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Review

Maternal, fetal and long-term neurodevelopmental outcomes after labor epidural analgesia: a narrative review

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Abstract

Labor pain is among the most intense pain a woman may endure in her lifetime. Without analgesia, labor pain could result in intense maternal emotional distress, postpartum depression and fetal distress. In the European countries and United States of America, up to 83% of pregnant women receive labor epidural analgesia (LEA) for delivery, which is considered effective and safe for both mother and fetus. The aim of this narrative review is to summarize maternal outcomes, pregnancy outcomes, neonatal outcomes and long-term neurodevelopmental outcomes after labor epidural analgesia. LEA reduces the risk for severe maternal morbidity (e.g. heart failure) in women with a medical indication (e.g., cardiovascular disease) for LEA and in preterm delivery. Modern LEA using low concentrations of local anesthetics does not result in a clinically relevant prolongation of labor, it does not increase the risk for instrumental vaginal delivery or cesarean sections. LEA does neither affect APGAR scores, nor acid-base status. There is ongoing debate whether LEA impacts neurodevelopmental outcomes such as autism spectrum disorder (ASD), but this association may be explained by unmeasured confounders. No significant association was found between LEA and other long-term neurodevelopmental outcomes (e.g., Attention-Deficit Hyperactivity Disorder), but this has been investigated by only a limited number of studies. There is need for high quality studies investigating long-term neurodevelopmental outcomes after LEA.

Key words: **Labor Epidural Analgesia, Pregnancy, Fetus, Neurodevelopment.**

Introduction

In 2023, approximately 3.7 million children were born in the European Union[1]. It can be estimated that during the delivery of more than 3 million of these children, the mother received labor epidural analgesia (LEA) to manage labor pain[2–4]. Labor pain is among the most intense pain a woman may endure in her lifetime[5]. The pain arises during the first stage of labor due to uterine contractions and cervical dilation[6–8]. As labor progresses into the second stage, the descent of the fetal head stretches the perineum and vagina, which may lead to perineal tissue damage[6–8]. Labor pain leads to intense maternal emotional distress and – without analgesia – to a high risk of postpartum depression[9,10]. Additionally, the maternal stress response to pain results in maternal hyperventilation and release of catecholamines, causing decreased uterine blood flow with fetal distress and neonatal asphyxia as potential consequences[11–13]. In the European countries and United States of America, up to 83% of pregnant women receive LEA for delivery[2–4,11,12]. Patient satisfaction is higher for LEA when compared with other approaches (e.g., nitrous oxygen, opioids), and LEA is considered

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safe during delivery for both the mother and the fetus[11,14–16].

However, it has been started only recently to investigate long-term consequences of the use of LEA. Recent studies have explored possible links between LEA and autism spectrum disorder (ASD)[17–19]. ASD typically emerges in early childhood, can have lifelong effects on individuals and pose significant societal and economic burdens[12,20]. ASD is a neurodevelopmental disorder characterized by deficits in communication, social interaction, and repetitive or restrictive behavior[21]. While known risk factors include genetic, environmental, prenatal, and postnatal, its precise etiology remains unclear[22,23].

The aim of this review is to summarize the most recent evidence on maternal outcomes, pregnancy outcomes, neonatal outcomes and long-term neurodevelopmental outcomes of the child after the use of labor epidural analgesia.

Materials and methods

Pubmed, Embase and Web of Science were searched using a search string comprising the concepts "labor epidural analgesia" AND ("maternal outcomes" OR "pregnancy outcomes" OR "neonatal outcomes" OR "long-term neurodevelopmental outcomes"). Filters were applied to select systematic reviews. Articles investigating maternal outcomes, pregnancy outcomes, neonatal outcomes and long-term neurodevelopmental outcomes of the child after the use of labor epidural analgesia were eligible.

Records were screened for eligibility by two authors (MA and TB). The authors focused on most recent systematic reviews and meta-analyses. The reference lists of included articles were further screened for relevant articles. The two authors obtained a consensus for inclusion of articles.

This review focused on systematic reviews and meta-analyses published between 1998 and 2024, with particular emphasis on studies from the past decade (2015–2025). A limited number of older studies were selectively included to provide historical context and to illustrate the evolution of labor analgesia practices. Systematic reviews and meta-analyses were prioritized as they represent the highest level of evidence, synthesizing data across multiple studies to offer more robust, unbiased and generalizable conclusions.

Labor epidural analgesia and maternal outcomes

LEA has been associated with a reduced risk of severe maternal morbidity[24–27]. The United States Centers for Disease Control and Prevention defines severe maternal morbidity as the occurrence of peri- or postpartum maternal acute myocardial infarction, acute renal failure, acute respiratory distress syndrome, amniotic fluid embolism, cardiac arrythmias/arrest, heart failure, eclampsia, pulmonary edema, shock, the need for maternal blood transfusion, hysterectomy, admission to the intensive care unit, among other complications[28].

The most recent large-scale observational study, encompassing over 500,000 laboring women between 2007 and 2019, showed that LEA was associated with a 35% relative risk reduction in severe maternal morbidity (adjusted Relative Risk (aRR): 0.65, 95% confidence-interval (CI): 0.50-0.85)[26]. Notably, among women with a medical indication for LEA—including significant cardiovascular or respiratory disease, pre-eclampsia, prior cesarean section, breech presentation, multiple gestation, and morbid obesity—the relative risk reduction was even more pronounced at 50% (aRR: 0.50; 95% CI: 0.34–0.72). Similarly, in women delivering preterm, LEA was associated with a 47% reduction in severe maternal morbidity (aRR: 0.53; 95% CI: 0.37–0.76). Conversely, there was no statistical significant association between LEA and a reduction in severe maternal morbidity in the subgroups of laboring women without a medical indication for LEA (aRR: 0.67; 95% CI: 0.43-1.03) and women delivering term or post-term (aRR: 1.09; 95% CI: 0.98-1.21). Two other studies on this subject also concluded that the use of LEA was associated with a reduced risk for severe maternal morbidity, but did not analyze the subgroups of women with a medical indication for LEA and women delivering preterm[24,25].

Labor epidural analgesia and pregnancy outcomes

In the early years following introduction of LEA (1970-1990s), it was perceived to be associated with adverse pregnancy outcomes[29]. However, high-quality study designs and advancements in anesthesia techniques have fundamentally altered this perspective[29]. Contemporary evidence indicates that modern LEA is safe with respect to pregnancy outcomes.

Studies conducted before 2005 reported several adverse pregnancy outcomes for LEA when compared to parenteral opioids or placebo. First, randomized controlled trials (RCTs) observed a significantly prolonged first stage of labor (weighted mean difference: 42 minutes; 95% CI: 17–68) and second stage of labor (weighted mean difference: 14 minutes; 95% CI: 5–23)[30]. Second, both RCTs[30,31] and retrospective observational

studies[32] reported increased rates of instrumental vaginal delivery [RCTs[31]: relative risk (RR) 1.38, 95% CI: 1.24–1.53; observational studies[32]: RR 4.72, 95% CI: 3.08–7.24]. Third, retrospective observational studies showed an increased risk of cesarean section (RR: 4.16, 95% CI: 2.56–6.76)[32]; however, RCTs failed to confirm this observation[30–32].

Studies conducted after 2005 represent more modern LEA and the study design improved[29]. Over the years, strategies have been developed to reduce the total dose of local anesthetics[29]. The modern use of low-concentration local anesthetics [≤ 0.1% (levo)bupivacaine and ≤ 0.17% ropivacaine] combined with opioids reduces the motoric block and thereby improves significantly above-mentioned pregnancy outcomes, when compared to the historic higher concentrations of local anesthetic[33,34]. Additionally, the continuous epidural infusion of local anesthetics has been replaced by programmed intermittent epidural bolus (PIEB) administration[29], which has been shown to further enhance pregnancy outcomes[35]. Furthermore, retrospective observational studies have been entirely superseded by randomized controlled trials (RCTs), ensuring a higher level of evidence[29]. However, a notable limitation of these RCTs is the high crossover rate from the control group to LEA[29].

The findings of these modern randomized controlled trials (RCTs) were summarized in 2018 in a Cochrane systematic review, which compared LEA with parenteral opioids[16]. The meta-analysis identified a statistically significant increase in the duration of both the first stage of labor (weighted mean difference: 32 minutes; 95% CI: 18-46) and the second stage of labor (weighted mean difference: 15 minutes; 95% CI: 2-28)[16]. However, while statistically significant, these time differences are clinically negligible in the context of the overall duration of labor[29]. This slight prolongation is generally considered acceptable given the superior analgesic efficacy of LEA[29]. No significant increase in the risk of cesarean section (RR: 1.07; 95% CI: 0.96-1.18) or instrumental vaginal delivery (RR: 1.19; 95% CI: 0.97-1.46) was observed[16].

In conclusion, modern LEA has no clinically relevant negative impact on pregnancy outcomes.

Labor epidural analgesia and neonatal outcomes

When LEA was compared with parenteral opioids, there was no evidence for worse APGAR scores, neonatal resuscitation, neonatal death or neonatal intensive care unit admission (RR 1.03; 95% CI: 0.95-1.12)[16,29,31]. LEA resulted in a reduced risk for neonatal acidosis (neonatal base excess: mean difference: 0.779 mEq/L; 95% CI: 0.056-1.502) when compared to parenteral opioids[29].

Labor epidural analgesia and autism spectrum disorder

In 2020, a first retrospective clinical cohort study showed an association between modern LEA and ASD (Hazard ratio (HR) 1.37, 95% CI: 1.23-1.53)[19]. Additionally, a clear relationship between the duration of LEA and the HR for ASD was reported, raising a safety concern for public health[19]. Thereafter, other retrospective observational studies corroborated this finding even when taking several confounders into account (e.g., maternal age at delivery, parental education and income, birth weight, prematurity, pregnancy complications etc.)[19,36–39]. In contrast, other retrospective observational studies failed to confirm an association between LEA and ASD, especially when using a sibling matched design[20,38–42]. Likewise, the only prospective observational study (using caregiver questionnaires) performed so far failed to prove this association[23].

Recent systematic reviews found a significantly increased risk for ASD when confounders were not taken into account [HR 1.3, CI: 1.25-1.35 and HR 1.24, 95% CI: 1.14-1.34][12,43]. When potential confounders (e.g., sociodemographic factors) were considered, the effect was smaller but still statistically significant [HR 1.13, 95% CI: 1.03-1.25 and HR 1.11, 95% CI: 1.06-1.16][12,43]. When only studies using a sibling-matched design were analyzed, one meta-analysis concluded that there was no significant association [HR 1.07, 95% CI: 0.99-1.16], whereas another meta-analysis demonstrated a significant association in sibling-matched designs [HR 1.10, 95% CI: 1.02-1.18], with however no dose-response effect[12,43]. It was concluded that the statistically significant association between LEA and ASD may be explained by unmeasured confounders (e.g., genetic factors)[43].

Labor Epidural analgesia and other long-term neurodevelopmental outcomes

While the major focus in most studies was on the association between LEA and ASD, other long-term neurodevelopmental outcomes have been reported only in a limited number of studies. There was no evidence for an association between LEA and learning disorders, Attention-Deficit Hyperactivity Disorder (ADHD) (HR: 0.99, 95% CI 0.96-1.02), intellectual development disorder, neurodevelopmental impairment (adjusted odds ratio (aOR): 1.14; 95% CI: 0.71-1.79), clinically relevant psychosocial problems, epilepsy,

neurodevelopmental impairments (HR: 0.99, 95% CI 0.96-1.02), cerebral palsy (aOR 0.84, 95% CI 0.35–1.81) and hypoxic-ischemic encephalopathy (RR 1.21, 95% CI 0.96-1.53)[21,38,44–46].

A single retrospective cohort study observed that LEA was even associated with a reduced risk for developmental concerns (gross and fine motor function, communication and social functioning[43], while another study observed an increased risk[53].

A summary of all outcomes after labor epidural analgesia can be found in Table I.

Discussion

Labor epidural analgesia remains one of the most effective and safe methods for pain relief during labor[12]. LEA reduces the risk of severe maternal morbidity in women with a medical indication for LEA and in preterm delivery[26]. With usage of modern low concentrations of local anesthetics, there is no increased risk for clinically relevant prolonged labor, instrumental delivery or cesarean section[34]. Research investigating neonatal outcomes and long-term neurodevelopment has largely reported no significant associations between LEA and adverse outcomes[44–47]. The potential association between LEA and ASD may be explained by unmeasured confounders[19,36,37,40]. No consistent link has been found between LEA and other neurodevelopmental disorders such as ADHD[38]. LEA has been used for decades in the vast majority of vaginal deliveries (up to 83%)[2–4,11,12] and remains the most effective and safest way to allow pregnant women a nearly pain-free labor- and birth experience[11,14–16].

While studies conducted before 2005 reported adverse pregnancy outcomes associated with LEA, such as prolonged labor and increased rates of instrumental or cesarean delivery, several factors may explain these findings[29]. First, high concentrations of local anesthetics (e.g., 0.2-0.25% bupivacaine) were used, leading to motor blockade that impaired both voluntary and involuntary expulsive efforts during labor[29]. Second, confounding factors in retrospective observational studies may have biased the results; for instance, patients experiencing more pain in early labor, which is associated with an increased risk of cesarean section, may have been more likely to self-select for LEA[29]. Additionally, high risk pregnancies, with a higher risk for instrumental vaginal deliveries and cesarean sections, are also more likely to receive early LEA.

Moreover, LEA has been associated with a reduced risk of severe maternal morbidity, particularly among women with medical indications for its use and those experiencing preterm labor[26]. These findings suggest the hypothesis that LEA may confer benefits to maternal health within these subgroups. However, caution is warranted, as the observational design of this study precludes the establishment of a causal relationship, demonstrating only an association. Several mechanisms may underlie this observed association[27]. First, LEA may mitigate physiological stress responses to labor pain, such as increased

Table I. — Summary of review: outcomes after labor epidural analgesia.

Outcome	Summary
Maternal outcomes	- LEA reduces the risk for severe maternal morbidity in women with a medical indication for LEA and in preterm labor.
Pregnancy outcomes	- Modern LEA using low concentrations of local anesthetics does not result in a clinically relevant prolongation of labor. - Contemporary LEA does not increase the risk for instrumental vaginal delivery or cesarean sections.
Neonatal outcomes	- LEA does not affect APGAR scores. - LEA was associated with an improved fetal acid-base status.
Long-term neurodevelopmental outcomes	- There is ongoing debate regarding the association between LEA and autism spectrum disorder, though this may be due to unmeasured confounders. - No significant association has been found between LEA and other long-term neurodevelopmental outcomes (e.g., Attention-Deficit Hyperactivity Disorder), but this has been investigated only in a limited number of studies.

cardiac output and respiratory rate, which could be particularly protective in patients with preexisting cardiac or respiratory diseases[27]. Second, women receiving LEA may receive heightened medical surveillance, facilitating earlier detection and intervention for maternal morbidity[27]. Third, LEA enables a seamless transition from analgesia to surgical anesthesia in the event of an emergent cesarean section, thereby reducing the maternal risks associated with general anaesthesia[27]. Lastly, the use of alternative pain management strategies, such as nitrous oxide or opioids, may contribute to an increased risk of severe maternal morbidity in the group of women not using LEA[27].

High quality studies and robust evidence was found for maternal outcomes, pregnancy outcomes and neonatal outcomes. However, it is crucial to acknowledge the limitations of the studies investigating long-term neurodevelopmental outcomes, such as ASD. Apart from being contradictory, the available studies suffer from several important limitations which may have induced significant bias. First, it is obvious that retrospective studies without sibling matching cannot correct for unmeasured/unmeasurable confounders such as genetic factors, which could contribute to the predisposition for neurodevelopmental disorders[43]. Second, with the exception of one study, all studies assessed the outcomes retrospectively, using already existing population-based datasets and administrative records (e.g., health insurance databases, which were obviously not specifically designed to investigate this subject). Third, there are no studies prospectively assessing investigator-assessed outcomes allowing an objective neurocognitive testing[23]. Fourth, in several studies, both vaginal deliveries and cesarean sections were included[39,41,48]. Fifth, the majority of studies focused on ASD and did not assess other cognitive functions. Last, the neurophysiological mechanism by which LEA could cause neurodevelopmental disorders remains entirely elusive.

In conclusion, LEA is safe with respect to maternal outcomes, pregnancy outcomes and neonatal outcomes. However, high-quality studies are needed to investigate the long-term neurodevelopmental outcomes following prenatal exposure to LEA.

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