Pain management during labor and vaginal birth

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Abstract

Neuraxial analgesia provides excellent pain relief in labor. Optimizing initiation and maintenance of neuraxial labor analgesia requires different strategies. Combined spinal-epidurals or dural puncture epidurals may offer advantages over traditional epidurals. Ultrasound is useful in certain patients. Maintenance of analgesia is best achieved with a background regimen (either programmed intermittent boluses or a continuous epidural infusion) supplemented with patient-controlled epidural analgesia and using dilute local anesthetics combined with opioids such as fentanyl. Nitrous oxide and systemic opioids are also used for pain relief. Nitrous oxide may improve satisfaction despite variable effects on pain. Systemic opioids can be administered by healthcare providers or using patient-controlled analgesia. Appropriate choice of drug should take into account the stage and progression of labor, local safety protocols, and maternal and fetal/neonatal side effects. Pain in labor is complex, and women should fully participate in the decision-making process before any one modality is selected.

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Introduction

Labor pain ranks consistently among the most severe types of pain that a woman will experience during her lifetime. Of the many pharmacological and non-pharmacological options for pain relief, neuraxial techniques such as epidurals are the most effective at providing labor analgesia and are the gold standard against which other modalities are compared. Modern neuraxial techniques for both initiation and maintenance of analgesia allow labor analgesia to be successfully provided with excellent maternal and fetal/neonatal safety profiles.

Consequently, when available, neuraxial analgesia is a highly requested modality for labor pain relief [1]. Non-neuraxial pharmacological options include nitrous oxide (N2O) and systemic opioids. N2O is a self-administered low-potency inhaled anesthetic with a long history of use for labor analgesia. Systemic opioids including meperidine (pethidine), fentanyl, and more recently remifentanil, are used by many parturients, either to avoid or delay using neuraxial analgesia or when it is contraindicated. This review will provide a brief overview of key pharmacological modalities currently used for labor pain relief, including discussions of both maternal and fetal/neonatal outcomes as they pertain to each. Although not the focus of this review, non-pharmacological methods for labor pain relief include relaxation and breathing exercises, antenatal education programs, transcutaneous electric nerve stimulation (TENS), acupressure/acupuncture, aromatherapy, and hypnosis, among others [2]. Depending on a woman's particular preferences, the World Health Organization (WHO) recommends epidural analgesia, systemic opioids, relaxation techniques, and manual techniques (such as massage) as pain relief options for women in labor [3].

An important question that has been asked by many clinicians and researchers is whether proven analgesic benefit as measured by a pain intensity score is the only outcome that matters when evaluating different pain relief options for laboring women. The experience of labor is complex, and the effectiveness of pain relief is only one of many dimensions that may affect a woman's overall experience with the labor and childbirth process. In addition to the degree of pain relief, any modality chosen may also impact a woman's (and her partner's) sense of focus, control, well-being, satisfaction, and feelings of support [4]. Before initiating any pain modality, a thorough informed consent discussion should take place between the woman and healthcare provider, reviewing risks, benefits, and alternatives to the modality in question, taking into account all of the above domains of the experience of childbirth.

Options for neuraxial labor analgesia initiation

Epidural analgesia

Lumbar epidural analgesia is considered the gold standard against which other pain relief modalities for labor are measured [5]. This technique has been employed for decades and consists of medications administered through an epidural catheter placed in the lumbar epidural space. An epidural needle (e.g. a Tuohy needle) is placed between spinous processes, usually in the mid to lower lumbar region, and advanced towards the dorsal epidural space; confirmation of correct placement occurs most commonly using the loss-of-resistance technique [6]. Pressure placed on the plunger of an air or saline-filled syringe, which cannot be compressed while in the interspinous ligaments and ligamentum flavum, suddenly gives way when the epidural space is reached. Once placed through this needle, an epidural catheter is used to administer medications to bathe the nerve roots exiting the spinal cord in order to provide labor pain relief. In contemporary practice, local anesthetics such as bupivacaine (with or without a lipophilic opioid such as fentanyl or sufentanil) are then administered either as a continuous infusion or on an intermittent basis. This may be supplemented with a patient-controlled component whereby the laboring woman can self-administer extra medication in case of breakthrough pain. In cases where the pain relief obtained is inadequate or incomplete at any point after initiation, the anesthesia provider should be alerted, so that steps may be taken to try to improve analgesia, which may include additional doses of medication, adjusting the position of the epidural catheter, or...
repeating the procedure altogether. Although it is common practice in many centers to place limitations on when a woman may obtain epidural pain relief, these are often based on logistical factors (e.g. patient load, number of available providers, etc.). A large systematic review of over 15,000 women concluded that the time to initiate epidural analgesia should be based on maternal request and that obstetric and fetal outcomes are similar regardless of early vs. late initiation [7].

Combined spinal-epidural

Compared to the traditional epidural technique, in which the dura is not intentionally breached, a combined spinal-epidural (CSE) consists of a small-gauge spinal needle being used to puncture the dura and administer intrathecal medication after the epidural space has been located using the traditional loss of resistance method. This is commonly performed “needle-through-needle” in which the spinal needle is advanced through the lumen of the epidural needle, or it can be performed using specific CSE kits in which the epidural needle has a separate lumen to accommodate the spinal needle.

A CSE results in significantly faster onset of pain relief when compared to a traditional epidural [8], and may provide better subsequent labor analgesia with reduced needs for additional physician doses for breakthrough pain [9], fewer unilateral blocks [10], fewer catheter failures [11], and higher maternal satisfaction [12].

Booth et al. [11] found a 7% failure rate with CSE compared to 12% with standard labor epidural analgesia. The authors demonstrated that epidural catheter failures were also recognized early (within 30 min) more frequently with CSE compared to standard epidural. This lower failure rate with CSE may be due to fewer false losses of resistance, as visualizing cerebrospinal fluid (CSF) in the hub of the spinal needle confirms correct placement. The absence of CSF return during the spinal portion of the CSE results in 29% of epidural catheters requiring subsequent replacement, compared to only 4% if CSF return was confirmed at the time of the procedure [13]. Successfully visualizing CSF with the CSE technique also helps to confirm midline placement and may explain the lower incidence of unilateral anesthesia with the technique relative to a traditional epidural [10]. Better subsequent analgesia with CSE compared to standard epidural may be due to some translocation of epidural solution through the spinal needle puncture site into the dura. Epidural catheters placed as part of a CSE are less likely to fail than standard epidurals both during labor and when attempting conversion from labor analgesia to anesthesia for cesarean delivery (CD) [14,15].

CSEs are however associated with some potential drawbacks. Side effects from the spinal medication include maternal hypotension and opioid-induced pruritus [8]. The CSE technique is associated with an increased incidence of fetal heart rate changes and bradycardia after block placement compared to epidural alone (Relative Risk, RR = 1.3) [16]. The postulated mechanism for this bradycardia is an abrupt reduction in maternal circulating catecholamines including epinephrine, a uterine relaxant, associated with the more rapid onset of pain relief after CSE compared to standard epidural. This catecholamine imbalance is hypothesized to result in uterine hypertonus and therefore in transiently reduced flow through the uteroplacental unit and therefore fetal bradycardia or heart rate changes [17,18]. The risk of fetal bradycardia is more prevalent when the parturient is in advanced labor with high presenting pain levels that are abruptly reduced [19]. There is also thought be a dose–response relationship of fetal bradycardia and the dose of spinal opioids administered [20]. Fetal bradycardia after initiation of labor analgesia with a CSE is treated with uterine relaxants such as nitroglycerin or terbutaline and correcting maternal blood pressure if there is concomitant hypotension. Occasionally the fetal bradycardia may necessitate urgent CD, but overall there does not appear to be a significant difference in the rates of CD between CSE and epidural analgesia or when comparing neuraxial techniques generally to other modalities [16,21].

The CSE technique does not appear to result in an increased incidence of dural puncture headaches when small gauge (26G or smaller) pencil-point spinal needles are used. No difference in the need for epidural blood patch was found in a large, retrospective review of over 19,000 women [22]. The theoretical concern that the epidural catheter placed as part of a CSE technique is “untested” and therefore not confirmed to truly be in the epidural space until the intrathecal dose has worn off is likely to be to be unfounded [23]. CSEs are associated with reduced failure rates for labor or CD anesthesia compared to standard epidural [11,15]. The rarity of serious complications such as nerve injury or
meningitis makes them difficult to study and to date no evidence exists that these are increased by using a CSE technique [8].

**Dural-puncture epidural**

A dural-puncture epidural (DPE) is a more recently described neuraxial block initiation method that aims to improve upon standard epidurals while mitigating some of the side effects seen with the CSE including pruritis and fetal heart rate abnormalities discussed above. The technique is similar to a CSE in that a small-gauge pencil-point spinal needle is inserted through a correctly sited epidural needle. However, unlike a CSE, after the dura is punctured, the spinal needle is then removed from the epidural needle without the administration of any spinal medications. The epidural catheter is threaded into the epidural space as per usual practice with standard epidural or CSE. The postulated benefit of simply creating this small-gauge hole in the dura is that this intentional dural puncture provides a conduit for medications subsequently administered epidurally to then slowly translocate into the intrathecal space and gain closer proximity to the spinal cord. Additionally, as with the CSE, positive return of CSF serves as a double confirmation (in addition to the loss of resistance) that the epidural needle is midline and in the actual epidural space.

There appears to be a marginally quicker onset of analgesia, better coverage of sacral dermatomes, and reduced incidence of unilateral block with DPE compared to standard epidural [24]. Chau et al. [25] compared this technique with both CSE and standard epidural for labor pain relief and found that the median onset of CSE is significantly quicker (2 min) compared to both DPE (11 min) and traditional epidurals (18 min). DPE is however associated with fewer side effects such as maternal pruritis and hypotension, as well as uterine hypertonus, compared to the CSE technique. Studies using 27G spinal needles have not found greater efficacy with DPE compared to standard epidural [26], and for the DPE to work optimally, a 25G or larger needle appears to be required. However, the post-dural puncture headache risk associated with intentionally creating a dural defect using the DPE technique using a 25G spinal needle compared to a standard epidural without an intentional dural puncture has not been well-elucidated and requires further study.

The CSE remains the technique of choice when rapid-onset analgesia in advanced labor is needed. The DPE technique, however, may be a useful option to help confirm needle placement when equivocal loss of resistance is obtained or to confirm midline placement especially when block placement is difficult or when anatomical landmarks are difficult to palpate (e.g. in morbidly obese parturients). As previously discussed, visualizing CSF flow through the spinal needle inserted through the epidural needle after a loss of resistance occurs can provide much needed reassurance that the epidural space has indeed been reached successfully and midline placement is likely.

**Ultrasound-assisted neuraxial techniques**

The widespread use of ultrasound (US) in anesthesia practice in settings like regional nerve blockade, vascular access, and point-of-care US has led to its investigation as a tool to aid with neuraxial anesthesia and analgesia [27]. Its role in neuraxial blockade is generally in the pre-procedure phase, to obtain landmarks and assess depth to the epidural space. Given the technical difficulties for a single operator to perform both the neuraxial block and real-time US and current image quality, pre-procedure US is the most utilized technique. Lumbar US assessment provides useful information prior to embarking on neuraxial anesthesia and analgesia including accurate identification of interspaces, establishment of midline structures, estimation of the depth to the epidural space, determination of an optimal interspace in which to attempt insertion, and required needle angulation for successful placement.

When compared to a traditional landmarks-based approach, neuraxial US is associated with reduced incidence of technical failure (RR = 0.51) and traumatic insertion (RR = 0.27) [28], as well as fewer insertions and redirections of the epidural needle [29]. Neuraxial US is an extremely valuable teaching tool especially in academic institutions where there are many learners, its use being associated with improved success of trainees when first learning neuraxial placement and a reduction in the number of catheters that subsequently need to be replaced [30,31]. These advantages may not apply
When more experienced providers are performing the procedures or in women who have easily palpable spinous processes [32].

Some authors have described superior epidural labor analgesia and increased maternal satisfaction when US is used prior to the procedure, perhaps due to better midline placement of the epidural catheters and more accurate selection of the desired interspace [33]. A lower (e.g. L4/5) interspace may provide better somatic, perineal pain relief in the second stage due to better coverage of sacral nerve roots compared to an insertion at a higher (e.g. L1/2) interspace [34]. Anesthesia providers correctly identify the actual spinal interspace only 29–41% of the time when using the traditional surface landmarks [28,35]. In this way, the use of US may help the provider correctly identify a lower interspace that is more likely to result in adequate pain relief as labor progresses and sacral coverage becomes necessary. Using traditional landmarks, providers are one to two spinal interspaces higher than they perceive themselves to be [28,35], and reducing accidental higher interspace placement may help improve safety. Additionally, knowing the depth of the epidural space prior to needle insertion allows the appropriate length of the needle to be selected, and may help decrease accidental dural puncture. However, outcome studies are still required to show that this theoretic advantage with US-assisted neuraxial placement leads to less accidental dural punctures or neurological complications.

Suggested clinical indications for the use of US use prior to neuraxial placement include any anticipated challenges with block placement (e.g. obesity, scoliosis, a personal history of failed or difficult neuraxial block in a previous labor) or as a rescue technique when a landmark-based approach has failed. Using US to assist with neuraxial placement can be particularly useful in women with significant scoliosis, any previous spinal surgery or instrumentation, morbid obesity, or difficult-to-palpate bony landmarks [36,37].

**Maintenance of neuraxial analgesia**

**Patient-controlled epidural analgesia**

Techniques to improve the quality of labor epidural analgesia have evolved considerably over the past few decades. The most common method of maintaining analgesia when epidurals were first used in clinical practice was repeated manual bolus administration of epidural medications by anesthesiologists, midwives, or obstetricians. These manual bolus doses were given when women expressed breakthrough discomfort or at prescribed time intervals but were labor-intensive and were associated with potential delays in treatment. As automated epidural infusion devices were developed, continuous epidural infusions (CEI) became the preferred maintenance technique due to reduced provider workload compared to manual boluses. Patient-controlled epidural analgesia (PCEA) for labor analgesia was first described by Gambling et al., in 1988 [38]. Compared to CEI alone, PCEA was shown to reduce overall local anesthetic doses, reduce the incidence of motor block, decrease the need for subsequent provider-administered top-ups, and improve maternal pain relief and satisfaction [39]. This has become the preferred labor epidural maintenance technique in many countries, including the United States and Canada [1,40]. However, better analgesia and further reduced anesthesia provider top-ups can be achieved when a background CEI is added to PCEA compared to using PCEA alone [41]. A background infusion added to PCEA can also increase overall local anesthetic consumption, so techniques to optimize background maintenance are important.

**Programmed intermittent epidural boluses**

Programmed intermittent epidural boluses (PIEB) was proposed as a more efficacious technique to maintain labor epidural analgesia compared to CEI and was described for labor analgesia in the early 2000s [42]. With PIEB, a programmed epidural infusion device administers automated boluses of epidural solution at set intervals (e.g. every 45–60 min). Proponents of PIEB suggest that the spread of epidural medications after boluses compared to infusions is more uniform in the epidural space [43],...
and that these rapidly administered epidural catheter boluses spread better than when the same volume is given by slow CEI over the hour [44]. Increased spinal segmental spread in the neuraxial space with boluses compared to infusions administration has been demonstrated in a porcine model [45].

Wong et al. [46] prospectively demonstrated that the combination of PIEB and PCEA resulted in reduced local anesthetic consumption, improved satisfaction, and fewer provider top-ups compared to CEI + PCEA. PIEB + PCEA compared to CEI + PCEA has also been shown to decrease maternal motor blockade and rates of instrumental vaginal delivery [47]. Meta-analysis data [48,49] demonstrate that PIEB is associated with decreased local anesthetic usage, improved maternal satisfaction, and less breakthrough pain when compared to CEI (with or without PCEA). Implementation studies after the replacement of CEI + PCEA with PIEB + PCEA at various institutions have shown improvements in certain outcomes such as reduced need for clinician top-ups, less incidence of unilateral sensory blockade, higher PCEA demand ratios, and lower peak pain scores [50–52].

In summary, the optimal method of maintenance of epidural labor analgesia at present is PCEA with a background PIEB regimen. PIEB provides the baseline level of analgesia irrespective of patient participation, and PCEA allows for a highly individualized approach which can account for variability in women’s perceptions of pain, the stage and progress of labor, and differences in patient engagement and preferred degree of analgesia.

**Optimal PCEA and PIEB settings**

Several studies have tried to determine the best parameters for PIEB and PCEA for labor analgesia maintenance. The medication solution (i.e. a combination of local anesthetic and opioid) and concentrations or dose used, programmed and patient-administered bolus volumes, the time interval between programmed boluses, and lockout time intervals for both the PIEB and PCEA components can all individually affect the efficacy of the maintenance regimen. A review [53] offers some suggestions of recipes that have successfully been used for PCEA and PIEB for labor analgesia. Data suggest that there is no one optimal recipe for labor epidural analgesia. Some studies suggest that a larger bolus dose given less frequently is preferable, however the longer lockout intervals needed to accommodate this may provide suboptimal pain relief due to breakthrough pain between programmed boluses, requiring additional provider intervention [52]. Epsztein Kanczuk et al. [54] found an optimal PIEB time interval (effective dose interval in 90% of women, ED90) of approximately 40 min using 10 mL PIEB boluses of 0.0625% bupivacaine with 2 mcg/mL of fentanyl. A subsequent study by the same group determined that the ED90 optimal PIEB bolus volume when using this time interval of 40 min was approximately 11 mL, and that reducing bolus volume below 10 mL resulted in inferior analgesia [55].

**Optimal epidural solution**

Historically, epidural solutions consisted of very concentrated local anesthetics (e.g. 0.25–0.5% bupivacaine) to achieve labor analgesia, but these high concentrations were associated with an unacceptably high degree of motor blockade, inability to ambulate or push effectively during the second stage of labor, increased assisted vaginal delivery rates, and lower maternal satisfaction. The use of more dilute local anesthetic solutions allows for the provision of effective analgesia without many of these negative adverse effects related to the high local anesthetic concentrations. Meta-analysis data comparing low concentration labor epidurals (i.e. ≤ 0.1% bupivacaine or equivalent potency of ropivacaine) to those of higher concentrations (i.e. > 0.1% bupivacaine) found less assisted vaginal delivery rates, shorter duration of labor, better maternal motor function and greater ambulation, without differences in the labor analgesia provided [56]. Maternal satisfaction is also higher with dilute local anesthetic epidural solutions than with concentrated ones [56] likely due to fewer side effects. A meta-analysis found no differences in assisted vaginal delivery, CD, or the duration of labor with labor epidural analgesia using low-concentration local anesthetics compared to non-epidural analgesic options [57]. Additionally, a large randomized controlled trial found a similar duration of the second stage of labor and similar rates of spontaneous vaginal delivery when comparing 0.08% ropivacaine (with 0.4 mcg/mL sufentanil) to placebo administered at the start of the second stage of labor [58]. At
the time of delivery, the use of dilute local anesthetics allows women to have excellent pain control while still retaining motor function in the legs and without impacting their ability to push effectively during the second stage.

Dilute local anesthetic epidural solutions allow for less local anesthetic use without compromising labor analgesia. Lyons et al. [59] demonstrated comparable analgesia at the time of epidural initiation while achieving an overall 25% dose reduction when comparing 0.25%–0.125% bupivacaine solution. For labor analgesia maintenance, Boselli et al. [60] reported similar analgesic efficacy with 0.1% ropivacaine compared to 0.15% ropivacaine (each with sufentanil 0.5 mcg/mL) throughout the labor process despite a 30% dose reduction in the more dilute (0.1% ropivacaine) group.

To facilitate the use of more dilute local anesthetics while maintaining similar levels of analgesia, a lipophilic opioid must be added into the labor epidural solution. Adding a highly lipophilic opioid such as sufentanil or fentanyl to a local anesthetic reduces the overall local anesthetic dose required to provide adequate labor analgesia by a factor of up to 4.2-fold [61]. Chestnut demonstrated that similar analgesia could be obtained by using 0.0625% bupivacaine with fentanyl 2 mcg/mL compared to 0.125% plain bupivacaine without any opioid [62]. By using a more dilute solution, larger overall volumes can be administered, improving the spread of the solution within the epidural space and thereby increasing pain relief. The benefits of bolus techniques such as PCEA and PIEB (as opposed to slow epidural infusions) are maximized by the use of dilute local anesthetic solutions, as large volume dilute solutions augment the bolus-associated improved spread of local anesthetic solution in the epidural space. Studies comparing fentanyl to sufentanil reveal comparable side effects with equianalgesic doses, so either of these two opioids is a reasonable choice. The recommended doses are fentanyl 2–3 mcg/mL or sufentanil 0.2–0.4 mcg/mL.

Nitrous oxide (N2O)

N2O has a long history of being utilized as an analgesic modality for labor in many parts of the world, with utilization rates between 50% and 75% of parturients in the United Kingdom, Australia, Canada, and Scandinavian countries [63,64]. N2O for labor is generally self-administered by mask and combined with oxygen (most commonly as a 50%/50% mixture). N2O is well suited for labor analgesia, given its low potency (and thus large margin of safety), fast onset and offset, and being non-irritant, odorless and tasteless. N2O is well tolerated and because it undergoes almost no metabolism, its effects are consistent and predictable, and not dependent on end-organ function. Its mechanism of analgesic action remains poorly understood, but likely is due to a combination of endogenous opioid release as well as N-methyl-D-aspartate (NMDA) receptor inhibition [65].

Despite decades of use, high-quality data supporting a proven analgesic benefit for N2O are sparse. A systematic review of N2O for labor pain revealed only two studies (out of 58 examined) to be of “good” methodological quality [63]. Thus, the evidence for N2O being an effective modality for labor pain relief was insufficient, with the authors noting a high risk of bias and inconsistent findings between the various studies examined. Many studies examining N2O for labor reveal highly variable analgesic effectiveness. In an observational study, Holdcroft and Morgan asked 130 women who used N2O alone (of a total of 663 who used N2O, meperidine or both) about pain relief obtained and found that 31% reported none, 18% slight, 47% satisfactory, while 4% complete pain relief [66].

Maternal expectations, the support of caregivers and healthcare providers, and perceived degree of control or autonomy over the process are more important determinants of satisfaction with the childbirth experience than pain relief provided. This may explain, in part, why N2O is associated with higher maternal satisfaction despite inferior analgesia compared to neuraxial techniques, and why a large percentage of women who use N2O in labor report that they would use it again for a future childbirth, even though the analgesia obtained was incomplete [65].

N2O has no effect on either oxytocin activity or the progress of labor [67–69]. Maternal side effects reported in the literature include nausea, vomiting, dizziness, and drowsiness [63]. Data on fetal outcomes are limited, but there does not appear to be any difference in neonatal Apgar scores when N2O is compared to other analgesia options or to placebo [63]. No data exist to suggest any effect of N2O on fetal heart rate, umbilical cord gases, newborn respiratory effort, or neonatal neurobehavioral outcomes [63,67,68]. The possibility of subtle neurological effects of this anesthetic agent on the...
developing fetal brain remains an important area of ongoing research [70]. Another concern with N2O is occupational exposure of healthcare providers to this gas and the risk of reproductive toxicity. This is more of a concern in settings where appropriate scavenging equipment is not readily available or commonly used [70].

**Systemic opioids**

Many different opioids administered systemically (intravenously, intramuscularly) have been used to provide analgesia during labor and delivery. Dating back to the early part of the last century, morphine in combination with scopolamine was administered to parturients — the so-called “twilight sleep” method of painless childbirth [71], which was associated with many of the undesirable maternal and neonatal side effects described below. Studies comparing N2O with systemic opioids (meperidine and diamorphine) found minimal reductions in pain scores with either technique [63]. Data suggest that the extent of labor analgesia provided with systemic opioids is similar to that of N2O, and significantly less than neuraxial analgesic techniques. Systemic opioids are also associated with undesired maternal side effects such as pruritis, constipation, nausea/vomiting, respiratory depression, and potential fetal/neonatal adverse effects such as decreased fetal heart rate variability, respiratory depression, neonatal abstinence syndrome, and neurobehavioral changes. Large or repeated doses of any systemic opioid may result in decreased Apgar scores, neonatal respiratory depression, and impaired early breastfeeding [72]. Some common opioids used in global obstetric practice include meperidine (pethidine), morphine, diamorphine, fentanyl, and remifentanil.

Meperidine (pethidine) is a commonly utilized opioid for labor analgesia, administered as intermittent boluses intravenously or intramuscularly by midwives, nurses, or physicians. Despite being utilized in this setting, meperidine provides limited labor analgesia, has less labor analgesia efficacy than other systemic opioids such as remifentanil [73], and has an active metabolite, normeperidine, which has a prolonged duration of action (2–3 days) and may result in neurobehavioral effects in the newborn days after birth [72]. Therefore, meperidine is not an ideal opioid for laboring women and their fetuses.

Fentanyl is a lipophilic synthetic opioid that is 50–100× more potent than morphine [74]. It is most commonly given intravenously to laboring women by intermittent bolus administration by nurses or midwives, or via patient-controlled analgesia (PCA). Its quick time to onset and relatively short duration of action of 45–60 min make it reasonably well-suited for labor pain relief. Although fentanyl has no active metabolites, larger doses are associated with longer duration of action and associated with increased needs for neonatal resuscitation compared to remifentanil [75]. Doses therefore should be limited to only the first stage of labor, and limits on maximum total dose set. When compared to equianalgesic doses of meperidine, fentanyl is associated with less maternal nausea, vomiting, maternal sedation, and need for neonatal naloxone [76].

Remifentanil has received much attention as the optimal labor pain relief opioid. Remifentanil has a rapid peak analgesic effect <2 min after intravenous administration [77], a short context-sensitive half-life of 2–3 min [78] not dependent on the dose or duration of administration, and no active metabolites. Remifentanil is metabolized by nonspecific plasma esterases independent of renal or hepatic function both in the mother and in the fetus. Its favorable pharmacokinetics make it an attractive choice even in the second stage of labor as the risk of accumulation and neonatal respiratory depression necessitating resuscitation is potentially reduced compared to other opioids such as fentanyl [75]. Remifentanil provides modest labor analgesia that is significantly less than that provided by neuraxial techniques [79,80]; however, the labor analgesic efficacy is greater than meperidine and nitrous oxide [73]. Women receiving remifentanil PCA are more satisfied with the pain relief obtained compared to other opioids, but less satisfied than those receiving neuraxial analgesia [81].

Remifentanil is administered to laboring women using intravenous PCA, with or without a background infusion. The PCA parameters must balance analgesic efficacy with maternal safety as remifentanil has a narrow therapeutic range. The PCA demand/bolus dose as well as the lockout interval often needs adjusting, especially as labor progresses. In doses sufficient to provide analgesia in labor, maternal respiratory depression is a significant concern [73]. A study using remifentanil PCA during labor with end-tidal CO2 capnography monitoring found that 26% of parturients using remifentanil had
apnea during the first hour using remifentanil to provide labor analgesia [82], and case reports of respiratory depression and arrest have been described [83]. Reduced PCA doses are recommended to improve safety, but this decreases its analgesic efficacy. Additionally, many women may still require supplemental oxygen [84]. Given the concerns of respiratory depression, standardized protocols for administration and monitoring, including one-to-one nursing care, pulse oximetry, and ideally capnography as well as the immediate availability of anesthesiology personnel should be implemented in any institution where remifentanil PCA is used as an option for labor analgesia [73]. Measures should be taken to prevent errors especially if infrequently used, as the relative lack of familiarity by healthcare providers in the obstetric unit can compound safety concerns. There is widespread variability between institutions about the ideal role for remifentanil as a labor pain relief option [85]. Many centers reserve it for use only in women who have contraindications to other options including neuraxial techniques [73], whereas others offer it more routinely as an option to any parturient who desires it [86].

Considerations for resource limited settings

The above discussion assumes that all options are available at a particular center along with necessary appropriate personnel, monitoring equipment, emergency supplies, etc. This may not apply in resource limited settings such as low-income or low-middle-income countries (LIC/LMIC), or even rural/community hospitals in some high-income countries (HIC). Co-operation and communication between obstetricians, midwives, anesthesia providers, and nursing staff is paramount to ensure the safe provision of any pharmacological pain relief modality especially in these situations. In some centers, this may preclude the use of resource-intensive options such as neuraxial analgesia or patient-controlled intravenous options such as remifentanil PCA. This may mean intermittent systemic opioids and/or N₂O may be the only pharmacological methods available to women delivering in these settings. Additional non-pharmacological methods, appropriate counseling and education, and a discussion about the expected course of labor become even more important to improve the childbirth experience for these women when all pharmacological options may not be available [87]. Unfortunately in many circumstances, pain management is not offered or even discussed with women (more than half in one study looking at four different countries [88]), clearly hampering their ability to have a fully informed, positive childbirth experience.

Summary

In conclusion, modern neuraxial techniques are the gold-standard technique for the optimal provision of labor analgesia and when managed appropriately are associated with maternal and fetal/neonatal safety. There are many strategies to optimize initiation and maintenance of neuraxial labor analgesia. The use of neuraxial techniques such as CSE or DPE may offer benefits over standard epidural. Pre-procedure US can assist with epidural placement and improve the ultimate success of the neuraxial technique. PCEA with a background of PIEB represents the maintenance technique of choice, providing effective patient-centered labor analgesia. The use of dilute local anesthetic solutions combined with lipophilic opioids is critical to minimize epidural-related side effects and reduce the impact of labor epidural analgesia on obstetric outcomes [57,89]. Techniques utilizing dilute local anesthetic plus lipophilic opioid solutions and administered with a background PIEB with PCEA for breakthrough pain provide highly effective labor analgesia with minimal maternal and fetal side effects. Adoption of state-of-the-art techniques outlined in this review can optimize both the initiation and maintenance of neuraxial labor analgesia. Although neuraxial analgesia is the gold-standard labor analgesic, N₂O and systemic opioids should be offered to women wishing to avoid or delay neuraxial analgesia or to those for whom neuraxial analgesia use is contraindicated. Remifentanil is the most effective opioid for use in the labor setting; however, this technique requires additional monitoring due to maternal respiratory depression safety concerns. The initiation of any labor analgesia modality should occur after a woman has given informed consent, taking into account her wishes, desires, and beliefs, hopefully contributing to a positive birth experience for her and her family.
Practice Points

- Satisfaction with labor analgesia has many determinants, with effectiveness of the pain relief obtained being only one of many.
- Neuraxial analgesic techniques such as epidurals or CSEs are the gold standard for labor pain relief.
- Nitrous oxide (N₂O) has a long history of use in obstetrics for labor analgesia, but strong evidence for its efficacy is lacking.
- Systemic opioids such as remifentanil can be used for effective pain relief in labor, although concerns about maternal and fetal side effects generally limit its routine use.

Research Agenda

- More high-quality studies examining the efficacy and safety of nitrous oxide for labor analgesia are required for us to have a full understanding of how to best use this modality in obstetric patients.
- Ongoing analysis of experience with remifentanil used as part of a PCA technique should help elucidate its optimal role and indications.

Declaration of Competing interest

The authors have no conflicts of interest.

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