REVIEW

Modern Neuraxial Anesthesia for Labor and Delivery [version 1; peer review: 2 approved]

Marie-Louise Meng , Richard Smiley

Department of Anesthesiology, Columbia University Medical Center, New York, NY, USA

V1 First published: 25 Jul 2017, 6(F1000 Faculty Rev):1211
<https://doi.org/10.12688/f1000research.11130.1>

Latest published: 25 Jul 2017, 6(F1000 Faculty Rev):1211
<https://doi.org/10.12688/f1000research.11130.1>

Abstract

The availability of safe, effective analgesia during labor has become an expectation for women in most of the developed world over the past two or three decades. More than 60% of women in the United States now receive some kind of neuraxial procedure during labor. This article is a brief review of the advantages and techniques of neuraxial labor analgesia along with the recent advances and controversies in the field of labor analgesia. For the most part, we have aimed the discussion at the non-anesthesiologist to give other practitioners a sense of the state of the art and science of labor analgesia in the second decade of the 21st century.

Keywords

neuraxial , analgesia , epidural ,

Open Peer Review

Approval Status

	1	2
version 1 25 Jul 2017

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Alex Tiong Heng Sia**, KK Women's and Children's Hospital, Bukit Timah, Singapore
2. **Paloma Toledo**, Northwestern University, Feinberg School of Medicine, Chicago, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Marie-Louise Meng (mm3847@cumc.columbia.edu)

Competing interests: The authors declare that the spouse of Richard Smiley owns stock in Abbott, AbbVie and Amgen Inc.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2017 Meng ML and Smiley R. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Meng ML and Smiley R. **Modern Neuraxial Anesthesia for Labor and Delivery [version 1; peer review: 2 approved]** F1000Research 2017, **6**(F1000 Faculty Rev):1211 <https://doi.org/10.12688/f1000research.11130.1>

First published: 25 Jul 2017, **6**(F1000 Faculty Rev):1211 <https://doi.org/10.12688/f1000research.11130.1>

Although neuraxial (caudal and single lumbar epidural) injections were used sporadically throughout the early 20th century to reduce labor pain, the provision of labor analgesia by administration of local anesthetics via catheters inserted into the epidural space or spinal fluid is a technique that dates from the mid-20th century and did not truly become widely available until the 1980s. Over the past two decades, there have been significant advances in the quality and safety of the analgesic techniques used. The long-standing and important controversy regarding whether and how neuraxial labor analgesia affects the course of labor has been addressed and at least partially resolved. The modern era of obstetric analgesia probably should be regarded as beginning in the 1990s with the widespread adoption into clinical practice of the understanding that one could reduce local anesthetic concentrations in epidural analgesia by 40% to 60% by adding small doses of opioids (usually fentanyl or sufentanil). Other advances have included the introduction of the combined spinal-epidural (CSE) technique and, more recently, the similar “dural puncture epidural” (DPE) technique. Equipment has driven improvements too; the almost universal use of continuous infusion pumps has replaced the need for anesthesiologists to dose catheters every hour or two, which improves the obvious issue of breakthrough pain if clinician-based dosing is not timed properly. Most epidural infusion pumps now allow patient-administered top-ups (extra doses), and the newest generation of epidural pumps can be programmed to administer intermittent timed boluses (programmed intermittent epidural bolus, or PIEB).

Anatomy and physiology

Labor pain, apart from the physical component, also has emotional and cognitive elements. Pain during labor and delivery is different for every woman, and the goals of each patient's pain relief vary, depending on how she perceives the physical, emotional, and cognitive dimensions of pain. For the parturient, satisfaction with pain relief during labor not only may be a function of relief of physical pain but also is very dependent on practitioners' attitudes, the parturient's expectations, and her ability to exercise some control over the delivery^{1,2}. Interestingly, it has been reported that partners of laboring patients have less anxiety and feel more involved in the labor process if their partners receive epidural analgesia³. Researchers are investigating the possibility that women who receive neuraxial pain relief in labor may be at a lower risk of post-partum depression and mood disorders⁴.

Pain and the stress response to labor induce the release of corticotropin, cortisol, norepinephrine, β -endorphins, and epinephrine into the maternal circulation and this can result in a decrease in uterine blood flow. Pain reduction and sympathectomy caused by neural blockade result in lower levels of catecholamines and improvement in uteroplacental perfusion, especially in states of low uterine blood flow (pre-eclampsia and intrauterine growth retardation)⁵⁻⁸. The pain of uterine contractions and cervical dilation originates in the visceral afferent nerve fibers that enter the spinal cord at the levels of T10–L1. As the fetus descends into the vaginal canal, the somatic pain arising from the maternal pelvic floor travels along the pudendal nerve fibers S2–4. The ability to rapidly convert labor epidural analgesia to epidural surgical anesthesia and avoid general anesthesia (for mom and

fetus) is generally regarded as an additional benefit of placing an epidural catheter during labor. Maternal airway anatomy changes during pregnancy, making difficult ventilation and difficult intubation real possibilities in the pregnant patient; multiple studies suggest that the incidence of failed intubation in pregnancy is much higher than in non-pregnant surgical patients⁹. A functioning epidural catheter in a patient who may be difficult to intubate or ventilate is a safety strategy, as the catheter can be used to provide surgical anesthesia and airway manipulation can be avoided should a patient require an emergency intrapartum cesarean delivery (CD).

Effect of presence and timing of analgesia on the course of labor

The possible effect of epidural analgesia on the course of labor has been and still is a subject of major controversy. Studies examining whether epidural analgesia (usually compared with intravenous opioids) slows labor or results in increased CD rates are very difficult to do because of ethical/consent issues and because of crossover from subjects who opt to receive epidural analgesia as “rescue” analgesia after being assigned to the non-epidural group. Still, the consensus from the studies that have been done is that if there is any effect, it is small and probably dose-dependent. The concern is that with larger doses of local anesthetic, the muscle relaxation and motor block may be greater, which may have an effect on the descent of the fetus and on the voluntary maternal expulsive efforts. Modern local anesthetic (combined with opioid) epidural techniques probably have little to no effect on CD rates^{10,11}. A multicenter randomized controlled trial (RCT) demonstrated that there is also no increase in operative vaginal delivery with the use of low-dose epidural anesthesia¹². A meta-analysis comparing epidural anesthesia with intravenous opioids for labor pain revealed that epidural anesthesia prolongs the second stage of labor (time from full cervical dilation to delivery of the fetus) by only 15 to 28 minutes¹³. Therefore, it has been well established and stated best by the American College of Obstetricians and Gynecologists and the American Society of Anesthesiologists that “In the absence of a medical contraindication, maternal request is a sufficient medical indication for pain relief during labor”¹⁴.

The *timing* of administration of epidural analgesia was also controversial until recently, and women were often told that they needed to wait until the cervix was dilated 4 or 5 cm before they could receive epidural analgesia¹⁵ because to have epidural analgesia earlier would slow labor and increase CD rates. The question of timing (“early” versus “later”) as opposed to use of analgesia at any time is much easier to study in an effective way. Several high-quality randomized trials performed in the first decade of the 21st century have demonstrated clearly that epidural (or CSE) analgesia provided very early in labor versus waiting for a pre-determined (4 or 5 cm) dilatation does not affect the overall course of labor and delivery. Wong *et al.* performed two RCTs, which demonstrated that in nulliparous women in either spontaneous or induced labor, early versus late initiation of neuraxial anesthesia did not increase the risk of CD or affect the time in labor^{16,17}. Two similar studies—one in Israel¹⁸ and an extremely large (>13,000 women) study from China¹⁹—confirmed

these results. Based on the consistent evidence above, the current consensus does appear to be that the timing of labor analgesia does not affect the mode of delivery and the course of delivery and that most women can receive analgesia upon request regardless of stage of labor²⁰.

Technique

In the standard epidural technique, a needle is placed into the epidural space, identifying the space by a “loss of resistance” to injection of saline or air because of the low pressure in the epidural space compared with the ligamentous structures that have been traversed. A catheter is generally placed via the needle, the needle removed, and medications given via the catheter to provide analgesia or anesthesia. In the 1990s, prompted by the availability of small-gauge “pencil point” spinal needles that rarely cause post-dural puncture headaches, many practitioners started placing long, thin spinal needles through the epidural needle, to allow a medications to be given into the cerebrospinal fluid, before threading the epidural catheter that will be used once the spinal dose wears off in 60 to 120 minutes²¹. Opioids alone (fentanyl, sufentanil, or morphine) were found to be effective for early- and mid-first-stage labor pain, providing pain relief with no associated sympathetic or motor block. A low dose of local anesthetic (bupivacaine or ropivacaine) is now usually added, providing improved analgesia particularly in women who are already in or near the second stage and experiencing the somatic pain in the sacral regions which is associated with second-stage labor^{22,23}. Another claimed advantage of the CSE technique is that, by seeing the return of cerebral spinal fluid via the spinal needle passed through the epidural needle and just beyond its tip, the anesthesiologist can confirm objectively that the epidural needle is actually in the epidural space. This may decrease the rate of “epidural failure” from misplaced catheters^{24,25}.

The technique of combined spinal epidural analgesia has been used broadly at academic medical centers to produce rapid onset of analgesia for labor pain and improve the spread of sacral analgesia. Widespread acceptance of the technique in the community has been limited somewhat by the complexity of the technique and requirement for the extra needle, but also by pruritus from spinal opioids and some evidence that the rapid onset or other factors in spinal analgesia may have effects on the fetal heart rate, possibly from increased rate or strength of uterine contraction^{26–28}. A new technique, DPE, involves the performance of a CSE but without administration of an intrathecal medication dose. A recent RCT by Chau *et al.* demonstrated that the DPE provided faster onset and greater spread of sacral analgesia and less asymmetric blocks compared with a standard epidural analgesic, suggesting that the dural puncture might facilitate medication transfer intrathecally or that the performance of a dural puncture truly aids in confirmation of midline placement of epidural, leading to a greater chance of bilateral block²⁹. The DPE may become a valuable technique for the anesthesiologist looking to avoid the mild hypotension that may be caused with rapid onset of spinal analgesia, pruritis, or alterations in the fetal heart tracing but wanting to provide improved sacral analgesia and a more certain midline epidural catheter²⁹.

Dosing

Labor analgesia is usually initiated with both dilute long-acting local anesthetic and a lipophilic opioid either in low doses through the spinal needle if a CSE is performed (for example, bupivacaine 2.5 mg with fentanyl 5 to 20 µg) or in higher dose and volume (for example, bupivacaine 0.125% 10 to 15 mL with fentanyl 100 µg) in the epidural space as an epidural “load” when epidural or DPE analgesia is performed. The optimal maintenance infusion of medication into the epidural space is a combination of dilute long-acting local anesthetic and lipophilic opioid. This combination is synergistic, improving the analgesia while minimizing the toxicity of either agent, limiting motor blockade and significant numbness^{30–32}. With optimal epidural analgesia, patients experience mild pressure with contractions, sense rectal pressure and the urge to bear down at the start of the second stage, and maintain the motor ability to push. This can frequently be achieved with concentrations of bupivacaine or ropivacaine in the 0.0625 to 0.125% range, combined with fentanyl 2 µg/mL, at infusion rates of around 10 to 12 mL/hour. In these doses, the concentration of local anesthesia is unlikely to impact labor outcomes^{33–35}.

Because labor pain and the effect of any given analgesia mixture and rate of infusion are unpredictable, contemporary practice frequently includes the option of patient-controlled administration, similar to the ubiquitous intravenous patient-controlled opioid administration that has been commonly used for post-operative analgesia. Patient-controlled epidural analgesia (PCEA) was first described by Gambling *et al.*³⁶ in 1988 and has become the standard approach³⁷. A button connected to the pump allows the parturient to dose herself with extra epidural infusion medication should she desire or require stronger analgesia. This PCEA results in increased maternal satisfaction, as control over one’s own analgesia is a factor that is highly valued by laboring women. Multiple recipes and strategies have been published and are used, as a wide range of acceptable doses is possible when the patient can “titrate” to what they need.

Newer epidural pumps can administer a programmed volume intermittently, at a higher infusion rate than the traditional continuous infusion, facilitating medication spread in the epidural space, resulting in improved analgesia with less motor block and with less overall consumption of local anesthesia^{38–41}. There is evidence that this mode of administration works slightly but consistently better than a continuous infusion and perhaps this is due to better spread of medication in the epidural space when larger volumes are infused over a relatively short time by the pump. This mode of dosing is called PIEB. The optimal dose volume and time interval of dosing are in early stages of investigation but are likely about 10 mL of epidural medication every 40 minutes with maternal option of periodic extra boluses^{41,42}.

Other analgesia options

There are few if any effective options for labor pain relief outside of neuraxial techniques. Intravenous and intramuscular opioids are still used but are well known to be relatively ineffective. The various breathing and relaxation and self-hypnotic techniques promoted over the years often as part of “natural childbirth” have some

benefit but rarely provide actual analgesia. Nitrous oxide (N_2O) has been used for decades in the United Kingdom and other countries in Europe but was almost absent from American labor suites until a few years ago. Its major purported advantage among its promoters seems to be that patients want it and perceive of it as less invasive (more “natural”) than neuraxial analgesia². Availability of N_2O for use during labor in US hospitals is increasing, but there is significant concern that the risks of N_2O outweigh the benefits of its use⁴³. N_2O has minimal if any analgesic advantage over placebo and is far less effective than neuraxial anesthesia⁴³. N_2O also produces nausea, vomiting, and dizziness, side effects that are much less common with epidural anesthesia. It is a known neurotoxic drug that is used less and less in operating rooms and has effects on DNA synthesis and repair. Occupational exposure to nurses and physicians in poorly ventilated and scavenged labor rooms is also a concern^{44,45}. Although there has been increased discussion about its use, N_2O is not currently used at our institution for labor analgesia.

For patients who cannot receive neuraxial anesthesia secondary to severe coagulopathy or anatomical abnormality such as scoliosis, a continuous intravenous infusion or patient-controlled administration of fentanyl or remifentanyl is an option. Fentanyl is a commonly used opioid in post-operative patient-controlled analgesia (PCA) and similar PCA infusions can be used in labor with modest efficacy. Remifentanyl is a synthetic, short-acting opioid that is readily hydrolyzed by plasma esterases, resulting in a short context-sensitive half-life in both mother and fetus/neonate. Because of its rapid clearance, remifentanyl may be administered at doses that cause effects that would not be acceptable for a drug that lasts hours. Although it is tricky and imperfect

to time boluses of medication with the onset of contraction well enough to provide analgesia during the contractions, the fast-on-and-fast-off analgesia and sedation of remifentanyl make it an effective opioid for continuous infusion or PCA infusion during labor^{46–48}. One-to-one nursing care is required for patients on remifentanyl infusions to monitor closely for sedation and respiratory depression⁴⁹.

In summary, labor analgesia in 2017 is a far different “product” and experience than two decades ago. Most women can expect rapid, effective analgesia with limited weakness and numbness for most of labor and a degree of control over the dosing and timing of medication and can be reassured that accepting effective pain relief for labor does not impair their labor process or negatively affect its outcome.

Abbreviations

CD, cesarean delivery; CSE, combined spinal-epidural; DPE, dural puncture epidural; PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; PIEB, programed intermittent epidural bolus; N_2O , nitrous oxide; RCT, randomized controlled trial.

Competing interests

The authors declare that the spouse of Richard Smiley owns stock in Abbott, AbbVie and Amgen Inc.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

- Angle P, Landy CK, Charles C, *et al.*: **Phase 1 development of an index to measure the quality of neuraxial labour analgesia: exploring the perspectives of childbearing women.** *Can J Anaesth.* 2010; 57(5): 468–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Camann W: **Pain, Pain Relief, Satisfaction and Excellence in Obstetric Anesthesia: A Surprisingly Complex Relationship.** *Anesth Analg.* 2017; 124(2): 383–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Capogna G, Camorcia M, Stirparo S: **Expectant fathers' experience during labor with or without epidural analgesia.** *Int J Obstet Anesth.* 2007; 16(2): 110–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ding T, Wang DX, Qu Y, *et al.*: **Epidural labor analgesia is associated with a decreased risk of postpartum depression: a prospective cohort study.** *Anesth Analg.* 2014; 119(2): 383–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Ginosar Y, Nadjari M, Hoffman A, *et al.*: **Antepartum continuous epidural ropivacaine therapy reduces uterine artery vascular resistance in pre-eclampsia: a randomized, dose-ranging, placebo-controlled study.** *Br J Anaesth.* 2009; 102(3): 369–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Strümpfer D, Louwen F, Durieux ME, *et al.*: **Epidural local anesthetics: a novel treatment for fetal growth retardation?** *Fetal Diagn Ther.* 2005; 20(3): 208–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ramos-Santos E, Devoe LD, Wakefield ML, *et al.*: **The effects of epidural anesthesia on the Doppler velocimetry of umbilical and uterine arteries in normal and hypertensive patients during active term labor.** *Obstet Gynecol.* 1991; 77(1): 20–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Abboud TK, Sarkis F, Hung TT, *et al.*: **Effects of epidural anesthesia during labor on maternal plasma beta-endorphin levels.** *Anesthesiology.* 1983; 59(1): 1–5.
[PubMed Abstract](#)
- Quinn AC, Milne D, Columb M, *et al.*: **Failed tracheal intubation in obstetric anaesthesia: 2 yr national case-control study in the UK.** *Br J Anaesth.* 2013; 110(1): 74–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Wang TT, Sun S, Huang SQ: **Effects of Epidural Labor Analgesia With Low Concentrations of Local Anesthetics on Obstetric Outcomes: A Systematic Review and Meta-analysis of Randomized Controlled Trials.** *Anesth Analg.* 2017; 124(5): 1571–80.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Cambic CR, Wong CA: **Labour analgesia and obstetric outcomes.** *Br J Anaesth.* 2010; 105(Suppl 1): i50–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Halpern SH, Muir H, Breen TW, *et al.*: **A multicenter randomized controlled trial comparing patient-controlled epidural with intravenous analgesia for pain relief in labor.** *Anesth Analg.* 2004; 99(5): 1532–8; table of contents.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Liu EH, Sia AT: **Rates of caesarean section and instrumental vaginal delivery**

- in nulliparous women after low concentration epidural infusions or opioid analgesia: systematic review. *BMJ*. 2004; 328(7453): 1410.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. ACOG Committee Opinion #295: pain relief during labor. *Obstet Gynecol*. 2004; 104(1): 213.
[PubMed Abstract](#)
 15. Goetzl LM; ACOG Committee on Practice Bulletins-Obstetrics: ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists Number 36, July 2002. Obstetric analgesia and anesthesia. *Obstet Gynecol*. 2002; 100(1): 177–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 16. Wong CA, McCarthy RJ, Sullivan JT, *et al.*: Early compared with late neuraxial analgesia in nulliparous labor induction: a randomized controlled trial. *Obstet Gynecol*. 2009; 113(5): 1066–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Wong CA, Scavone BM, Peaceman AM, *et al.*: The risk of cesarean delivery with neuraxial analgesia given early versus late in labor. *N Engl J Med*. 2005; 352(7): 655–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. **F** Ohel G, Gonen R, Vaida S, *et al.*: Early versus late initiation of epidural analgesia in labor: does it increase the risk of cesarean section? A randomized trial. *Am J Obstet Gynecol*. 2006; 194(3): 600–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 19. Wang F, Shen X, Guo X, *et al.*: Epidural analgesia in the latent phase of labor and the risk of cesarean delivery: a five-year randomized controlled trial. *Anesthesiology*. 2009; 111(4): 871–80.
[PubMed Abstract](#) | [Publisher Full Text](#)
 20. Nageotte M: Timing of conduction analgesia in labor. *Am J Obstet Gynecol*. 2006; 194(3): 598–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Eisenach JC: Combined spinal-epidural analgesia in obstetrics. *Anesthesiology*. 1999; 91(1): 299–302.
[PubMed Abstract](#)
 22. Abouleish A, Abouleish E, Camann W: Combined spinal-epidural analgesia in advanced labour. *Can J Anaesth*. 1994; 41(7): 575–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Goodman SR, Smiley RM, Negron MA, *et al.*: A randomized trial of breakthrough pain during combined spinal-epidural versus epidural labor analgesia in parous women. *Anesth Analg*. 2009; 108(1): 246–51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 24. **F** Booth JM, Pan JC, Ross VH, *et al.*: Combined Spinal Epidural Technique for Labor Analgesia Does Not Delay Recognition of Epidural Catheter Failures: A Single-center Retrospective Cohort Survival Analysis. *Anesthesiology*. 2016; 125(3): 516–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 25. Groden J, Gonzalez-Fiol A, Aaronson J, *et al.*: Catheter failure rates and time course with epidural versus combined spinal-epidural analgesia in labor. *Int J Obstet Anesth*. 2016; 26: 4–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Abrão KC, Francisco RP, Miyadaira S, *et al.*: Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. *Obstet Gynecol*. 2009; 113(1): 41–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Clarke VT, Smiley RM, Finster M: Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: a cause of fetal bradycardia? *Anesthesiology*. 1994; 81(4): 1083.
[PubMed Abstract](#)
 28. Van de Velde M, Teunkens A, Hanssens M, *et al.*: Intrathecal sufentanil and fetal heart rate abnormalities: a double-blind, double placebo-controlled trial comparing two forms of combined spinal epidural analgesia with epidural analgesia in labor. *Anesth Analg*. 2004; 98(4): 1153–9, table of contents.
[PubMed Abstract](#) | [Publisher Full Text](#)
 29. **F** Chau A, Bibbo C, Huang CC, *et al.*: Dural Puncture Epidural Technique Improves Labor Analgesia Quality With Fewer Side Effects Compared With Epidural and Combined Spinal Epidural Techniques: A Randomized Clinical Trial. *Anesth Analg*. 2017; 124(2): 560–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 30. Ginosar Y, Columb MO, Cohen SE, *et al.*: The site of action of epidural fentanyl infusions in the presence of local anesthetics: a minimum local analgesic concentration infusion study in nulliparous labor. *Anesth Analg*. 2003; 97(5): 1439–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Polley LS, Columb MO, Naughton NN, *et al.*: Effect of intravenous versus epidural fentanyl on the minimum local analgesic concentration of epidural bupivacaine in labor. *Anesthesiology*. 2000; 93(1): 122–8.
[PubMed Abstract](#)
 32. Polley LS, Columb MO, Wagner DS, *et al.*: Dose-dependent reduction of the minimum local analgesic concentration of bupivacaine by sufentanil for epidural analgesia in labor. *Anesthesiology*. 1998; 89(3): 626–32.
[PubMed Abstract](#)
 33. Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK: Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. *Lancet*. 2001; 358(9275): 19–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Chestnut DH, Vandewalker GE, Owen CL, *et al.*: The influence of continuous epidural bupivacaine analgesia on the second stage of labor and method of delivery in nulliparous women. *Anesthesiology*. 1987; 66(6): 774–80.
[PubMed Abstract](#)
 35. Chestnut DH, Laszewski LJ, Pollack KL, *et al.*: Continuous epidural infusion of 0.0625% bupivacaine-0.0002% fentanyl during the second stage of labor. *Anesthesiology*. 1990; 72(4): 613–8.
[PubMed Abstract](#)
 36. Gambling DR, Yu P, Cole C, *et al.*: A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labour. *Can J Anaesth*. 1988; 35(3 (Pt 1)): 249–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Smiley RM, Stephenson L: Patient-controlled epidural analgesia for labor. *Int Anesthesiol Clin*. 2007; 45(1): 83–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. **F** Carvalho B, George RB, Cobb B, *et al.*: Implementation of Programmed Intermittent Epidural Bolus for the Maintenance of Labor Analgesia. *Anesth Analg*. 2016; 123(4): 965–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 39. Fettes PD, Moore CS, Whiteside JB, *et al.*: Intermittent vs continuous administration of epidural ropivacaine with fentanyl for analgesia during labour. *Br J Anaesth*. 2006; 97(3): 359–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
 40. **F** Sia AT, Lim Y, Ocampo C: A comparison of a basal infusion with automated mandatory boluses in parturient-controlled epidural analgesia during labor. *Anesth Analg*. 2007; 104(3): 673–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 41. Wong CA, McCarthy RJ, Hewlett B: The effect of manipulation of the programmed intermittent bolus time interval and injection volume on total drug use for labor epidural analgesia: a randomized controlled trial. *Anesth Analg*. 2011; 112(4): 904–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. **F** Epszstein Kanczuk M, Barrett NM, Arzola C, *et al.*: Programmed Intermittent Epidural Bolus for Labor Analgesia During First Stage of Labor: A Biased-Coin Up-and-Down Sequential Allocation Trial to Determine the Optimum Interval Time Between Boluses of a Fixed Volume of 10 mL of Bupivacaine 0.0625% With Fentanyl 2 µg/mL. *Anesth Analg*. 2017; 124(2): 537–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 43. **F** King TL, Wong CA: Nitrous oxide for labor pain: is it a laughing matter? *Anesth Analg*. 2014; 118(1): 12–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 44. **F** Wrońska-Nofer T, Nofer JR, Jajte J, *et al.*: Oxidative DNA damage and oxidative stress in subjects occupationally exposed to nitrous oxide (N₂O). *Mutat Res*. 2012; 731(1–2): 58–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 45. Wrońska-Nofer T, Palus J, Krajewski W, *et al.*: DNA damage induced by nitrous oxide: study in medical personnel of operating rooms. *Mutat Res*. 2009; 666(1–2): 39–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Aaronson J, Abramovitz S, Smiley R, *et al.*: A Survey of Intravenous Remifentanyl Use for Labor Analgesia at Academic Medical Centers in the United States. *Anesth Analg*. 2017; 124(4): 1208–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 47. **F** Birnbach DJ, Ranasinghe JS: Is remifentanyl a safe and effective alternative to neuraxial labor analgesia? It all depends. *Anesth Analg*. 2014; 118(3): 491–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 48. **F** van de Velde M, Carvalho B: Remifentanyl for labor analgesia: an evidence-based narrative review. *Int J Obstet Anesth*. 2016; 25: 66–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 49. **F** Stocki D, Matot I, Einav S, *et al.*: A randomized controlled trial of the efficacy and respiratory effects of patient-controlled intravenous remifentanyl analgesia and patient-controlled epidural analgesia in laboring women. *Anesth Analg*. 2014; 118(3): 589–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1. **Paloma Toledo**

Northwestern University, Feinberg School of Medicine, Chicago, IL, USA

Competing Interests: No competing interests were disclosed.

2. **Alex Tiong Heng Sia**

Department of Women's Anaesthesia, KK Women's and Children's Hospital, Bukit Timah, Singapore

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research