anesth Analg 2014;118(3):598–603.
[59] World Health Organisation. Essential nutrition actions: improving maternal, newborn, infant and young child health and nutrition. 2013. https://www.who.int/publications/i/item/9789241505550. [Accessed 4 September 2022]. Accessed.
[60] Payne S, Quigley MA. Breastfeeding and infant hospitalisation: analysis of the UK 2010 infant feeding survey. Matern Child Nutr 2017;13(1):e12263.
[61] Sankar MJ, Sinha B, Chowdhury R, et al. Optimal breastfeeding practices and infant and child mortality: a systematic review and meta-analysis. Acta Paediatr 2015;104(467):3–13.
[62] French CA, Cong X, Chung KS. Labor epidural analgesia and breastfeeding: a systematic review. J Hum Lact 2016;32(3):507–20.
[63] Lee AI, McCarthy RJ, Toledo P, et al. Epidural labor analgesia-fentanyl dose and breastfeeding success: a randomized clinical trial. Anesthesiol 2017;127(4):614–24.
[64] Ding T, Wang DX, Qu Y, et al. Epidural labor analgesia is associated with a decreased risk of postpartum depression: a prospective cohort study. Anesth Analg 2014;119(2):383–92.
[65] Almeida M, Kosman KA, Kendall MC, et al. The association between labor epidural analgesia and postpartum depression: a systematic review and meta-analysis. BMC Womens Health 2020;20(1):99.
[66] Kountanis JA, Vahabzadeh C, Bauer S, et al. Labor epidural analgesia and the risk of postpartum depression: a meta-analysis of observational studies. J Clin Anesth 2020;61:109658.
*[67] Flick RP, Lee K, Hofer RE, et al. Neuraxial labor analgesia for vaginal delivery and its effects on childhood learning disabilities. Anesth Analg 2011;112(6):1424–31.

[68] Deng CM, Ding T, Liu ZH, et al. Impact of maternal neuraxial labor analgesia exposure on offspring's neurodevelopment: a longitudinal prospective cohort study with propensity score matching. Front Public Health 2022;10:831538.
*[69] Butwick AJ, Abrams DA, Wong CA. Epidural labour analgesia and autism spectrum disorder: is the current evidence sufficient to dismiss an association? Br J Anaesth 2022;128(3):393–8.
[70] Sauer AK, Stanton JE, Hans S, et al. Autism spectrum disorders: etiology and pathology. In: Grabrucker AM, editor. Autism spectrum disorders. Brisbane (AU): Exon Publications; 2021.
[71] Haar S, Berman S, Behrmann M, et al. Anatomical abnormalities in autism? Cereb Cortex 2016;26(4):1440–52.
[72] Mohammad-Rezazadeh I, Frohlich J, Loo SK, et al. Brain connectivity in autism spectrum disorder. Curr Opin Neurol 2016;29(2):137–47.
[73] Guang S, Pang N, Deng X, et al. Synaptopathology involved in autism spectrum disorder. Front Cel Neurosci 2018;12:470.
[74] Rogers GB, Keating DJ, Young RL, et al. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol Psychiatry 2016;21(6):738–48.
[75] Yuan X, Nan Z, Wei Z, et al. Bupivacaine indirectly potentiates glutamate-induced intracellular calcium signaling in rat hippocampal neurons by impairing mitochondrial function in cocultured astrocytes. Anesthesiology 2018;128:539–54.
[76] Zhiliang G, Yuanyuan L, Min C. Resveratrol protects bupivacaine-induced neuro-apoptosis in dorsal root ganglion neurons via activation on tropomyosin receptor kinase A. Biomed Pharmacother 2018;103:1545–51.
[77] Golub MS, Germann SL. Perinatal bupivacaine and infant behavior in rhesus monkeys. Neurotoxicol Teratol 1998;20(1):29–41.
[78] Golub MS, Kaaekuahiwi MA, Eisele PH, et al. Newborn tissue concentrations of bupivacaine following maternal epidural administration during labor in Guinea pigs. Biol Neonate 1998;74(4):304–13.
[79] Decocq G, Brazier M, Hary L, et al. Serum bupivacaine concentrations and transplacental transfer following repeated epidural administrations in term parturients during labour. Fundam Clin Pharmacol 1997;11:365–70.
[80] Van Zundert A, Burm A, Van Kleef, et al. Plasma concentrations of epidural bupivacaine in mother and newborn: 0.125% versus 0.375. Anesth Analgesia 1987;66(5):435–41.
[81] Duarte LdB, Móises ECD, Cavalli RC, et al. Distribution of bupivacaine enantiomers and lidocaine and its metabolite in the placental intervillous space and in the different maternal and fetal compartments in term pregnant women. J Clin Pharmacol 2011;51:212–7.
[82] Qiu C, Lin JC, Shi JM, et al. Association between epidural analgesia during labor and risk of autism spectrum disorders in offspring. JAMA Pediatr 2020;174(12):1168–75.
[83] Joint Statement of the Society for Obstetric Anesthesia and Perinatology, American Society of Anesthesiologists, Society for Pediatric Anesthesia, American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine. Labor Epidurals Do Not Cause Autism; Safe for Mothers and Infants, say Anesthesiology, Obstetrics, and Pediatric Medical Societies. https://www.asahq.org/about-asa/newsroom/news-releases/2020/10/labor-epidurals-and-autism-joint-statement Accessed September 5 2022.
[84] Mikkelsen AP, Greiber IK, Scheller NM, et al. Association of labor epidural analgesia with autism spectrum disorder in children. JAMA 2021;326(12):1170–7.
[85] Wall-Wieler E, Bateman BT, Hanlon-Dearman A, et al. Association of epidural labor analgesia with offspring risk of autism spectrum disorders. JAMA Pediatr 2021;175(7):698–705.
[86] Hanley GE, Bickford C, Ip A, et al. Association of epidural analgesia during labor and delivery with autism spectrum disorder in offspring. JAMA 2021;326(12):1178–85.
[87] Ren T, Zhang J, Yu Y, et al. Association of labour epidural analgesia with neurodevelopmental disorders in offspring: a Danish population-based cohort study. Br J Anaesth 2022;128(3):513–21.