

Effectiveness of Nitrous Oxide for Women in Labor  
*A Literature Review of the Evidence*

**Clinical Question:** What is the quantity, quality, consistency, and effectiveness of nitrous oxide use for pain management for women in labor?

**Conclusions:** Labor pain and methods to relieve it have considerable implications to the clinical course, quality, outcome and cost of intrapartum care.<sup>3</sup> This literature review was requested to assess effectiveness of nitrous oxide (N<sub>2</sub>O) for women in labor. The 3 articles meeting inclusion criteria revealed inconsistent evidence for the effectiveness of N<sub>2</sub>O for labor pain management. However, the evidence was consistent regarding the safety for maternal and fetal/neonatal during N<sub>2</sub>O administration.<sup>1,2,3</sup>

Inhaled analgesia appears to be effective in reducing pain intensity and in managing the mother's perception of pain during labour.<sup>1,3</sup> A N<sub>2</sub>O/50% oxygen blend is safe for the mother and fetus due to the rapid elimination. The maternal respiratory circuit has with no passage through the placental unit and therefore the risk of neonatal depression is lower than that observed with opioids.<sup>3</sup> Despite substantial variations in pain intensity<sup>1,2</sup>, pain perception of laboring women was found to be significantly reduced throughout the labor process.<sup>3</sup> Overall the strength of evidence was insufficient for effectiveness in labor pain management, low for maternal satisfaction, and moderate for harms, due to heavy observational research studies and unclear randomization.<sup>2</sup>

**Key Summary of the Evidence:** Nitrous oxide provides analgesia, decreases women's perception of pain, and has an anxiolytic effect that may be helpful if women are restless or doubt their ability to cope with labor pain.<sup>2</sup> The rapid onset and offset of N<sub>2</sub>O provides women with the ability to switch pain management options, unlike the prolonged effects of epidural analgesia and systemic opioids that diminish gradually.<sup>2</sup> Table 1 (Page 3) and Appendix (Page 4) present the evidence from three selected studies, which include the following:

- N<sub>2</sub>O can provide useful pain management options when a woman wants to delay use of epidural analgesia, when epidural analgesia is not immediately available, when an epidural analgesia is not an option, or when epidural analgesia is ineffective or inadequate.<sup>2</sup>
- N<sub>2</sub>O has other benefits beyond pain relief, including the preservation of mobility and no additional monitoring while avoiding potential anesthesia related interventions (e.g., bladder catheterization).<sup>2</sup>
- Pain relief may be an inadequate measure of N<sub>2</sub>O effectiveness in the absence of other outcomes such as women's satisfaction.<sup>2</sup> N<sub>2</sub>O is not intended to provide complete pain relief; birth experience satisfaction may be a more relevant measure of effectiveness than assessment of pain.<sup>2</sup>
- Maternal Adverse Effects: Most maternal adverse effects included unpleasant side effects affecting tolerability, such as nausea, vomiting, dizziness, and drowsiness.<sup>1,2,3</sup> Some maternal adverse effects of analgesia are common in all laboring women regardless of whether analgesia is used<sup>2</sup> (Table 1, Page 3; Appendix, Page 4)
- Fetal/Neonatal Adverse Effects: Apgar scores in newborns whose mothers used nitrous oxide did not differ significantly from those of newborns whose mothers used other labor pain management methods.<sup>1,2,3</sup> One study reported no admissions to the Neonatal Intensive Care Unit (NICU) or complications.<sup>3</sup>
- Occupational Exposure: Conclusions regarding potential occupational harms of exposure was difficult to discern, due to limited data.<sup>1,2</sup> Some studies were conducted before room ventilation systems use or scavenging systems. The implementation of these systems appears to reduce occupational exposure, which in could turn mitigate potential risks of exposure.<sup>2</sup>

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**Recommendations:** Inhaled analgesia is an effective and safe method to humanize the birth process for the management of pain during labor.<sup>3</sup> The literature indicates that pain relief through inhaled analgesia may be a useful form of pain management for some women in labor, especially for those who wish some form of pharmacological relief without invasive methods.<sup>1</sup> The following recommendations are offered for clinicians to consider when administering N<sub>2</sub>O to laboring women for pain management:

- Provide pain management options to women in labor beyond epidural analgesia.<sup>2</sup>
- Ensure nurses, physicians, patients, and family receive adequate information and education regarding the benefits, risks, and adverse effects of N<sub>2</sub>O and other pain management options, as well as maternal, fetal, and occupational exposure adverse effects.<sup>2</sup>
- Consider the use of self-administrated N<sub>2</sub>O to allow women to control the amount of the analgesia they perceive needing while in labor.<sup>2</sup>
- Evaluate other measures of effective labor managements, such as women's satisfaction with the labor and birth experience.<sup>1,2,3</sup>
- Identify health system factors influencing N<sub>2</sub>O use for labor pain management,<sup>2</sup> which include but are not limited to provider preferences,<sup>2</sup> availability,<sup>2</sup> setting,<sup>2</sup> resource utilization,<sup>2</sup> cost benefit analyses,<sup>1,2</sup> clinician/patient/family educational needs,<sup>2</sup> and occupational exposure.<sup>2</sup>

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Table 1  
Study Results for Nitrous Oxide for Women in Labor

Study/Design/Sample	Reported Effectiveness	Clinical Considerations & Implications
Klomp et al. (2012)  Systematic review: 26 studies- randomizing 2959 women	Assessed laboring women's pain relief satisfaction rather than pain assessment scores:  <u>Satisfaction with Pain Relief (1<sup>st</sup>/2<sup>nd</sup> Stage of Labor):</u> No difference in women's pain relief satisfaction with methoxyflurane as compared with N2O.  <u>Satisfaction with Pain Relief: Second Stage:</u> Good to excellent pain relief satisfaction (4 studies, N=323). No difference in pain relief satisfaction for women receiving N2O (self-administered, intermittent, continuous) compared with women receiving an agent from flurane derivatives group (self-administered or continuous).	<p style="text-align: center;"><b>Maternal Adverse Effects</b></p> <ul style="list-style-type: none"> <li>• Meta-analysis highlighted adverse effects (nausea, drowsiness, etc.) associated with some types of inhaled analgesia such as N2O</li> <li>• <b>Drowsiness:</b> No difference in drowsiness between the N2O group and Isoflurane group.</li> <li>• <b>Nausea:</b> Reported in two trials with 98 women: N2O group reported more nausea compared with the flurane derivatives group.</li> <li>• <b>Vomiting:</b> Three trials with 203 women: No difference in vomiting between N2O group compared with the flurane derivatives group.</li> </ul> <p style="text-align: center;"><b>Fetal/Neonatal Adverse Effects</b></p> <ul style="list-style-type: none"> <li>• Reported in five trials with 373 women with single births. No differences reported in Apgar scores.</li> </ul> <p style="text-align: center;"><b>Occupational Exposure</b></p> <ul style="list-style-type: none"> <li>• No trials reported on differences in occupational exposure and toxic effects on reproduction for the professional.</li> </ul>
Likis et al. (2014)  Systematic review: 59 distinct study populations	Satisfaction with birth experience may be a more relevant measure of effectiveness than assessment of pain.  N2O is not intended to provide complete pain relief.  Epidural provided more effective pain relief than N2O.  Pain relief likely to be inadequate measure of N2O effectiveness in absence of other outcomes such as women's satisfaction.  Substantial variation of pain assessment timing may have affected outcomes.	<p style="text-align: center;"><b>Maternal Adverse Effects</b></p> <ul style="list-style-type: none"> <li>• 16 studies conducted before 1980 when N2O was often used in combination with sedatives and other inhaled anesthetics in labor. Studies reporting harms associated with sedative analgesic regimens may not translate effectively to contemporary labor analgesia practice. For example, in older studies, amnesia in labor was considered a positive outcome.</li> <li>• Most maternal adverse effects were unpleasant side effects affecting tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Some maternal adverse effects of analgesia (e.g., nausea) are common in all laboring women regardless of whether analgesia is used. Study sizes were inadequate to assess unusual or rare harms that might be more serious in terms of morbidity.</li> </ul> <p style="text-align: center;"><b>Fetal/Neonatal Adverse Effects</b></p> <ul style="list-style-type: none"> <li>• Apgar scores in newborns whose mothers used nitrous oxide did not differ significantly from those of newborns whose mothers used other labor pain management methods or no analgesia.</li> <li>• Follow-up of newborns was short, most frequently lasting only to birth or hospital discharge of the neonate</li> </ul> <p style="text-align: center;"><b>Occupational Exposure</b></p> <ul style="list-style-type: none"> <li>• Evidence about occupational levels of N2O is limited; some studies were conducted before the use of room ventilation systems or scavenging systems.</li> </ul>
Pita et al. (2012)  Prospective observational pilot study: 126 singleton pregnancies 35 or more weeks gestation in active phase of labor and cephalic.	96% of studied women would recommend the analgesia mixture for labor pain 92.9% graded the procedure as Good/Excellent.  56.2% reduction in pain perception amongst laboring women, with an increase of cervical dilatation and effacement.	<p style="text-align: center;"><b>Maternal Adverse Effects</b></p> <ul style="list-style-type: none"> <li>• Main adverse effect was dizziness (43.7%), (mild and tolerable with sleepiness) (25.4%) and vomiting (5.6%).</li> </ul> <p style="text-align: center;"><b>Fetal/Neonatal Adverse Effects</b></p> <ul style="list-style-type: none"> <li>• 50/50% blend effective and rapidly eliminated through the maternal respiratory circuit with no passage through the placental unit; the risk of neonatal depression was lower than that observed with opioids.</li> <li>• No infants presented with Apgar scores &lt;7 at 5 minutes and no admissions to the NICU or complications.</li> </ul>

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Appendix A

<b>Table 4. Clinically Relevant and Frequently Reported Maternal Adverse Effects Associated with Nitrous Oxide Use During Labor</b>					
<b>Author, y, country, study type</b>	<b>Intervention (N)</b>	<b>Nausea (%)</b>	<b>Vomiting (%)</b>	<b>Dizziness (%)</b>	<b>Drowsiness (%)</b>
Talebi et al., <sup>42</sup> 2009, Iran, RCT	50% nitrous in oxygen (260)	8	2	23	8
	50% oxygen (249)	0	0	0	0
Arora et al., <sup>44</sup> 1992, United Kingdom, RCT	Entonox (39)	NR	NR	3	NR
	Entonox and 0.25% Isoflurane (39)	5	NR	10	NR
Constantine et al., <sup>45</sup> 1989, United Kingdom, RCT	Entonox, via mask (49) <sup>a</sup>	45	NR	NR	NR
	Entonox, via mask and humidifier (36) <sup>a</sup>	25	NR	NR	NR
	Entonox, via mouthpiece (37) <sup>a</sup>	36	NR	NR	NR
	Entonox, via mouthpiece and humidifier (27) <sup>a</sup>	41	NR	NR	NR
Yeo et al., <sup>23</sup> 2007, United Kingdom, Crossover RCT	Entonox (22)	28	14	NR	0
	Sevoflurane (22)	3	0	NR	0
Westling et al., <sup>48</sup> 1992, Sweden, Crossover RCT	40% nitrous oxide in oxygen, intermittent (24)	0	0	NR	NR
	70% nitrous oxide in oxygen, intermittent (24)	0	0	NR	NR
	40% nitrous oxide in oxygen, continuous (24)	4	0	NR	NR
	Oxygen, intermittent (24)	0	0	NR	NR
McGuinness et al., <sup>26</sup> 1984, United Kingdom, Crossover RCT	50% nitrous in oxygen (20)	5	NR	NR	NR
Paech, <sup>63</sup> 1991, Australia, Cross-sectional	Nitrous oxide (220)	13 <sup>b</sup>	13 <sup>b</sup>	5	4
	Epidural (112)	14 <sup>b</sup>	14 <sup>b</sup>	0	0
	Meperidine (83)	16 <sup>b</sup>	16 <sup>b</sup>	6	11
	Nonpharmacological (140)	0	0	0	0
	Enflurane in air (20)	15	NR	NR	NR
McLeod et al., <sup>25</sup> 1985, United Kingdom, Prospective cohort	50% nitrous oxide in oxygen (32)	3	NR	6	More drowsy with Entonox: 10
	0.75% Isoflurane in oxygen (32)	3	NR	0	More drowsy with isoflurane: 58
Abboud et al., <sup>20</sup> 1981, United States, RCT	30%–60% nitrous in oxygen (50) <sup>c</sup>	NR	2	NR	NR
	0.25%–1.25% Enflurane in oxygen (55) <sup>c</sup>	NR	0	NR	NR
Soyannwo, <sup>57</sup> 1985, Nigeria, Prospective cohort	Entonox (114)	NR	4 <sup>d</sup>	NR	Mild: 67 Moderate: 31 Severe: 2
	Entonox with 100 mg meperidine or pethilorphan (36)	NR	4 <sup>d</sup>	NR	Mild: 56 Moderate: 44 Severe: 0.0

Studies are grouped by drug(s) administered. Studies of nitrous oxide as a sole drug are listed first, followed by nitrous/opioid, nitrous/other anesthetic, nitrous/opioid/sedatives, and nitrous/other anesthetic gases/opioids/sedatives or combinations thereof. Within each drug designation, randomized controlled trials are listed first followed by nonrandomized clinical trials and observational studies, and each group of study type is in reverse chronological order. Studies published before 1980 are not included in this table. Numerous studies did not provide the *N* for these outcomes; therefore, only percentages are reported in this table.

<sup>a</sup>Some patients used meperidine.

Likis, F.E., Andrews, J.C., Collins, M.R., Lewis, R.M., Seroogy, J.J., Starr, S.A., Walden, R.R., & McPheeters, M.L. (2014). *Anesthesia & Analgesia*, 118(1), 153-167

## References

1. Klomp, T., van Poppel, M., Jones, L., Lazet, J., DiNisio, M., Lagro-Janssen, ALM (2012) Inhaled analgesia for pain management in labour. *Cochrane Database of Systematic Reviews*, 2012 (9), 1-86. Doi:10.1002/14651858.CD009351.pub.2
2. Likis, F.E., Andrews, J.C., Collins, M.R., Lewis, R.M., Seroogy, J.J., Starr, S.A., Walden, R.R., & McPheeters, M.L. (2014). Nitrous Oxide for the management of labor pain: A systematic Review. *Anesthesia & Analgesia*, 118(1), 153-167
3. Pita, C.P., Pazmino, S., Vallejo, M. Salazar-Pousada, D., Hidalgo, L., Perez-Lopez, F.R., Chedraui, P. (2012). Inhaled intrapartum analgesia using a 50-50% mixture of nitrous oxide-oxygen in a low-income hospital setting. *Arch Gynecol Obstet*, 286, 627-631. DOI 10.1007/s00404-012-2359-6.

**Evidence Search Strategies:** A literature review on the selected clinical question was conducted during February 2019. This review examined the quantity, quality, consistency, and effectiveness of nitrous oxide for pain management for women in labor. The patient population was restricted to laboring women using Nitrous Oxide for pain management in the acute care setting.

Search terms were broad and included “laboring women,” “nitrous oxide, and “pain management” either alone or in combination. Limitors included English language, human, and included pregnant adults and adolescents. Electronic databases included PubMed, CINAHL, Google Scholar, and Cochrane Library. Websites for professional organizations were also searched which included Association of Women’s Health Obstetrical and Neonatal Nursing (AWHONN), American College of Obstetrics and Gynecology (ACOG), and American College of Nurse-Midwives (ACNM). Searches were individualized for each database for years 2008 to 2019 (See Database Search Methodology, Pages 8).

This review yielded 10 relevant hits after initial de-duplication from 176 total hits between databases. Detailed examination of abstracts and full text articles resulted in the elimination of 7 articles, as they did not answer the clinical question, were non-research studies, or focused on medications and interventions other than nitrous oxide. Three (3) articles pertained to the clinical area of inquiry. The citations were ranked using the Academy of Evidence-Based Practice Evidence Leveling System and graded using the Johns Hopkins Evidence Appraisal tools (See Page 7). The strength and the final grade of the evidence ranged from moderate to high quality.

**Evidence Review Results:** The evidence from the 3 studies consisted of 2 systematic reviews<sup>1,2</sup> and 1 observational descriptive study.<sup>2</sup> One systematic review 26 studies randomizing 2959 women.<sup>1</sup> Another systematic review included 13 randomized control trials,<sup>7</sup> cross-over RCTs,<sup>4</sup> nonrandomized clinical trials, 14 prospective cohorts, 1 retrospective cohort, 3 case series, 4 case-control studies, 11 cross-sectional studies, 2 trend studies.<sup>2</sup> The second systematic review examined 59 distinct study populations.<sup>2</sup> The evidence revealed inconsistent evidence for the effectiveness of N2O for labor pain management. However, the evidence was consistent regarding the safety for maternal and fetal/neonatal during N2O administration.<sup>1,2,3</sup>

There are limitations to this literature review. One study analyzed data from cross-over studies.<sup>1</sup> There were deficiencies in evidence strength most often related to poor study designs with high risk of bias, inconsistent findings across studies, inconsistencies among outcomes that would be expected to show corresponding benefit, use of intermediate outcomes, and studies with poor precision (See Appendix A)<sup>2</sup> Study sizes were inadequate to assess unusual or rare harms that might be more serious in terms of morbidity.<sup>2</sup> Additionally, there are limited statistics and poor descriptive analysis.<sup>3</sup>

Further research should be adequately powered to examine the following clinical issues:

- Anxiolytic effects of nitrous oxide during labor.<sup>2</sup>
- Net effect of the nitrous oxide and oxygen mixture over cesarean section rate<sup>3</sup> and assessing fetal/neonatal clearance of nitrous oxide.<sup>2</sup>
- Women’s experience with sense of control in labour,<sup>1</sup> alternate labor pain management methods,<sup>2</sup> breastfeeding,<sup>1,2</sup> bonding,<sup>2</sup> and birth satisfaction.<sup>1,2</sup>
- Optimal methods for minimizing occupational exposures/harms, such as room ventilation, scavenging measures, and N2O abuse/addiction.<sup>2</sup>

**Academy of Evidence Based Practice® (EBP)  
Evidence Leveling System (ELS)**

LEVEL	DESCRIPTION	RELEVANT ARTICLES	EVIDENCE TYPE
A	Meta-analysis of multiple large sample or small sample* randomized controlled studies, or meta-synthesis of qualitative studies with results that consistently support a specific action, intervention, or treatment		
B	Well-designed controlled studies, both randomized and nonrandomized, prospective or retrospective studies, and integrative reviews with results that consistently support a specific action, intervention, or treatment	2	#1: Systematic Review #2: Systematic Review
C	Qualitative studies, descriptive or correlational studies, integrative reviews, systematic reviews, or randomized controlled trials with inconsistent results	1	#3: Observational Pilot Study
D	Peer-reviewed professional organizational standards, with clinical studies to support recommendations		
E	Theory-based evidence from expert opinion or multiple case reports, case studies, consensus of experts, and literature reviews		
MA	Manufacturer's recommendation; Anecdotes		
LR	Laws and Regulations (local, state, federal; licensing boards; accreditation bodies, etc.)		
	<b>Total</b>	<b>3</b>	

\* A large sample has adequate power to detect the observed effect with confidence (as seen in significant Confidence Intervals). A small sample may lack confidence in the power of the desired effect (Polit & Beck, 2008)

Designed by Emma M. Cuenca and Cecelia L. Crawford, Academy of EBP; ©Kaiser Permanente SCAL Regional Nursing Research Program, May 2011

Adapted from AACN Evidence Leveling System (2009) and Canadian Medical Association & Centre for Evidence-Based Medicine, Levels of the Evidence (2001)

**High Quality: #1, #2 = 2 articles**

(Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough reference to scientific evidence OR expertise is clearly evident; draws definitive conclusions; provides scientific rationale; thought leader in the field)

**Moderate Quality: #3= 1 article**

(Reasonably consistent results; sufficient sample size for the study design; some control, and fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence OR expertise appears to be credible; draws fairly definitive conclusions; provides logical argument for opinions)

**Low Quality: 0 articles**

Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn

**Final Summary of the Body of Evidence = Moderate to High Quality**

### Electronic Database Search Methodology

Date(s): 1/28/19, 2/11/19, 2/12/19

**Literature search topic/clinical question:** What is the quantity, quality, consistency, and effectiveness of nitrous oxide use for pain management for women in labor?

**Inclusion Criteria:** laboring women; nitrous oxide; pain management

**Exclusion Criteria:** medications other than nitrous oxide

Database	Key Word(s) and/or Controlled Vocabulary Terms #	Total References Identified (hits)	No. of Relevant References	No. of Total Duplicate Articles	No. of Articles Selected for Review	No. of Articles Excluded	Final Total Relevant References
Name: PubMed Years: 2012-19	Nitrous Oxide for women in labor	53	29	0*	10	7	3
Name: Cochrane #1 Years: 2012-19	Nitrous Oxide for women in labor	5	2	2	0	0	0
Name: Cochrane #2 Years: 2012-19	Nitrous Oxide for women in labor	17	4	2	0	2	0
Name: Google Scholar Years: Open	Nitrous Oxide for labor pain	30	15	0	15	15	0
Name: ACNM Years: 2008-2018	laboring women; nitrous oxide; pain management	3	0	0	0	0	0
Name: AWHONN Years: 2008-2018	laboring women; nitrous oxide; pain management	3	0	0	0	0	0
Name: CINAHL Years: 2008-2018	laboring women; nitrous oxide; pain management	50	6	1	5	5	0
Name: ACOG Years: no dates excluded	Nitrous Oxide	15	3	0	0	3	0
<b>TOTALS</b>		<b>176</b>	<b>59</b>	<b>5</b>	<b>30</b>	<b>32</b>	<b>3</b>

#Controlled vocabulary (subject terms, MESH terms, tagged terms specific to database)

\*Use the first database as the main comparison for subsequent database searches and identifying duplicate articles

**Total Articles Included in Literature Review: Database (3) + Contextual Links\* (0) = 3**

\*Additional articles/information found in references lists and/or article review



<b>Clinical Question</b>				
<b>Population and/or Patient(s)</b>	<b>Intervention/Interest Area</b>	<b>Comparison Intervention (Often current practice)</b>	<b>Outcome</b>	<b>Time Period (If Applicable; Optional)</b>
P: laboring women	I: nitrous oxide use	C: Current standard	O: <ul style="list-style-type: none"> <li>• Effectiveness of nitrous oxide use</li> <li>• Satisfaction of laboring women</li> <li>• Safety of nursing staff</li> </ul>	T: childbirth
Final Clinical Question: What is the quantity, quality, consistency, and effectiveness of nitrous oxide use for pain management for women in labor?				

<b>Searchable Question</b>
Key Search Terms: laboring women; nitrous oxide; pain management
Inclusion Criteria: laboring women; nitrous oxide; pain management
Exclusion Criteria: medications other than nitrous oxide
Limiters (Open year or year ranges, age ranges, and language, etc.): 2008-2019
Databases: PubMed*, Cochrane Library, Google Scholar, CINAHL; Anesthesiology organization; AWHONN; ACOG; midwifery organization

## Purpose/intended Audience

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