# **REVIEW ARTICLE**

Obstetrics





# Epidural analgesia in labor: A narrative review

Lucy Halliday 💿 🕴 Scott M. Nelson 🕴 Rachel J. Kearns

School of Medicine, University of Glasgow, Glasgow, UK

#### Correspondence

Lucy Halliday, School of Medicine, University of Glasgow, 2nd Floor, Lister Building, Glasgow Royal Infirmary, 10-16 Alexandra Parade, Glasgow G31 2ER, UK. Email: lucy.halliday@glasgow.ac.uk

#### **Funding information**

Department of Health; National Institute for Health Research: National Institute of Academic Anesthesia

# Abstract

Lumbar epidural is the most effective form of pain relief in labor with around 30% of laboring women in the UK and 60% in the USA receiving epidural analgesia. Associations of epidural on maternal, obstetric, and neonatal outcomes have been the subject of intense study, though a number of uncertainties persist. The present narrative review explores important areas of research surrounding epidural analgesia in obstetric patients including methods of initiation and administration, choice of local anesthetic solution, and the addition of adjuvants. Key meta-analyses exploring associations of epidural analgesia on maternal and neonatal outcomes are identified and summarized.

### KEYWORDS

epidural, labor analgesia, maternal outcomes, neuraxial, obstetric analgesia, obstetric outcomes

#### INTRODUCTION 1

Lumbar epidural is considered the gold standard for analgesia in labor and is recommended by WHO, with estimates of use in the range of 10%–64% in high-income countries.<sup>1</sup> During labor, uterine contraction and cervical dilatation stimulate nociceptive afferent fibers that travel to spinal nerves T10-L1, producing poorly localized visceral pain. As the fetal head descends, stretching the perineum and vagina, pain fibers via the pudendal nerve and spinal roots S2-4 are also activated.<sup>2</sup> To modify these afferent pathways and achieve analgesia, local anesthetics, opioids, and other adjuvants can be administered to the epidural space by an epidural catheter.

Despite widespread use, there are many uncertainties regarding the optimal epidural regime. Different combinations and concentrations of drugs administered epidurally have been shown to have varying effects in both the partum and postpartum periods. With so many variables surrounding childbirth, it can be difficult to separate association and causation. Epidurals are associated with, but probably do not cause, prolonged labor and increased risk of operative delivery.<sup>3</sup> These factors directly affect obstetric decision making. For certain maternal conditions that may be decompensated by labor and delivery, such as pre-eclampsia or cardiac disease, labor epidural

is indicated. In cases where epidural is contraindicated (such as severe thrombocytopenia, coagulopathy, or sepsis) other analgesic regimes (e.g. patient-controlled remifentanil) may be available.

Improving communication and understanding between anesthetists and obstetricians is mutually beneficial. The aim of the present narrative review was to provide an overview of epidural literature for the obstetric audience, incorporating techniques of insertion, medications used, and associations with maternal and neonatal outcomes. Spinal anesthesia, and the use of epidural anesthesia for cesarean/ operative delivery are outwith the scope of the present review.

#### **METHODS** 2

# 2.1 | Search strategy

A literature search without language restriction was conducted (MEDLINE Ovid, Embase Ovid, CINAHL EBSCO, and Cochrane Central Register of Controlled Trials [CENTRAL]) from date of inception to October 5, 2020. Randomized controlled trials (RCTs), reviews, and relevant references were included. Search terms were "neuraxial analgesia," "epidural," "peridural," "combined spinal-epidural," "CSE,"

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

356

<sup>© 2022</sup> The Authors. International Journal of Gynecology & Obstetrics published by John Wiley & Sons Ltd on behalf of International Federation of Gynecology and Obstetrics.

"obstetric analgesia," "labor analgesia," and "labor pain." Relevant articles were obtained, and the reference sections of these articles were reviewed to identify additional relevant literature.

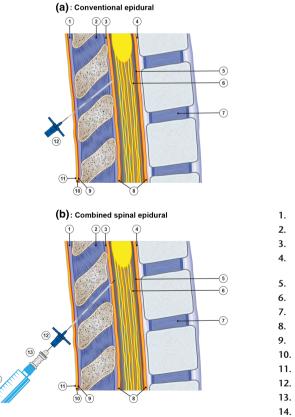
The population of interest was women receiving epidural analgesia for labor. All obstetric, maternal, neonatal, and early childhood outcomes were considered. This article was prepared using the SARNA guidelines for quality assessment of narrative review articles.<sup>4</sup>

# 2.2 | Epidural anatomy and insertion techniques

The epidural space is a potential space containing fat, blood vessels, and spinal nerve roots and lies between the ligamentum flavum and dura mater (Figure 1).<sup>2</sup> The spinal cord ends around L1/L2 and becomes a loose bundle of intradural nerves, the cauda equina. Labor epidurals are sited below the level of the spinal cord to minimize risk of nerve injury. Before insertion of the epidural, parturients should be counseled on the risks and benefits (Table 1). As pain and analgesic agents may influence the ability to give informed consent during labor, this should be initially discussed during the antenatal period as part of a delivery plan. There are two well-established techniques for initiating labor epidural analgesia: conventional lumbar epidural and combined spinal epidural (CSE).

# 2.3 | Conventional lumbar epidural

Epidurals are most commonly inserted using a Tuohy needle and "loss of resistance technique." A low resistance syringe containing a column of saline or air is attached to the Tuohy needle after insertion into the inter-spinous ligaments. Continuous pressure is applied to the plunger of the syringe as the needle is slowly advanced. A sudden loss of resistance as the needle exits the ligamentum flavum identifies the epidural space. In conventional lumbar epidural, once the epidural space is identified, a thin catheter is threaded through the hollow Tuohy needle to lie 3-5 cm within the epidural space, and the needle removed. The epidural catheter lies near the T10-L1 nerve roots, providing excellent coverage for the first stage of labor. The sacral nerve roots lie further away from the epidural catheter and therefore second-stage analgesia may be less effective.<sup>2</sup> An initial "test dose" of local anesthetic is given, and the patient is closely observed to assess for inadvertent intrathecal placement (effects more in keeping with spinal anesthesia) or intravascular placement (signs of local anesthetic toxicity). Identification of the epidural space can be technically challenging and even when inserted without difficulty, unilateral block and missed segments can result in inadequate analgesia in up to one in eight women.<sup>2</sup>



- 1. Supraspinous ligament
- 2. Interspinous ligament
- 3. Ligamentum flavum
- 4. Posterior longitudinal ligament
- 5. Dura mater
- 6. Cauda equina
- 7. Intervertebral discs
- 8. Epidural space
- 9. Muscle
- 10. Fat
- 11. Skin
- 12. Tuohy needle
- 13. Spinal needle
- 14. Intrathecal medication

**FIGURE 1** (a) Conventional epidural catheter insertion and (b) combined spinal epidural. (a) The Tuohy needle within the epidural space before threading of epidural catheter through the hollow Tuohy needle to lie within the epidural space demonstrates (b) the Tuohy needle within the epidural space and the spinal needle puncturing the dura mater and the delivery of intrathecal medication into the subarachnoid space

UFV- GYNECOLOG TABLE 1 Counseling women before insertion of labor epidural<sup>a</sup>

····			
Risk	Frequency		
Additional pain relief required on top of epidural	1 in 8		
Epidural not functioning well enough for cesarean delivery—require a spinal or general anesthetic	1 in 20		
Significant drop in blood pressure	1 in 50		
Severe headache	1 in 100		
Temporary nerve damage (e.g. patch of numbness on leg or weakness in leg)	1 in 1000		
Permanent nerve damage	1 in 13000		
Epidural abscess (infection)	1 in 50000		
Meningitis	1 in 100000		
Epidural hematoma (blood clot)	1 in 170000		
Severe injury (including paralysis)	1 in 250000		

<sup>a</sup>Before insertion of the epidural, women should be counseled on the risks and benefits of the procedure. Information leaflets can be downloaded from www.labourpains.com-the public information website of the Obstetric Anesthetists' Association (OAA). These leaflets are currently available in up to 40 languages. In addition, the anesthetics performing the procedure should discuss the risks with the parturients and allow the opportunity for questions.

#### 2.4 **Combined spinal epidural**

In the needle-through-needle technique of CSE, the dura mater is intentionally punctured with a spinal needle after the epidural space is identified. Intrathecal drugs are administered before threading the epidural catheter into the epidural space (Figure 1).<sup>2,5</sup> CSE has potential advantages of rapid-onset analgesia, improved sacral analgesia, reduced failure rate, and high maternal satisfaction. Furthermore, CSE may be advantageous for anesthesia in the high-risk parturient (e.g. cardiac disease) where gradual and incremental onset of sympathetic block is desirable. CSE is more technically challenging than conventional lumbar epidural and is associated with a higher incidence of permanent neurological complications (9.6/100000 vs 6.1/100000 for conventional lumbar epidural).<sup>6</sup> A 2016 systematic review and meta-analysis comparing CSE and conventional lumbar epidural demonstrated a significantly increased risk of nonreassuring fetal heart rate (FHR) tracings with CSE (relative risk [RR] 1.31, 95% confidence interval [CI] 1.02–1.67).<sup>7</sup> CSE remains a popular technique in some centers, though there is insufficient evidence to suggest it should replace conventional lumbar epidural for analgesia in labor.<sup>5</sup>

#### 2.5 Ultrasound

Palpation of bony landmarks is traditionally used to identify a site for epidural insertion. Identifying a space can be challenging, especially in patients with obesity, scoliosis, or previous spinal surgery. A study in non-obstetric patients assessing the ability of anesthesiologists to identify a lumbar interspace found that the correct interspace was identified in just 29% of cases with

68% being one or more vertebral spaces higher than predicted, increasing the potential risk of neurological injury.<sup>8</sup> This may be even more challenging in obstetric patients due to the limitation of a gravid uterus on forward flexion. Ultrasound can be used as a pre-procedural tool to identify specific intervertebral spaces and depth of epidural and intrathecal spaces. Three meta-analyses have investigated the use of pre-procedural ultrasound for epidural. A meta-analysis of 14 RCTs (eight obstetric epidural, three orthopedic spinal, and three lumbar puncture, 1786 patients in total) found a 49% reduction in procedural failure and a significantly reduced number of needle passes (mean difference 0.75) with pre-procedural ultrasound compared to palpation alone, though data for the obstetric subgroup were not provided. They also found a non-significant trend towards a lower incidence of headache and backache but did not provide results for analgesic efficacy.<sup>9</sup> A 2020 meta-analysis (18 RCTs, 1844 obstetric patients) looked at the effect of ultrasound on first pass success rate for neuraxial analgesia in non-urgent obstetric patients. In a subgroup of patients receiving epidural or CSE, the first pass success rate was equivocal for epidural (RR 1.20, 95% CI 0.88-1.64) but improved with use of ultrasound for CSE placement (RR 1.63, 95% CI 1.18-2.25). Incidence of vascular puncture was reduced with ultrasound in the combined epidural/CSE subgroup (RR 0.39, 95% CI 0.18–0.89), though quality of anesthesia was not mentioned.<sup>10</sup> A further meta-analysis looking at epidural, but not limited to obstetric patients (nine studies, 1014 patients), looked at efficacy, including requirement for replacement for operative delivery of labor analgesia and ability to place the catheter. Pre-procedural ultrasound reduced the risk of both failed epidural (mean difference [MD] 0.23, 95% CI 0.09-0.60) and of traumatic insertion of epidural (MD 0.28, 95% CI 0.09-0.92).<sup>11</sup> Guidelines from the National Institute for Health and Care Excellence endorse the use of pre-procedural ultrasound.<sup>12</sup>

#### 2.6 **Epidural agents**

Once an epidural catheter has been inserted, local anesthesia, with or without adjuvant medications, are used to provide analgesia. In the UK, levobupivacaine with fentanyl is most commonly used,<sup>13</sup> but there is no universally accepted standard injectate to optimize analgesia and avoid adverse outcomes.

#### Local anesthetics 2.7

Bupivacaine, levobupivacaine, and ropivacaine are most commonly used for labor epidural analgesia.<sup>13</sup> Levobupivacaine and bupivacaine are almost equipotent<sup>14,15</sup> and produce a dosedependent motor block. Ropivacaine has a relative potency of 0.6 when compared to bupivacaine, is less cardiotoxic/neurotoxic, and is associated with less motor block.<sup>16</sup> When ropivacaine and bupivacaine are used in equipotent doses, the incidence of adverse

obstetric, neonatal, and maternal outcomes, including motor block, are similar.<sup>16</sup>

Historically, labor epidurals were maintained with 0.25% bupivacaine. In 2001, the COMET trial enrolled 1054 nulliparous women and randomized them to "traditional" epidural management (0.25% bupivacaine), low dose epidural, or low dose CSE using 0.1% bupivacaine combined with 2  $\mu$ g/ml fentanyl.<sup>17</sup> Techniques utilizing the lower concentration of local anesthesia were associated with a reduction in the rate of assisted vaginal delivery (AVD) with no compromise in analgesia. This difference was attributed to the preservation of motor tone, shorter second stage of labor, and reduced total dose of local anesthetic.<sup>17</sup> Since 2001, the use of lower concentrations of local anesthesia has increased, and a 2014 survey by the Obstetric Anesthetists' Association found that 0.1% bupivacaine was the standard concentration used in the UK.<sup>13</sup>

# 2.8 | Opioids

Epidural opioids act synergistically with local anesthetics. The minimum local analgesic concentration (MLAC) is the median effective concentration to produce analgesia. MLAC studies are used to compare relative potencies of local anesthesia and the effect of adding adjuvant medications. Fentanyl is short-acting and reduces the MLAC of bupivacaine by 31%–72% depending on the dose used.<sup>18</sup> Sufentanil has a more rapid onset, shorter duration of action, and is 4.5 times more potent than fentanyl, reducing the MLAC of bupivacaine by up to 91%.<sup>19</sup> Diamorphine and morphine are long-acting opiates and are less suitable for epidural maintenance solutions. Epidural opioids can also be used in bolus doses for rescue analgesia.<sup>20</sup>

Non-opioid adjuvants may be added to the epidural solution to prolong duration and limit overall dose of local anesthesia, thus reducing the incidence of dose-dependent side effects. These additional adjuncts may be beneficial in parturients who wish to avoid exposure to opioids.

#### 2.9 | Adrenaline

The effects of adrenaline are thought to be due to both alphareceptor activation and limiting the systemic absorption of local anesthesia by local vasoconstriction.<sup>21</sup> Adrenaline is associated with reduced MLAC, and increased duration of action/reduced cumulative dose of local anesthesia. It is not commonly used for labor analgesia.

# 2.10 | Clonidine

Clonidine is an alpha-2 receptor agonist which can be given via the epidural route, reducing requirements for local anesthesia by around 30%, and increasing duration of anesthesia with or without opioids.<sup>22</sup> Despite concerns about side effects of hypotension, 🛞-WILEY-

bradycardia, and maternal sedation, a RCT of 98 parturients found no difference in analgesic efficacy between clonidine/bupivacaine and fentanyl/bupivacaine and no difference in adverse outcomes.<sup>22</sup>

## 2.11 | Neostigmine

Neostigmine prevents the breakdown of acetylcholine, which stimulates production of nitric oxide in the spinal cord, providing analgesia. It can cause nausea but is not associated with respiratory depression or pruritis. A meta-analysis of 16 RCTs (1183 parturients) found that neostigmine reduced consumption of local anesthesia with no increased risk of adverse neonatal outcomes.<sup>23</sup> This evidence supports a potential role for neostigmine in patients wishing to avoid opioids.

# 3 | DRUG DELIVERY SYSTEMS

Epidural drug delivery systems affect the efficacy of analgesia. Intermittent bolus, continuous infusion, patient-controlled epidural analgesia (PCEA), and computer integrated patient-controlled epidural analgesia (CIPCEA) have been described.<sup>24-26</sup> A meta-analysis of 22 RCTs (2573 parturients) comparing intermittent physician bolus with continuous infusion epidurals identified a significantly longer duration of labor in patients receiving continuous epidural infusion (weighted MD 21.46 minutes, 95% CI 25.07–17.85). Intermittent bolus regimes were associated with a reduction in anesthetic interventions for pain, reduced dose of local anesthesia, and improved maternal satisfaction. There was no significant difference observed in adverse events nor mode of delivery.<sup>24</sup>

PCEA may improve maternal satisfaction and reduce total dose of local anesthesia.<sup>27</sup> It can be used with or without continuous background infusion or intermittent clinician-delivered boluses. The addition of a background infusion increases the risk of AVD and prolongs the second stage of labor; however, it reduces the number of rescue doses required when compared to PCEA alone.<sup>26</sup> CIPCEA automatically adjusts a continuous background infusion based upon PCEA requirements. Only small trials have been conducted and more research into this delivery system is required.<sup>25</sup>

# 4 | OBSTETRIC OUTCOMES

#### 4.1 | Mode of delivery

Rates of AVD are falling independently with use (or not) of epidural analgesia.<sup>28</sup> This is accompanied by a worldwide annual increase in rates of cesarean delivery of 4%.<sup>3,29</sup> Three key metaanalyses have explored the influence of epidural analgesia on mode of delivery (Table 2). A Cochrane meta-analysis looking at epidural versus no epidural (40 RCTs, 11000 parturients) found an increased duration of both the first and second stages of labor TABLE 2 Key systematic reviews/meta-analyses reviewing associations of labor epidural analgesia on outcomes

 $(\hat{\mathbf{x}})$ 

360

-WILEY- GYNECOLOGY OBSTETRICS

Name, authors, and year of publication	Trials and participants	Key findings
Epidural versus non-epidural or no analgesia for pain management in labour. Anim- Somuah et al. (2018) <sup>3</sup>	40 RCTs >11000 parturients	<ul> <li>Epidural compared to systemic opioids (34 trials):</li> <li>1. Lower pain scores</li> <li>2. Higher maternal satisfaction</li> <li>3. Less additional pain relief</li> <li>4. Longer first and second stages of labor</li> <li>5. Increased risk of AVD; however, a subgroup analysis excluding trials conducted before 2005 found no significant difference</li> <li>6. More hypotension, motor block, fever, and urinary retention</li> <li>7. Less respiratory depression, less nausea and vomiting</li> <li>8. Neonate less likely to receive naloxone</li> <li>9. No difference for rates of cesarean delivery, long-term maternal backache, or neonatal outcomes</li> <li>Epidural compared to no analgesia—seven trials</li> <li>1. Less pain reported</li> <li>2. Few trials reported on maternal side effects</li> </ul>
Effects of epidural labor analgesia with low concentrations of local anesthetics on obstetric outcomes: a systematic review and meta-analysis of randomized controlled trials. Wang et al. (2017) <sup>14</sup>	10 RCTs 1809 parturients	No significant difference between groups in: 1. Duration of the first or second stage of labor 2. Rate of instrumental birth 3. Rate of cesarean delivery 4. Rates of spontaneous vaginal delivery
Combined spinal-epidural versus epidural analgesia in labor. Simmons et al. (2012) <sup>5</sup>	27 RCTs 3274 parturients	<ul> <li>CSE versus traditional epidural:</li> <li>1. CSE has a faster speed of onset of analgesia from time of injection</li> <li>2. CSE is less likely to need rescue analgesia</li> <li>3. CSE is less likely to go into urinary retention</li> <li>4. CSE has a lower rate of instrumental delivery</li> <li>5. Traditional epidural was more favorable in relation to umbilical venous pH</li> <li>CSE versus low-dose epidural:</li> <li>1. Faster onset of effective analgesia from time of injection with CSE</li> <li>2. More pruritus with CSE compared to low-dose epidural</li> <li>No significant difference in maternal satisfaction, need for rescue analgesia, mobilization in labor, incidence of post dural puncture headache, known dural tap, blood patch for post dural headache, urinary retention, nausea/vomiting, hypotension, headache, the need for labor augmentation, mode of delivery, umbilical pH, Apgar score, or admissions to the neonatal unit</li> </ul>
The effect of combined spinal-epidural versus epidural analgesia in laboring women on nonreassuring fetal heart rate tracings: Systematic review and meta- analysis. Hattler et al. (2016) <sup>7</sup>	17 RCTs 3947 parturients	<ul> <li>CSE showed an increased risk of non-reassuring FHR tracings overall and in two subgroup analyses:</li> <li>1. Compared to conventional epidural (both high- and low-dose epidural) (RR 1.31, P = 0.03)</li> <li>2. Subgroup analysis of 10 trials using low-dose epidural (RR 1.12, P = 0.12)</li> <li>3. Sensitivity analysis of low-dose epidural bupivacaine studies that ensured blinding of the outcome assessor (RR 1.41, P = 0.06)</li> </ul>
Intermittent epidural bolus versus continuous epidural infusions for labor analgesia: A meta-analysis of randomized controlled trials. Liu et al. (2020) <sup>24</sup>	22 RCTs 2573 parturients	<ul> <li>No significant differences for the incidences of cesarean or AVD or risk of adverse events</li> <li>Intermittent bolus technique associated with:</li> <li>1. Shorter duration of the total, first and second of stages of labor</li> <li>2. Fewer anesthetic interventions</li> <li>3. Lower hourly consumption of local anesthetic</li> <li>4. Better maternal satisfaction</li> </ul>
Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a meta-analysis. Van der Vyver et al. (2002) <sup>27</sup>	9 RCTs 640 parturients	Compared to continuous infusion group, the PCEA group had: 1. Fewer anesthetic interventions 2. Lower total dose of local anesthetic 3. Fewer motor blocks

T,	AΒ	LE	2	(Continued)
----	----	----	---	-------------

HALLIDAY ET AL.

Name, authors, and year of publication	Trials and participants	Key findings
The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis. Sultan et al. (2013) <sup>15</sup>	11 RCTs 1997 parturients	<ul> <li>Compared to high concentration, low concentration local anesthetics are associated with:</li> <li>1. Reduced incidence of AVD</li> <li>2. Shorter second stage of labor</li> <li>3. Fewer motor blocks</li> <li>4. Less urinary retention</li> <li>5. More pruritis</li> <li>6. Greater incidence of 1-min Apgar score &lt;7</li> <li>No significant differences for incidence of cesarean delivery, pain scores, maternal nausea and vomiting, hypotension, FHR abnormalities, 5-min Apgar scores, or need for neonatal resuscitation</li> </ul>
The effects of epidural/spinal opioids in labor analgesia on neonatal outcomes: a meta-analysis of randomized controlled trials. Wang et al. (2014) <sup>30</sup>	21 RCTs 2859 parturients	<ul> <li>Neonates whose mother received neuraxial opiates in labor compared to those not receiving neuraxial opioids:</li> <li>1. No difference in Apgar score &lt;7 at 1 min</li> <li>2. No difference in Apgar score &lt;7 at 5 min</li> <li>3. No significant differences were found in umbilical cord arterial or venous pH</li> </ul>

Abbreviations: AVD, assisted vaginal delivery; CSE, combined spinal epidural; FHR, fetal heart rate; PCEA, patient-controlled epidural analgesia; RCT, randomized controlled trial.

with epidural.<sup>3</sup> A statistically significant increase in rates of AVD with epidural was reported, but this association disappeared when studies before 2005 were excluded (when higher-dose epidural regimes were common practice).<sup>3</sup> There was no difference in rates of cesarean delivery. Overall, the authors commented on the low methodological quality due to limitations of study design and possible publication bias. A further meta-analysis (11 RCTs, 1997 women) comparing low-concentration (≤0.1% bupivacaine) and high-concentration (>0.1% bupivacaine) epidurals found that lower concentration local anesthesia reduced the duration of the second stage of labor and incidence of AVD (odds ratio [OR] 0.70) but did not alter rates of cesarean delivery.<sup>15</sup> A third metaanalysis (10 RCTs, 1809 women) compared low-dose epidural with no epidural and found no statistically significant differences.<sup>14</sup> Collectively, these trials suggest that the concentration of local anesthesia has a significant effect on duration of labor and rate of AVD but not of cesarean delivery. These meta-analyses contain a large number of small studies of variable methodological quality.

Studies comparing low (~0.1%) with very low concentrations of bupivacaine/levobupivacaine (0.0568%-0.0625%) support the finding of reduced incidence of AVD with lower concentrations.<sup>30</sup> More research is needed to determine whether further reducing the concentration of local anesthesia will improve outcomes.

#### 5 | MATERNAL OUTCOMES

# 5.1 | Adverse effects

Epidurals reduce ambulation, which is known to shorten labor time, and reduce the need for analgesia. Furthermore, women may find excessive motor and sensory block uncomfortable.<sup>5</sup> Blockade of autonomic nerves may also cause hypotension and FHR abnormalities.<sup>7</sup> If epidural opioids are used, pruritus is a common side effect, affecting 60%–100% of parturients, which may require symptom control with antihistamines or, in severe cases, opioid receptor antagonists, e.g. naloxone.<sup>31</sup> Epidural opioids are also associated with nausea/vomiting and urinary retention, affecting 30% and 21%–53% of recipients, respectively, in a dosedependent manner.<sup>31</sup>

#### 5.2 | Maternal satisfaction

Uncontrolled labor pain significantly affects maternal satisfaction (independent of mode of delivery) but analgesia is only one component of maternal satisfaction.<sup>32</sup> A RCT comparing three different concentrations of local anesthetic found that the lowest concentration was associated with higher pain scores, but maternal satisfaction scores were unaffected.<sup>30</sup> This is consistent with a prospective study (294 women) that used 0.0625% bupivacaine with fentanyl and found that although almost one-quarter of women required a clinician-administered top-up, 92% were satisfied with their labor analgesia. Overweight women and those undergoing induced labor showed lower rates of maternal satisfaction.<sup>32</sup> Other factors influencing maternal satisfaction included quality of caregiver-patient relationship and involvement in decision making.<sup>32</sup>

### 5.3 | Maternal hyperthermia

Maternal hyperthermia may be caused by intrapartum events such as infection and obstructed labor and is strongly associated with poorer neonatal neurological outcome.<sup>33</sup> It is unclear whether this is due to hyperthermia itself exacerbating an energy WILEY- GYNECOLOGY OBSTETRICS

deficit in the fetus, or maternal proinflammatory mediators triggering an inflammatory response in the fetus. Epidural hyperthermia affects one in five women receiving epidural analgesia, with risk increasing as duration of infusion increases.<sup>34</sup> The etiology is not understood though there are two main theories: sympathetic blockade and immunomodulation. Blockade of sympathetic nerves may prevent vasodilatation and sweating, thus reducing heat loss.<sup>34</sup> The immunomodulation theory suggests that temperature increase is centrally mediated and driven by proinflammatory mediators triggered by epidural medications.<sup>34</sup> These two theories are not mutually exclusive and may both contribute to the development of hyperthermia. The use of epidural analgesia does not increase the risk of intrapartum infection.<sup>34</sup> which affects approximately 5% of parturients and is associated with poorer neonatal outcomes. Around one-quarter of hyperthermic women with epidurals have concurrent intrapartum infection<sup>34</sup> and the two pathologies can be difficult to distinguish. It is unclear whether epidural hyperthermia itself has negative consequences for the neonate. A recent systematic review identified two observational studies that have attempted to address this guestion.<sup>33</sup> A Swedish retrospective population study (294329 women) found that epidural hyperthermia was associated with lower Apgar scores at 5 min, but not with the neonatal encephalopathy classically associated with maternal fever (OR 1.11, 95% CI 0.96-1.29).<sup>35</sup> A retrospective regression analysis of 1246 women who received epidural and were pyrexial found that increasing maximum maternal intrapartum temperature was associated with adverse neonatal outcomes, including a significantly increased risk of neonatal seizures (>101°F vs <99.5°F; OR 6.5, no confidence interval provided). However, the actual number of events was very small (n = 8) and the group not receiving epidural was excluded due to inadequate patient numbers.<sup>36</sup> This is a key knowledge gap that needs addressing.<sup>33</sup>

# 5.4 | Postpartum depression

Labor is one of the most painful human experiences, with the effectiveness of labor analgesia potentially contributing to the longerterm emotional and psychological state of the mother and their initial interaction with their newborn.<sup>37</sup> Uncontrolled pain during childbirth is a well-established risk factor for the development of postpartum depression but there is limited information on whether epidural positively or negatively impacts on its development.<sup>37</sup>

# 6 | OFFSPRING OUTCOMES

Both local anesthetics and opioids can cross the placenta and can be detected in the umbilical vein and neonatal urine after delivery.<sup>38</sup> These drugs may accumulate and lead to neonatal depression due to ion-trapping in the more acidic fetal circulation and impaired clearance due to immature liver enzymes.<sup>38</sup> Epidural is associated with a reduction in uterine artery blood flow during contractions, even when using low concentrations of local anesthetic. This does not appear to be associated with any significant difference in Apgar score or degree of neonatal acidosis<sup>39</sup> though studies are small and inadequately powered to find these differences. There is evidence that labor epidural analgesia makes little or no difference to FHR abnormalities, need for neonatal resuscitation, 5-min Apgar scores, nor rates of admission to neonatal intensive care.<sup>3,15</sup> There is, however, contradictory evidence about the effect of epidural on 1-min Apgar score. In a meta-analysis of high- versus low-concentration local anesthetic, 1-min Apgar scores favored the higher concentration of local anesthetics (OR 1.53, 95% CI 1.07-2.21). This was hypothesized to be due to the addition of epidural fentanyl in the lower concentration group<sup>15</sup>; however, a 2014 meta-analysis (21 trials, 2859 participants) found no significant differences in Apgar score below 7 at 1 or 5 min between patients receiving epidural or spinal opioid compared to those who received no epidural/spinal opioid.<sup>20</sup>

# 6.1 | Breastfeeding

Breastfeeding has significant well-established benefits for both the neonate and the mother.<sup>40</sup> Epidural analgesia can modify the stress response in labor in women, which may increase levels of oxytocin and chances of breastfeeding success. However, potential prolongation of labor, mode of delivery, and adverse neonatal outcomes may negatively impact on breastfeeding behaviors. Overall, the literature on epidurals and breastfeeding has largely been limited to observational studies, or small RCTs, but is reassuring with limited evidence of a detrimental effect.<sup>40</sup>

# 7 | LONG-TERM CHILDHOOD OUTCOMES

Studies with long-term follow-up of offspring after maternal epidural analgesia in labor are limited. An American cohort study of 4684 mother-baby pairs (1495 of whom received epidural analgesia) found no significant difference in the presence of learning difficulties before the age of 19 years.<sup>41</sup> A well-publicized retrospective cohort study of almost 150000 children born vaginally showed a 37% relative increase in the risk of developing autism in babies whose mothers had epidural analgesia compared to those without epidural analgesia.<sup>42</sup> That study was widely criticized by professional bodies including the Royal College of Anesthetists and the American Society of Anesthesiologists<sup>43</sup> for the lack of adjustment for important confounders such as duration of labor, fetal distress, and method of delivery. A Canadian population-based study (123175 children), which performed robust correction for confounding variables, found no association between labor epidural and autism.<sup>43</sup> A more recent analysis of 435 281 births in Scotland, including 94 323 patients receiving epidural in labor, also found no adverse impact on neurodevelopment at the age of 2 years.<sup>41</sup> Further studies assessing longer-term outcomes are warranted.

# 8 | CONCLUSION

Lumbar epidural provides highly effective labor analgesia and has become the benchmark against which other forms of analgesia are compared. Despite this, research into labor epidural analgesia is heterogeneous with no universally agreed standard technique and inconsistency in outcome reporting. Data on epidural hyperthermia, breastfeeding, postpartum depression, and longer-term childhood developmental outcomes are lacking. Future research should focus on addressing these issues.

#### ACKNOWLEDGMENTS

This work was supported by the National Institute of Academic Anesthesia/Obstetric Anesthetists' Association (grant to RK) and an NHS Research Scotland Career Researcher Fellowship (RK). The views expressed in this publication are those of the author(s) and not necessarily those of the UK National Health Service, the National Institute for Health Research, or the UK Department of Health and Social Care, or any other funders mentioned here.

#### CONFLICTS OF INTEREST

All authors completed the ICMJE uniform disclosure form at www. icmje.org/coi\_disclosure.pdf and declare: support via grant funding form the Obstetric Association of Anesthetists and Scottish Society of Anesthetists for the submitted work. SMN 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. There are no other relationships or activities that could appear to have influenced the submitted work.

#### AUTHOR CONTRIBUTIONS

RK, LH, and SMN designed the study. LH, RK, and SMN drafted the initial manuscript. All authors contributed to critical revision and final approval of the submitted manuscript.

#### DATA AVAILBAILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

# ORCID

Lucy Halliday 🕩 https://orcid.org/0000-0002-0468-7941

# REFERENCES

- 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:e1003103.
- Arendt K, Segal S. Why epidurals do not always work. Rev Obstet Gynecol. 2008;1:49-55.
- Anim-Somuah MSR, Cyna AM, Cuthbert A. Epidural versus nonepidural or no analgesia for pain management in labour. *Cochrane Database Syst Rev.* 2018;2018:CD000331.
- Baethge C, Goldbeck-Wood S, Mertens S. SANRA–a scale for the quality assessment of narrative review articles. *Res Integr Peer Rev.* 2019;4:5.

- Simmons SW, Taghizadeh N, Dennis AT, Hughes D, Cyna AM. Combined spinal-epidural versus epidural analgesia in labour. Cochrane Database Syst Rev. 2012;10:CD003401.
- Cook TM, Counsell D, Wildsmith JAW, on behalf of The Royal College of Anaesthetists Third National Audit P. Major complications of central neuraxial block: report on the third National Audit Project of the Royal College of Anaesthetists<sup>†</sup>. Br J Anaesth 2009;102:179–190.
- 7. Hattler J, Klimek M, Rossaint R, Heesen M. 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;123:955-964.
- 8. Broadbent CR, Maxwell WB, Ferrie R, Wilson DJ, Gawne-Cain M, Russell R. Ability of anaesthetists to identify a marked lumbar interspace. *Anaesthesia*. 2000;55:1122-1126.
- 9. Perlas A, Chaparro LE, Chin KJ. Lumbar neuraxial ultrasound for spinal and epidural anesthesia: a systematic review and metaanalysis. *Reg Anesth Pain Med*. 2016;41:251-260.
- Jiang L, Zhang F, Wei N, Lv J, Chen W, Dai Z. Could preprocedural ultrasound increase the first-pass success rate of neuraxial anesthesia in obstetrics? A systematic review and meta-analysis of randomized controlled trials. J Anesth. 2020;34:434-444.
- 11. Shaikh F, Brzezinski J, Alexander S, et al. Ultrasound imaging for lumbar punctures and epidural catheterisations: systematic review and meta-analysis. *Br J Anaesth*. 2013;346:f1720.
- National Institute for Health and Care Guidance. Ultrasoundguided catheterisation of the epidural space. [Internet]. Jan 2008. https://www.nice.org.uk/guidance/ipg249/resources/ultrasound guided-catheterisation-of-the-epidural-space-pdf-1899865404 843973. Accessed October 31st 2021
- 13. V Nalawade, U Misra Choice of drugs for neuraxial labour analgesia: an OAA approved survey of current practice. *Int J Obstet Anesth* 2014;23:s8.
- 14. Wang T-T, Sun S, Huang S-Q. 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;124:1571-1580.
- 15. Sultan P, Murphy C, Halpern S, Carvalho B. The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a metaanalysis. *Can J Anaesth*. 2013;60:840-854.
- 16. Beilin Y, Halpern S. Ropivacaine versus bupivacaine for epidural labor analgesia. *Anesth Analg.* 2010;111:482-487.
- 17. UK COMETCSG. Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet.* 2001;358:19-23.
- Lyons G, Columb M, Hawthorne L, Dresner M. Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent. *Br J Anaesth*. 1997;78:493-497.
- Polley LS, Columb MO, Wagner DS, Naughton NN. Dose-dependent reduction of the minimum local analgesic concentration of bupivacaine by sufentanil for epidural analgesia in labor. *Anesthesiology*. 1998;89:626-632.
- 20. 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 Anaesth*. 2014;61:695-709.
- Collins JG, Kitahata LM, Matsumoto M, Homma E, Suzukawa M. Suppression by spinally administered epinephrine on noxiously evoked dorsal horn neuron activity in cats. Evidence for spinal epinephrine analgesia. *Anesth Analg.* 1983;62:253-254.
- 22. Lee A, Landau R, Lavin T, Goodman S, Menon P, Smiley R. Comparative efficacy of epidural clonidine versus epidural fentanyl for treating breakthrough pain during labor: a randomized doubleblind clinical trial. *Int J Obstet Anesth*. 2020;42:26-33.
- 23. Cossu AP, De Giudici LM, Piras D, et al. A systematic review of the effects of adding neostigmine to local anesthetics for neuraxial

🥮-WILEY

administration in obstetric anesthesia and analgesia. Intl J Obstet Anesth. 2015;24:237-246.

 Liu X, Zhang H, Zhang H, Guo M, Gao Y, Du C. Intermittent epidural bolus versus continuous epidural infusions for labor analgesia: a meta-analysis of randomized controlled trials. *PLoS One*. 2020;15(6):e0234353.

WILEY- OBSTETRIC

- Sng BL, Sia ATH, Lim Y, Woo D, Ocampo C. Comparison of computer-integrated patient-controlled epidural analgesia and patient-controlled epidural analgesia with a basal infusion for labour and delivery. *Anaesth Intensive Care*. 2009;37:46-53.
- Heesen M, Böhmer J, Klöhr S, Hofmann T, Rossaint R, Straube S. The effect of adding a background infusion to patient-controlled epidural labor analgesia on labor, maternal, and neonatal outcomes: a systematic review and meta-analysis. *Anesth Analg.* 2015;121:149-158.
- 27. van der Vyver M, Halpern S, Joseph G. Patient-controlled epidural analgesia versus continuous infusion for labour analgesia: a metaanalysis. *Br J Anaesth*. 2002;89:459-465.
- Nolens B, Capelle M, van Roosmalen J, et al. Use of assisted vaginal birth to reduce unnecessary caesarean sections and improve maternal and perinatal outcomes. *Lancet Glob Health*. 2019;7:e408-e409.
- 29. Lancet T. Stemming the global caesarean section epidemic. *Lancet*. 2018;392:1279.
- Baliuliene V, Macas A, Rimaitis K. The optimal concentration of bupivacaine and levobupivacaine for labor pain management using patient-controlled epidural analgesia: a double-blind, randomized controlled trial. *Int J Obstet Anesth*. 2018;35:17-25.
- Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth. 1995;42:891-903.
- Clivatti J, Siddiqui N, Goel A, Shaw M, Crisan I, Carvalho JCA. Quality of labour neuraxial analgesia and maternal satisfaction at a tertiary care teaching hospital: a prospective observational study. *Can J Anaesth.* 2013;60:787-795.
- Morton S, Kua J, Mullington CJ. Epidural analgesia, intrapartum hyperthermia, and neonatal brain injury: a systematic review and meta-analysis. Br J Anaesth. 2021;126:500-515.

- 34. Jansen S, Lopriore E, Naaktgeboren C, et al. Epidural-related fever and maternal and neonatal morbidity: a systematic review and meta-analysis. *Neonatology*. 2020;117:259-270.
- Törnell S, Ekéus C, Hultin M, Håkansson S, Thunberg J, Högberg U. Low Apgar score, neonatal encephalopathy and epidural analgesia during labour: a Swedish registry-based study. *Acta Anaesthesiol Scand.* 2015;59:486-495.
- Greenwell EA, Wyshak G, Ringer SA, Johnson LC, Rivkin MJ, Lieberman E. Intrapartum temperature elevation, epidural use, and adverse outcome in term infants. *Pediatrics*. 2012;129:e447-e454.
- Söderquist JWKWB. Traumatic stress after childbirth: the role of obstetric variables. J Psychosom Obstet Gynaecol. 2002;23:31-39.
- Loftus JR, Hill H, Cohen SE. Placental transfer and neonatal effects of epidural Sufentanil and fentanyl administered with bupivacaine during labor. *Anesthesiology*. 1995;83:300-308.
- 39. Fratelli N, Prefumo F, Andrico S, et al. Effects of epidural analgesia on uterine artery doppler in labour. *Br J Anaesth*. 2011;106:221-224.
- 40. French CACX, Chung KS. Labor epidural analgesia and breastfeeding: a systematic review. J Hum Lact. 2016;32:507-520.
- Kearns RJSM, Gromski PS, Iliodromiti S, Lawlor DA, Nelson SM. Association of epidural anesthesia in women in spontaneous labor with neonatal and childhood outcomes in a population cohort. JAMA Netw Open. 2021;4:e2131683.
- 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;174:1168-1175.
- Wall-Wieler E, Bateman BT, Hanlon-Dearman A, Roos LL, Butwick AJ. Association of epidural labor analgesia with offspring risk of autism spectrum disorders. JAMA Pediatr. 2021;175:698-705.

**How to cite this article:** Halliday L, Nelson SM, Kearns RJ. Epidural analgesia in labor: A narrative review. *Int J Gynecol Obstet*. 2022;159:356–364. doi:10.1002/ijgo.14175