Effective Health Care Program

Comparative Effectiveness Review
Number 67

Nitrous Oxide for the Management of Labor Pain

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Ms. Kerry Jordan served as project coordinator shepherding innumerable planning, implementation, and writing tasks to completion. She guided and contributed to production of the plethora of forms, spreadsheets, and tables that are required to produce reliable evidence tables and summary data. Her attentiveness to the needs of the investigator team and to pacing the work was especially valued.

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Nitrous Oxide for the Management of Labor Pain

Structured Abstract

Objectives. The Vanderbilt Evidence-based Practice Center systematically reviewed evidence addressing the use of nitrous oxide for the management of labor pain.

Data Sources. We searched the MEDLINE®, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for articles published in English.

Review Methods. We excluded studies that did not address a Key Question, were not original research, or had fewer than 20 participants. We identified a total of 58 publications, representing 59 distinct study populations: 2 of good quality, 11 fair, and 46 poor.

Results. Inhalation of nitrous oxide provided less effective pain relief than epidural analgesia, but the quality of studies was predominately poor. The heterogeneous outcomes used to assess women's satisfaction with their birth experience and labor pain management made synthesis of studies difficult. The strength of evidence was insufficient to determine the effect of nitrous oxide on route of birth. Most maternal harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Apgar scores in newborns whose mothers used nitrous oxide were similar to those of newborns whose mothers used other labor pain management methods or no analgesia. Evidence about occupational harms and exposure was limited.

Conclusions. The literature addressing nitrous oxide for the management of labor pain has few studies of good or fair quality. Synthesis of effectiveness and satisfaction studies is challenging because of heterogeneous interventions, comparators, and outcome measures. Research assessing nitrous oxide is needed across all of the Key Questions addressed: effectiveness, women's satisfaction, route of birth, harms, and health system factors affecting use.

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Executive Summary

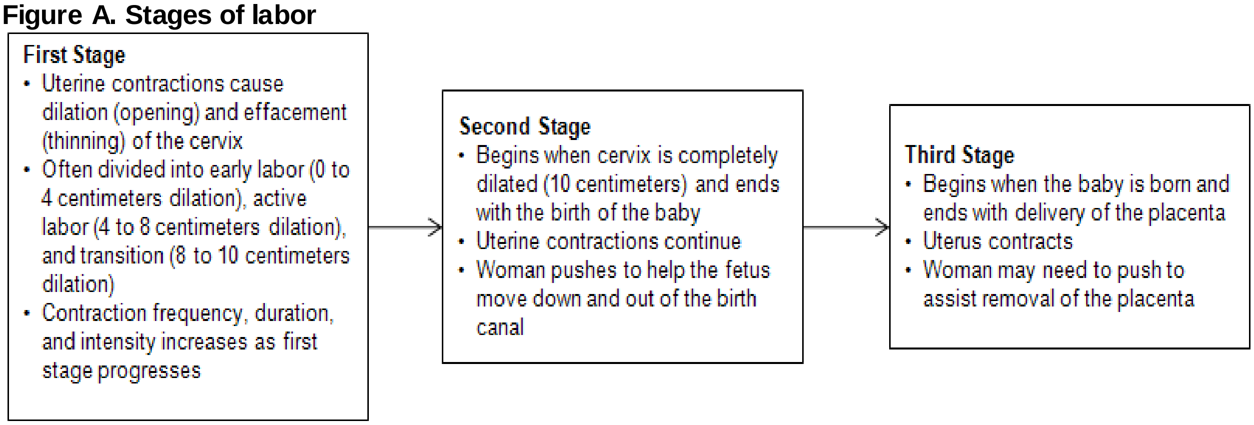
Background

More than 4 million births occur in the United States each year; in 2008, there were 4,247,694 births.[1] The most commonly used labor pain management method in the United States is epidural analgesia (hereafter epidural).[2] Use of inhaled nitrous oxide is a common option for labor pain management in several countries outside the United States, including the United Kingdom, Finland, Sweden, Canada, Australia, and New Zealand. Only five centers in the United States are known to currently provide nitrous oxide as an option for labor pain management: the Birth Center at the University of California San Francisco Medical Center; the University of Washington Hospital in Seattle; St. Joseph Regional Medical Center in Lewiston, ID; Okanogan Douglas Hospital in Brewster, WA; and Vanderbilt University Medical Center in Nashville, TN (which began offering nitrous oxide in June 2011 after this review was under way). A significant barrier to use in the United States is limited availability of equipment to blend and deliver a mixture of nitrous oxide and oxygen for self-administration by laboring women.

Nitrous oxide, sometimes called "laughing gas" because it can produce euphoria, is an inhalational anesthetic and analgesic gas. Nitrous oxide has been used in dental care since the mid-1800s[3] and is commonly used for this indication today. Use of nitrous oxide during labor began in the late 1800s, and equipment for self-administration was introduced by Minnitt in England in 1934.[4]

The mechanism of action of nitrous oxide is thought to be an increased release of endorphin, dopamine, and other natural pain relievers in the brain, which modulate pain stimuli via descending spinal cord nerve pathways. Nitrous oxide does not completely relieve the pain of labor but creates "diminished pain, or a continued awareness of pain without feeling bothered by it."[5] Nitrous oxide also has an antianxiety effect, which may be helpful if laboring women are restless and doubt their ability to cope, emotions that are not uncommon, especially during transition (see Figure A for an overview of the stages of labor).

Figure A. Stages of labor



The most common concentration of nitrous oxide administration for labor pain management in the biomedical literature and in current clinical practice is 50 percent nitrous oxide in oxygen, which can be mixed from two separate gas sources with a blender device (e.g., Nitronox®) or premixed in a single cylinder (e.g., Entonox®). Nitrous oxide is usually self-administered via a facemask or mouthpiece on an intermittent basis, beginning about 30 to 60 seconds before each contraction.[6]

A variety of pain management methods were described in studies in this review (Table A). Epidural analgesia is the most commonly used method in the United States and may block pain entirely. Although epidurals are more effective for pain relief than other pain management methods, epidurals are associated with increased risk of assisted (vacuum or forceps) vaginal birth, use of oxytocin, maternal hypotension, motor blockade, urinary retention, maternal fever, and cesarean for maternal distress.[7] Women who have epidurals must have additional monitoring and may need confinement to bed, which limits mobility and options for positioning, and placement of a Foley catheter.

Although nitrous oxide would not be expected to be as effective for analgesia as an epidural because of the differences in their mechanism of action, nitrous oxide has other benefits, including its lower cost and less invasive nature. Nitrous oxide has a rapid onset and end of action. Thus women who do not like nitrous oxide or find it inadequate for pain management can easily discontinue its use and switch to another method, unlike epidurals and systemic opioids, which diminish gradually over a much longer period. Mobility and options for positioning are not limited and nitrous oxide does not require additional monitoring and potential anesthesia-related interventions (e.g., bladder catheterization). Women self-administer nitrous oxide, which allows them to control the amount they need.[8] Nitrous oxide may not be an ideal method for women who want maximum pain relief, but it could be preferable to other pharmacologic pain management methods for women who want increased mobility with less intervention and monitoring. Nitrous oxide might also be useful when a woman wants to delay use of epidural anesthesia until later in labor, when epidural anesthesia is not immediately available (e.g., in hospitals that do not have in-house anesthesia staff and must call in an anesthesia provider), when a woman arrives at the hospital too far along in labor to allow for an epidural to be placed and take effect, and when a woman finds epidural analgesia ineffective or inadequate.

One concern with nitrous oxide use is the potential for the gas to escape into the room and potentially affect health care workers as well as other individuals present with laboring women. For this reason, multiple organizations are responsible for regulating the use of nitrous oxide, and factors other than clinical outcomes are important to decisionmaking about its use (Appendix F). Room ventilation systems and scavenging systems that remove waste gases are used to reduce exposure to caregivers and others present for labor. Equipment capable of scavenging provides constant negative pressure so that the woman's exhalations, which contain nitrous oxide, are captured and removed from the room and facility.[6]

Finding the appropriate measure of effectiveness on which to assess nitrous oxide with other pain management methods is challenging. Nitrous oxide is not intended to provide the extent of pain relief expected with epidural. Therefore, rather than a direct comparison of effectiveness, the more important questions are whether women are satisfied with the use of nitrous oxide for labor pain management and if it is safe for the woman and her fetus/newborn.

Table A. Labor pain management methods used in studies included in this review

Method	Description	Timing and Frequency of Administration
Nitrous oxide	Anesthetic and analgesic gas usually inhaled intermittently via a facemask or mouthpiece, can be given continuously via nasal cannula Reduces the perception of pain, alters consciousness, decreases anxiety	Can be used for first- and second-stage labor pain Self-administered between and/or during contractions May be continued into third stage if procedures, such as perineal repair or manual removal of the placenta, are needed
Other inhalational anesthetic gases (desflurane, sevoflurane, isoflurane, enflurane, methoxyflurane, trichloroethylene, cyclopropane)	Anesthetic gas usually inhaled intermittently via a facemask or mouthpiece, can be given continuously via nasal cannula Reduces the perception of pain, alters consciousness	None is used currently used for management of labor pain in the United States Desflurane, sevoflurane, and isoflurane are used for other types of anesthesia in the United States
Epidural	Injection of medications (usually a combination of local anesthetic and opioid) into the epidural space around the spinal cord Blocks pain in lower half of body May partially or fully block voluntary motor control in lower half of body	Initiated during first stage of labor with infusion usually continuing into second stage May be continued into third stage if procedures, such as perineal repair or manual removal of the placenta, are needed
Opioids (for example, pethidine/meperidine)	Medication given intravenously or by intramuscular injection Provides some relief of labor pain and causes sedation, which can also alter perception of pain Opioids commonly used in labor include meperidine/pethidine, morphine, fentanyl, remifentanil, butorphanol, and nalbuphine	Used during the first stage of labor Administered at regular intervals as needed for pain (usually every 1 to 4 hours depending on specific medication)
Paracervical block	Injection of local anesthetic at lateral cervix Provides some relief from the pain of cervical dilation	Rarely used in the United States because it causes fetal bradycardia (slow heart rate) Used during the first stage of labor Can be repeated
Pudendal block	Injection of local anesthetic in the vaginal wall near the pudendal nerves, bilaterally Relieves pain in the lower vagina, perineum, and external genitalia that occur when the woman is pushing	Used during the second stage of labor Administered once

Table A. Labor pain management methods used in studies included in this review (continued)

Method	Description	Timing and Frequency of Administration
Transcutaneous electrical nerve stimulation (TENS)	Low-voltage electrical impulses are sent from a handheld device controlled by the woman to electrodes placed on the skin of the lower back	Used during the first stage of labor Used as needed
Sterile water injections	Injection of sterile water intradermally (just below the skin) in four locations on the lower back	Used during the first stage of labor, most commonly for low back pain Can be repeated
Hydrotherapy	Immersion of the laboring woman in water	Can be used during the first and second stages of labor Used as needed
Psychoprophylaxis	Use of breathing and relaxation techniques taught during pregnancy	Can be used during the first and second stages of labor Used as needed

Scope of this Report

Most women in the United States use some type of medication for labor pain management. However, the option of using nitrous oxide to relieve labor pain is limited by its lack of availability. Use of nitrous oxide during labor is common in other countries, increasing interest in this method i n the United States, in part because it is less expensive and invasive than widely used regional anesthesia. This review attempts to assess the effectiveness of nitrous oxide in managing labor pain and to identify potential factors that may influence its availability and use within the United States. Our Key Questions have been structured with this goal in mind. The primary questions include the comparative effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on women's satisfaction with their birth experience, the health system factors influencing its use within the United States, and any adverse effects associated with this intervention. With the rate of cesarean birth continuing to rise—32.3 percent of all U.S. births reported in 2008[1]—it is also important to address whether the use of nitrous oxide during labor influences the route of birth in women initially intending a vaginal birth.

Objectives

Population

We focused this review on pregnant women in first and second stages of labor, other attendees and health care providers present during labor, and the fetus/neonate.

Intervention(s)

We examined the use of nitrous oxide for the management of labor pain.

Comparators

We compared nitrous oxide with the following pain management methods: no analgesic/anesthetic intervention, other inhalational anesthetic gases, epidural, opioids, paracervical block, pudendal block, transcutaneous electrical nerve stimulation (TENS), sterile water injections, hydrotherapy, and psychoprophylaxis (see Table A).

Outcomes

Our primary outcomes included pain management, satisfaction with pain management, satisfaction with birth experience, effect of nitrous oxide on the route of birth, adverse effects associated with the use of nitrous oxide for the management of labor pain, and health system factors associated with the use of nitrous oxide for the management of labor pain.

Timing

Intermediate outcomes include associated labor outcomes, while long-term outcomes include associated birth outcomes. We did not place a restriction of the duration of followup.

Setting

We considered all birth settings, including hospital, birth center, and home.

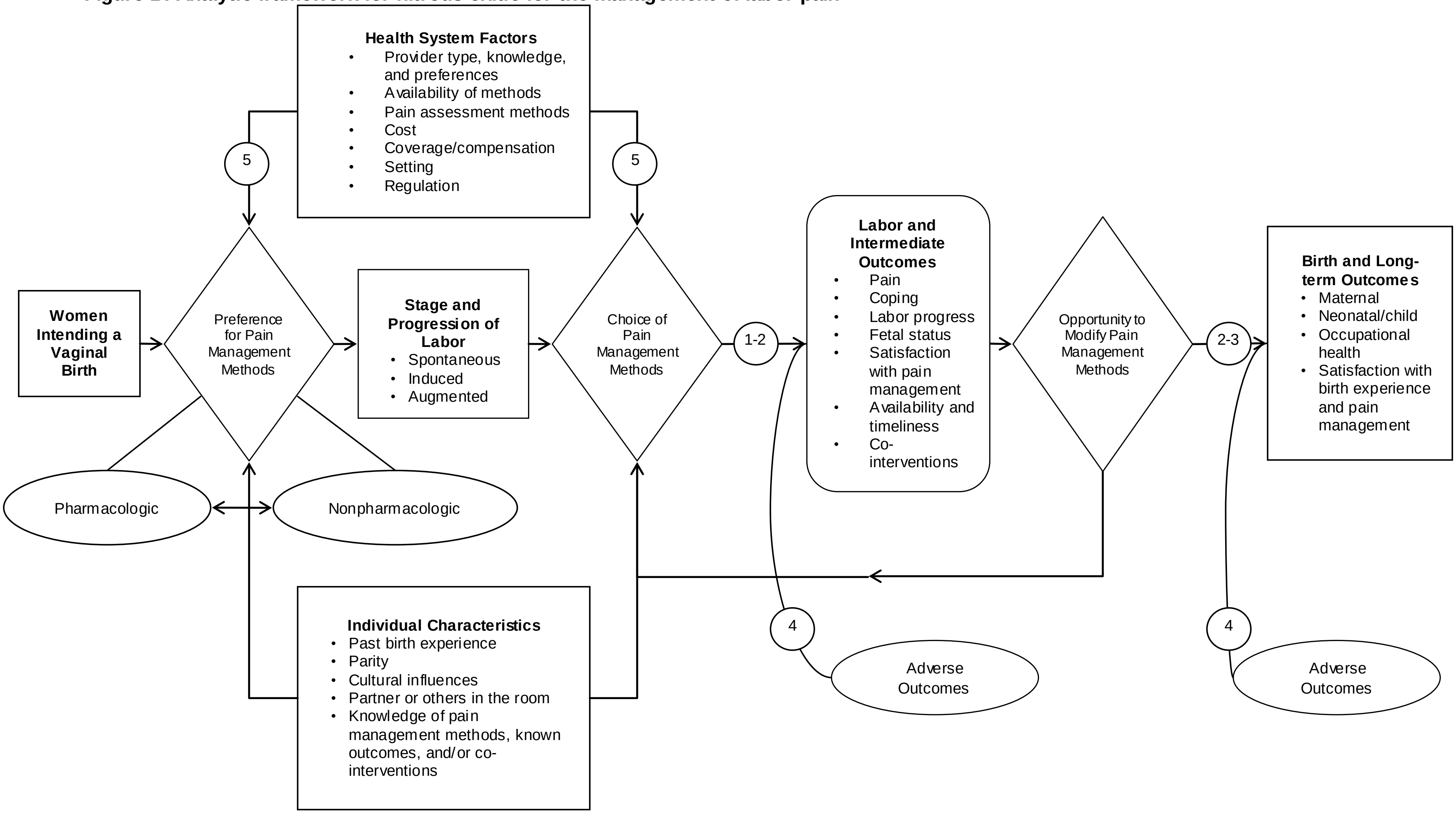
Key Questions

1. What is the effectiveness of nitrous oxide when compared with other methods for the management of labor pain among women intending a vaginal birth?
2. What is the comparative effectiveness of nitrous oxide on women's satisfaction with their birth experience and pain management?
3. What is the comparative effectiveness of nitrous oxide on the route of birth?
4. What is the nature and frequency of adverse effects associated with the use of nitrous oxide for the management of labor pain, including but not limited to:
    - Maternal adverse effects, such as nausea and vomiting, dreams, dizziness, unconsciousness, and postpartum complications.
    - Fetal/neonatal adverse effects, such as low Apgar scores and abnormal fetal cord blood gases.
    - Childhood adverse effects, such as drug dependency and developmental complications.
    - Adverse effects on health care providers and other individuals present for labor.
5. What are the health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization?

Analytic Framework

We developed the analytic framework (Figure B) based on clinical expertise and refined it with input from our key informants and Technical Expert Panel (TEP) members. The figure represents the population of interest, women intending a vaginal birth, and the factors and decision points that influence the use of nitrous oxide for the management of labor pain. The initial preference for pain management methods, which is often determined prior to the onset of labor, can be shaped by past birth experience, cultural or familial influence, and knowledge of various pain management options. Women acquire knowledge about pain management options from a variety of sources including health care providers, childbirth educators, patient education books and other materials, popular media, friends, and family. Once labor begins, health system factors such as availability, setting, and provider preference may affect the utilization of the desired pain management methods (Key Question [KQ] 5). The first two decision points reflect the initial preference for and actual implementation of pain management methods. A third decision point occurs after the onset of labor but prior to birth, at which point the woman in labor may opt to modify the pain management method. We sought to examine how the administration of nitrous oxide at various mixes, routes, and intervals affects outcomes that occur during labor, after birth, and in the long term (KQs 1–3). Adverse effects of treatment are examined in KQ4. Portions of the framework that are unexplored in the scientific literature are highlighted in the discussion of future research needs.

Figure B. Analytic framework for nitrous oxide for the management of labor pain



Methods

Input From Stakeholders

The topic was nominated in a public process. With key informant input, we drafted initial KQs, which were reviewed by the Agency for Healthcare Research and Quality (AHRQ) and posted to a public Web site for public comment. Using public input, we drafted final KQs, which were reviewed by AHRQ. We convened a technical expert panel to provide input during the project on issues such as setting inclusion/exclusion criteria and refining the analytic framework

Literature Search

Our search included the MEDLINE®, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases. Reviews conducted by the Cochrane Collaboration are indexed in the MEDLINE database and were also included in the search. We also hand-searched references of included articles to identify additional studies. Controlled vocabulary terms served as the foundation of our search, complemented by additional keyword phrases to represent the myriad ways in which nitrous oxide is referred to in the clinical literature. We also employed indexing terms within each database to exclude ineligible publication types and articles in languages other than English.

Inclusion and Exclusion Criteria

We excluded studies that:

- Were not original research
- Did not include 20 or more pregnant women in labor
- Did not address adverse effects or occupational exposure during labor
- Did not report information pertinent to any KQ
- Were not published in English

Article Selection Process

We examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts for inclusion or exclusion. If one reviewer concluded the article could be eligible for the review based on the abstract, we retained it. Full publications were then dually reviewed for final inclusion, with disagreements resolved via adjudication by an independent third reviewer. Reasons and process for exclusions are described in the full report.

Data Extraction

All team members shared the task of entering information into evidence tables. After initial data extraction, another member checked table entries for accuracy, completeness, and consistency. Abstractors reconciled inconsistencies.

Quality Assessment

The quality of individual studies was assessed using existing, widely accepted tools for each type of study. For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool was employed. Fundamental domains include: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and free of selective reporting bias. For nonrandomized and observational studies, the Newcastle-Ottawa Quality Assessment Scale was utilized. The scale assesses three broad perspectives: (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Both tools are presented in the full report. Additionally, the thresholds for converting the Cochrane Risk of Bias tool and Newcastle-Ottawa Quality Assessment Scale results to the AHRQ standard of “good,” “fair,” and “poor” quality designations are presented in the full report.

Evidence Synthesis

Text that summarizes the research evidence is organized by KQ. Within each KQ, evidence is organized by aspects of the question, such as the compared intervention and outcomes. In the full report, we include evidence tables for individual studies and summary tables of common outcomes and provide extended analysis.

Grading Strength of Evidence

We evaluated the overall strength of the evidence for the primary outcomes. We graded available evidence for each key outcome for each of the following domains:

- Risk of bias (low, medium, or high)
- Consistency of findings (inconsistency not present, inconsistency present, or unknown or not applicable)
- Directness (direct comparison of influence on outcomes in RCT, or indirect information from observational research)
- Precision (precise or imprecise based on outcomes rates, size of the individual studies and the total number of women in the studies for the category of intervention)

We combined the grades of each domain to develop the strength of evidence for each key outcome. Possible grades for each domain were: low, moderate, or high risk of bias; consistent or inconsistent; direct or indirect; and precise or imprecise. We considered additional domains, including publication bias and large effect size, on a per-KQ basis.

We graded the body of literature for effectiveness of nitrous oxide, women’s satisfaction with their birth experience and pain management, effect of nitrous oxide on route of birth, and adverse effects associated with nitrous oxide. The possible grades were:

High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.

Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.

Insufficient: Evidence is either unavailable or does not permit a conclusion.

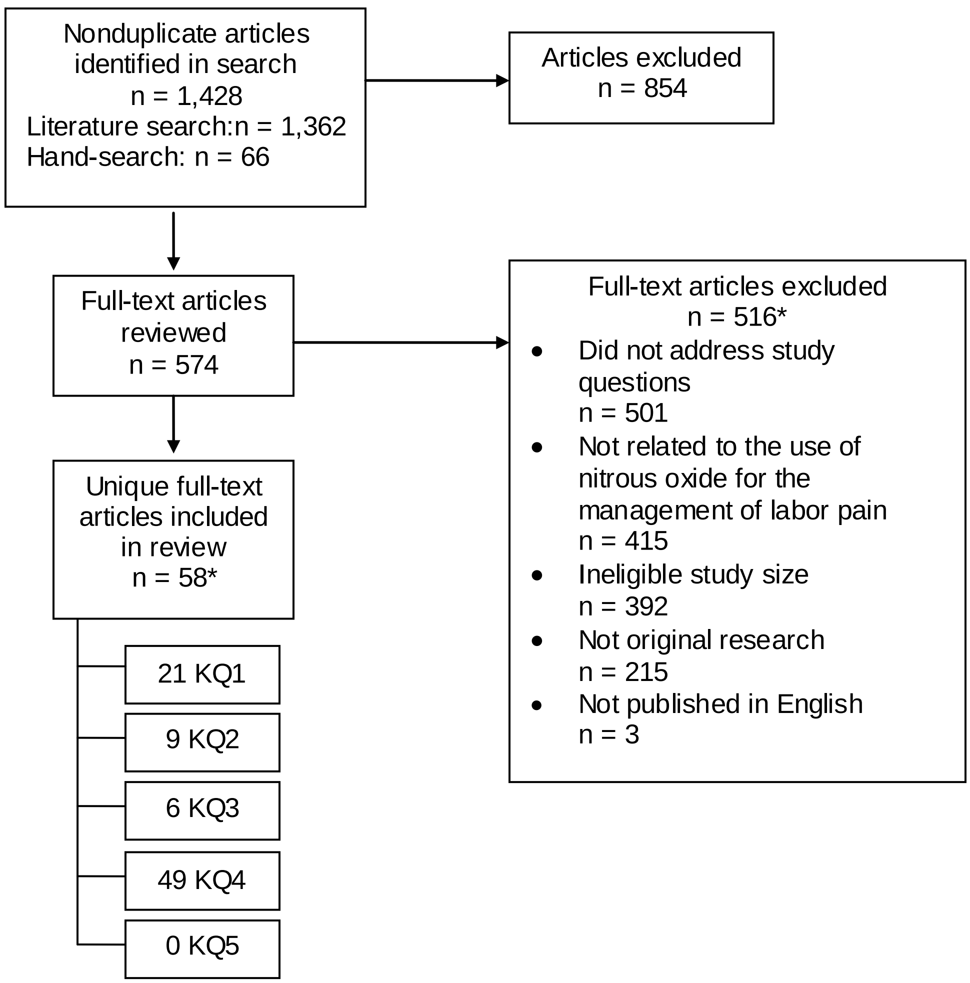
When no studies were available for an outcome or comparison of interest, we assessed the evidence as insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

Results

Literature Search Yield

We identified 1,428 nonduplicate titles or abstracts. Fifty-eight publications were included in the review (Figure C), representing 59 distinct study populations: 13 RCTs, 7 crossover RCTs, 4 nonrandomized clinical trials, 14 prospective cohorts, 1 retrospective cohort, 3 case series, 4 case-control studies, 11 cross-sectional studies, and 2 trend studies. The most common reasons for exclusion were irrelevance to the topic and ineligible study size. Twenty-one articles pertain to KQ1, 9 articles to KQ2, 6 articles to KQ3, 49 articles to KQ4, and 0 articles to KQ5.

Figure C. Disposition of articles identified by the search strategy



KQ = Key Question
*The number of articles addressing Key Questions and those excluded exceed the total number of articles in each category because some articles fit multiple exclusion categories or addressed more than one Key Question.

KQ1. Effectiveness of Nitrous Oxide for Labor Pain Management

Twenty-one studies addressed the effect of nitrous oxide on pain or pain relief.[9-29] Four studies were of fair quality,[19, 22-23, 25] and 17 were of poor quality.[9-18, 20-21, 24, 26-29] There was considerable variation in the concentration of nitrous oxide and frequency (continuous vs. intermittent) administered, additional pain management methods used, and methods and persons (i.e., women, obstetricians, midwives, and anesthesia providers) assessing pain and pain relief. The substantial variation in timing of assessment may have affected the reported outcomes because women's opinions about pain relief change with time lapsed after birth.[10-11, 14]

The majority of the effectiveness studies (12 of 21) had as comparators other inhalational anesthetic gases that are not used to manage labor pain in the United States. Only one study compared nitrous oxide with placebo and found no significant difference in pain scores. As expected, epidurals provide more effective pain relief than nitrous oxide. The evidence is insufficient to determine the effectiveness of nitrous oxide for the management of labor pain compared with other, nonepidural labor pain management methods because the studies are predominately of poor quality, use heterogenous outcome measures, and have inconsistent findings.

KQ2. Effect of Nitrous Oxide on Women's Satisfaction

Nine studies addressed women's satisfaction with their birth experience or pain management.[16-17, 20-21, 24, 27, 30-32] One study was of good quality,[31] one of fair quality,[32] and seven of poor quality.[16-17, 20-21, 24, 27, 30] Measures of satisfaction were not uniform, making it difficult to synthesize studies. The strength of the evidence is low for equivalence or superiority of nitrous oxide compared with other pain management methods for women's satisfaction with their birth experience and pain management.

KQ3. Effect of Nitrous Oxide on the Route of Birth

Six studies compared the route of birth in women who used nitrous oxide with that in women who used other pain management methods.[10, 14, 17, 24, 27, 31] Two of these included only women who had vaginal births,[10, 17] and five were of poor quality.[10, 14, 17, 24, 27] The evidence is insufficient to determine the effect of nitrous oxide on the route of birth because the studies are predominately of poor quality and have inconsistent findings.

KQ4. Adverse Effects of Nitrous Oxide for Labor Pain Management

Forty-nine studies addressed the maternal, fetal, neonatal, and occupational harms related to nitrous oxide use during labor.[9-14, 17-21, 24, 26, 29, 31, 33-65] Two were of good quality,[31, 54] 7 of fair quality,[19, 33, 45, 47, 57, 59, 66] and 40 of poor quality.[9-14, 17-18, 20-21, 24, 26, 29, 34-44, 46, 48-53, 55-56, 58, 60-65] Although these 49 studies report data from more than 27,000 women, only 6 were conducted in the United States (n = 2,445 women).

One-third (16 of 49) of studies reporting harms were conducted prior to 1980, when nitrous oxide was often used in combination with sedatives, tranquilizers, and other inhaled anesthetics in labor, a practice that has largely been abandoned. 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 to be a positive outcome.

Most maternal harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Some maternal harms (e.g., nausea and oxygen desaturation) are common in all laboring women regardless of the type of analgesia used. Study sizes were inadequate to assess for unusual or rare harms that might be more serious.

Nitrous oxide is transmitted via the placenta and is rapidly eliminated by the neonate following birth once breathing begins. 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. Followup of newborns was short, most frequently lasting only to birth or discharge of the neonate from the hospital.

Few data are available to draw conclusions regarding potential occupational harms as a result of exposure to nitrous oxide. Evidence about occupational levels of nitrous oxide is limited, and some studies were conducted prior to the use of room ventilation systems or scavenging systems. The implementation of these systems in clinical practice has reduced occupational exposure, which should mitigate potential risks.

KQ5. Effects of Provider and Health System Factors

No studies addressed KQ5.

Discussion

Summary Strength of Evidence and Findings

Overall, the strength of evidence to answer the KQs was insufficient for effectiveness for the management of labor pain (KQ1), route of birth (KQ3), and health system factors (KQ5); low for satisfaction with birth experience and pain management (KQ2); and moderate for harms (KQ4) (Table B). Deficiencies in the strength of evidence most often related to a preponderance of study designs with high risk of bias; inconsistent findings across studies and inconsistencies among outcomes that would be expected to show corresponding benefit; use of intermediate outcomes; and small studies with poor precision.

Table B. Strength of evidence for nitrous oxide for the management of labor pain

Total Studies (Total Participants)	Domains Pertaining to Strength of Evidence				Strength of Evidence
	Risk of Bias	Consistency	Directness	Precision	
Effectiveness of Nitrous Oxide vs. Other, Nonepidural Labor Pain Management Methods for the Management of Labor Pain (KQ1)					
25 (15,991)	High	Inconsistent	Indirect	Imprecise	Insufficient; includes 6 RCTs; 5 studies of fair quality and 20 studies of poor quality total
Equivalence or Superiority of Nitrous Oxide vs. Other Labor Pain Management Methods for Women's Satisfaction With Their Birth Experience (KQ2)					
2 (1,303)	High	Consistent	Direct	Imprecise	Low; includes no RCTs; 1 study of fair quality and 1 study of poor quality total
Equivalence or Superiority of Nitrous Oxide vs. Other Labor Pain Management Methods for Women's Satisfaction With Their Pain Management (KQ2)					
8 (2,825)	High	Consistent	Direct	Imprecise	Low; includes 2 RCTs; 1 study of good quality and 7 studies of poor quality total
Effect of Nitrous Oxide for the Management of Labor Pain on Route of Birth (KQ3)					
6 (33,031)	High	Inconsistent	Direct	Imprecise	Insufficient; includes 2 RCTs; 1 study of good quality and 5 studies of poor quality total
Adverse Effects Associated With Nitrous Oxide for the Management of Labor Pain are Primarily Unpleasant Side Effects That Affect Tolerability (KQ4)					
48 (27,530)	High	Consistent	Direct	Imprecise	Moderate; includes18 RCTS; 2 studies of good quality, 6 studies of fair quality, and 40 studies of poor quality total

KQ = Key Question, RCT = randomized controlled trial

Note: Domains pertaining to SOE are taken from the AHRQ methods guide and are explained in the Methods section.

Applicability

Applicability describes the extent to which study populations and characteristics in the literature reviewed apply to the larger population. In this report, the study populations were healthy women in labor who should be similar to the target population. Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox®. The 50/50 mix is available, although Entonox is not used in the United States and has not been reviewed by the U.S. Food and Drug Administration. In addition, mechanical equipment for administration of nitrous oxide in labor and delivery has very limited availability in the United States at the time of this writing. The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women, such as other inhalational anesthetic gases.

For KQ1, the most frequent outcome was an assessment of pain, generally during labor but sometimes in the immediate postpartum period and/or weeks to months after birth. Those assessing outcomes included participants, obstetricians, midwives, and anesthesia providers. These studies are unable to demonstrate whether nitrous provided adequate pain relief for women who knowingly accept less effective pain relief in exchange for increased mobility, less intervention and monitoring, and avoidance of potential complications associated with epidurals. Generally speaking, therefore, pain relief is likely to be an inadequate measure of effectiveness for nitrous oxide in the absence of other outcomes such as women's satisfaction. Satisfaction with pain management and the birth experience were assessed in KQ2. Satisfaction is a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief. The outcomes for KQ3 were vaginal birth, assisted vaginal birth, and cesarean. For KQ4, the most frequent outcomes were assessments of nausea, vomiting, dizziness, drowsiness, hypoxia, oxygen saturation, Apgar scores, and cord blood gases.

Only 6 of 58 studies were conducted in the United States. The options for labor pain management in the United States are somewhat dissimilar to those in other countries because nitrous oxide for laboring women is widely available outside of the United States, whereas in this country its availability is extremely limited. All of the studies were conducted in hospitals; thus, the effectiveness, women's satisfaction, route of birth, and harms associated with nitrous oxide in birth centers and the home setting have not been reported.

Conclusions

The literature addressing nitrous oxide for the management of labor pain has few studies of good or fair quality. Synthesis of effectiveness and satisfaction studies was challenging because of heterogenous interventions, comparators, and outcome measures. Satisfaction may be a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief. The strength of evidence for the effect of nitrous oxide on route of birth was insufficient. Most maternal harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness), and Apgar scores did not differ significantly across labor pain management methods. Data for occupational harms were limited. Research assessing nitrous oxide is needed across all of the KQs examined: effectiveness, women's satisfaction, route of birth, harms, and health system factors affecting use.

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Introduction

Background

More than 4 million births occur in the United States each year; in 2008, there were 4,247,694 births.[1] A 2002 review of labor pain management in United States hospitals—stratified by number of yearly births and size of hospital—found that, among women who gave birth in 1997, 21 to 50 percent received epidural analgesia (hereafter epidural), 5 to 11 percent received combined spinal-epidural analgesia, 40 to 56 percent received parenteral analgesia, and 2 to 13 percent received paracervical or spinal analgesia. Ten to 17 percent of women did not receive any form of analgesia.[2] The 2006 Listening to Mothers II survey found that 86 percent of 1,573 responding women reported using one or more types of medication for pain relief during labor; 76 percent used epidural or spinal analgesia/anesthesia, 22 percent received narcotics, 3 percent received general anesthesia, and 3 percent used nitrous oxide.[3] Although limited by reliance on women's self-report, this survey provides data on the relative use of each method in the United States.[3] Given that so few facilities offer nitrous oxide, a survey intended to provide national estimates of medication use may not provide accurate numbers.

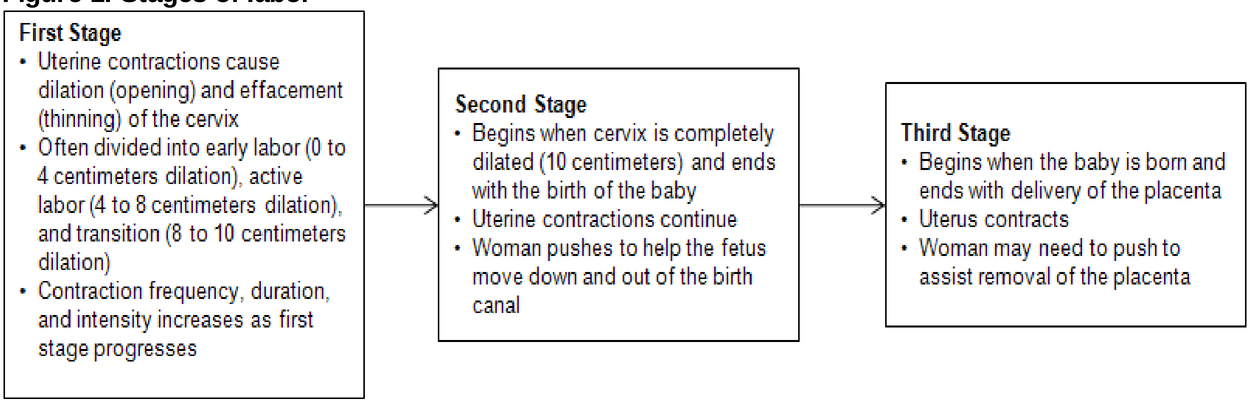
Use of inhaled nitrous oxide is a common option for labor pain management in several countries outside the United States. A 2002 systematic review on the topic, the most recent source available, cites evidence that nitrous oxide is used in the United Kingdom by approximately 50 to 75 percent of women and in Finland by approximately 60 percent of women.[4] In one study, 65 percent of women in Sweden received nitrous oxide for labor pain in 1991,[5] and a 1995 survey of hospitals in Ontario, Canada, found that nitrous oxide was available for labor pain analgesia in 75 percent of responding hospitals.[6] Nitrous oxide is also commonly used for labor analgesia in Australia and New Zealand.[4] Five centers in the United States are known to currently provide nitrous oxide as an option for labor pain management: the Birth Center at the University of California San Francisco (UCSF) Medical Center; the University of Washington Hospital in Seattle; St. Joseph Regional Medical Center in Lewiston, ID; Okanogan Douglas Hospital in Brewster, WA; and Vanderbilt University Medical Center in Nashville, TN (which began offering nitrous oxide in June 2011 after this review was under way). The UCSF practices have been described in the literature, including contraindications, preparation of the patient, and the documentation and competency requirements for midwives.[7] The UCSF model uses a mixture of 50 percent nitrous oxide and 50 percent oxygen that is self-administered by the patient after initial instruction on use and potential side effects. No related publications or descriptions of the option used at the University of Washington Hospital, St. Joseph Regional Medical Center, Okanogan Douglas Hospital, or Vanderbilt University could be located in the literature. A significant barrier to use in the United States is limited availability of equipment to blend and deliver a mixture of nitrous oxide and oxygen for self-administration by laboring women.

Nitrous Oxide as a Labor Pain Management Option

Nitrous oxide, sometimes called "laughing gas" because it can produce euphoria, is an inhalational anesthetic and analgesic gas. Nitrous oxide has been used in dental care since the mid-1800s[8] and is commonly used for this indication today. Use of nitrous oxide during labor began in the late 1800s, and equipment for self-administration was introduced by Minnitt in England in 1934.[4]

The mechanism of action of nitrous oxide is thought to be an increased release of endorphin, dopamine, and other natural pain relievers in the brain, which modulate pain stimuli by way of descending spinal cord nerve pathways.[9-10] Nitrous oxide does not completely relieve the pain of labor but instead creates “diminished pain, or a continued awareness of pain without feeling bothered by it.”[11] Nitrous oxide also has an anti-anxiety effect, which may be helpful if laboring women are restless and doubt their ability to cope, emotions that are not uncommon especially during transition (the end of the first stage of labor, see Figure 1 for an overview of the stages of labor).

Figure 1. Stages of labor



Nitrous oxide in a 50/50 mix, which can be mixed with a blender device (e.g., Nitronox®) or premixed (e.g., Entonox®), is the most common concentration of nitrous oxide administered for labor pain management, although some literature addresses varying concentrations of nitrous oxide in oxygen.[12-13] Nitrous oxide is usually self-administered via a facemask or mouthpiece on an intermittent basis, beginning about 30 to 60 seconds before each contraction.[14] Some literature addresses continuous vs. self-administered/intermittent administration.[15-16]

A variety of pain management methods are available for the pain women experience during the different stages of labor. See Table 1 for the labor pain management methods found in studies in this review. Epidural analgesia is the most commonly used method in the United States[17] and may block pain entirely. Although epidurals are more effective for pain relief than other pain management methods, epidurals are associated with increased risk of assisted (vacuum or forceps) vaginal birth, use of oxytocin, maternal hypotension, motor blockade, urinary retention, maternal fever, and cesarean for fetal distress.[18] In addition, the second stage of labor can be longer in women who have epidurals than in women who receive other pain management methods.[19] Women who have epidurals must have additional monitoring and may need confinement to bed, which limits mobility and options for positioning, and placement of a Foley catheter. Epidural placement is an invasive procedure that can have uncommon but clinically significant complications such as spinal headache.[20] Catastrophic complications, such as epidural hematoma and epidural abscess, are very rare but do occur.[20]

Although nitrous oxide would not be expected to be as effective for analgesia as an epidural because of the differences in their mechanism of action, nitrous oxide has other benefits including that it is inexpensive and noninvasive. Nitrous oxide has a rapid onset and end of action. Thus women who do not like nitrous oxide or find it inadequate for pain management can easily discontinue its use and switch to another method, unlike epidurals and systemic opioids that diminish gradually over a much longer time period. Mobility and options for positioning are not limited nor does nitrous oxide require additional monitoring and potential anesthesia-related interventions (e.g., bladder catheterization). Women self-administer nitrous oxide, which allows them to control the amount they need.[21] Nitrous oxide may not be an ideal method for women who want maximum pain relief, but it could be preferable to other pharmacologic pain management methods for women who want increased mobility with less intervention and monitoring. Nitrous oxide might also be useful when a woman wants to delay use of epidural analgesia until later in labor, when epidural anesthesia is not immediately available (e.g., in hospitals that do not have in-house anesthesia staff and must call in an anesthesia provider), when a woman arrives at the hospital too far along in labor to allow for an epidural to be placed and take effect, and when a woman finds epidural analgesia ineffective or inadequate.

One concern with nitrous oxide use is the potential for the gas to escape into the room and potentially affect health care workers as well as other individuals present with laboring women. For this reason, there are multiple organizations responsible for regulation of the use of nitrous oxide and factors other than clinical outcomes are important to decisionmaking about its use (see Appendix F for a description of regulatory considerations). Room ventilation systems and scavenging systems that remove waste gases are used to reduce exposure to caregivers and others present for labor. Equipment capable of scavenging provides constant negative pressure so that the woman's exhalations, which contain nitrous oxide, are captured and removed from the room and facility.[14]

Identifying the appropriate outcome measure by which to assess nitrous oxide is challenging. Nitrous oxide is not intended to provide the extent of pain relief expected with epidural. Rather than a head to head comparison of effectiveness, the benefits of nitrous oxide rest on women's satisfaction and safety of the approach for the woman and her fetus/newborn.

Table 1. Labor pain management methods used in studies included in this review

Method	Description	Timing and Frequency of Administration
Nitrous oxide	Anesthetic and analgesic gas usually inhaled intermittently via a facemask or mouthpiece, can be given continuously via nasal cannula Reduces the perception of pain, alters consciousness, decreases anxiety	Can be used for first- and second-stage labor pain Self-administered between and/or during contractions May be continued into third stage if procedures, such as perineal repair or manual removal of the placenta, are needed
Other inhalational anesthetic gases (desflurane, sevoflurane, isoflurane, enflurane, methoxyflurane, trichloroethylene, cyclopropane)	Anesthetic gas usually inhaled intermittently via a facemask or mouthpiece, can be given continuously via nasal cannula Reduces the perception of pain, alters consciousness	None are used used for management of labor pain in the United States Desflurane, sevoflurane, and isoflurane are used for other types of anesthesia in the United States

Table 1. Labor pain management methods used in studies included in this review (continued)

Method	Description	Timing and Frequency of Administration
Epidural	Injection of medications (usually a combination of local anesthetic and opioid) into the epidural space around the spinal cord Blocks pain in lower half of body May partially or fully block voluntary motor control in lower half of body	Initiated during first stage of labor with infusion usually continuing into second stage May be continued into third stage if procedures, such as perineal repair or manual removal of the placenta, are needed
Opioids (for example, pethidine/meperidine)	Medication given intravenously or by intramuscular injection Provides some relief of labor pain and causes sedation, which can also alter perception of pain Opioids commonly used in labor include meperidine/pethidine, morphine, fentanyl, remifentanil, butorphanol, and nalbuphine	Used during the first stage of labor Administered at regular intervals as needed for pain (usually every 1 to 4 hours depending on specific medication)
Paracervical block	Injection of local anesthetic at lateral cervix Provides some relief from the pain of cervical dilation	Rarely used in the United States because it causes fetal bradycardia (slow heart rate) Used during the first stage of labor Can be repeated
Pudendal block	Injection of local anesthetic in the vaginal wall near the pudendal nerves, bilaterally Relieves pain in the lower vagina, perineum, and external genitalia that occur when the woman is pushing	Used during the second stage of labor Administered once
Transcutaneous electrical nerve stimulation (TENS)	Low-voltage electrical impulses are sent from a handheld device controlled by the woman to electrodes placed on the skin of the lower back	Used during the first stage of labor Used as needed
Sterile water injections	Injection of sterile water intradermally (just below the skin) in four locations on the lower back	Used during the first stage of labor, most commonly for low back pain Can be repeated
Hydrotherapy	Immersion of the laboring woman in water	Can be used during the first and second stages of labor Used as needed
Psychoprophylaxis	Use of breathing and relaxation techniques taught during pregnancy	Can be used during the first and second stages of labor Used as needed

Scope of This Report

Most women in the United States use some type of medication for labor pain management. However, the option of using nitrous oxide to relieve labor pain is limited by its lack of availability. With such prevalent use of nitrous oxide during labor in other countries, increasing interest in this method in the United States, and potential advantages of this pain management method, such as being less expensive and invasive than widely used regional anesthesia, this review attempts to assess the effectiveness of nitrous oxide in managing labor pain and to identify potential factors that may influence its availability and use within the United States. Our Key Questions have been structured with this goal in mind. The primary outcomes for consideration, as identified by our technical expert panel, include the comparative effectiveness of nitrous oxide for the management of labor pain, the influence of nitrous oxide on women's satisfaction with their birth experience, the health system factors influencing its use within the United States, and any adverse effects associated with this intervention. With the rate of cesarean birth continuing to rise—32.3 percent of all U.S. births reported in 2008[1]—it is also important to address whether the use of nitrous oxide during labor influences the route of birth in women initially intending a vaginal birth.

Key Questions

We have synthesized evidence in the published literature to address these Key Questions:

1. What is the effectiveness of nitrous oxide when compared with other methods for the management of labor pain among women intending a vaginal birth?
2. What is the comparative effectiveness of nitrous oxide on women's satisfaction with their birth experience and pain management?
3. What is the comparative effectiveness of nitrous oxide on the route of birth?
4. What is the nature and frequency of adverse effects associated with the use of nitrous oxide for the management of labor pain, including but not limited to:
    - Maternal adverse effects, such as nausea and vomiting, dreams, dizziness, unconsciousness, and postpartum complications.
    - Fetal/neonatal adverse effects, such as low Apgar scores and abnormal fetal cord blood gases.
    - Childhood adverse effects, such as drug dependency and developmental complications.
    - Adverse effects on health care providers and other individuals present for labor.
5. What are the health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization?

Organization of This Evidence Report

The following chapter describes our methods, including our search strategy, inclusion and exclusion criteria, approach to review of abstracts and full publications, and methods for extraction of data into evidence tables, and compiling evidence. We also describe our approach to grading the quality of the literature and to describing the strength of the literature.

In the Results chapter, we review the evidence identified by Key Question. We report the number and type of studies identified and we differentiate between total numbers of publications and unique studies to bring into focus the number of duplicate publications in this literature in which multiple publications are derived from the same study population. In the final chapter of the report we discuss the results and enlarge on the methodologic considerations relevant to each Key Question. We also outline the current state of the literature and challenges for future research on the use of nitrous oxide for the management of labor pains.

Uses of This Report

We anticipate this report will be of value to all health care providers who take care of women of childbearing age, including members of the American Congress of Obstetricians and Gynecologists; the Association of Women's Health, Obstetric and Neonatal Nurses; the American College of Nurse-Midwives; the American Association of Birth Centers; the American Society of Anesthesiologists; the Society for Obstetric Anesthesia and Perinatology; the American Association of Nurse Anesthetists; the American Academy of Family Physicians; and other clinical professional organizations. In addition, this review will be of use to the National Institutes of Health, Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, and the Health Resources and Services Administration – all of which have offices or bureaus devoted to women's health issues. This report can bring providers up to date about the current state of evidence, and it provides an assessment of the quality of studies that aim to determine the outcomes of the use of nitrous oxide for the management of labor pain. It will be of interest to individual women and the general public because millions of women per year give birth in the United States, and the recurring need for women and their health care providers to decide among numerous options for labor pain management. This report will also be useful to facilities considering providing nitrous oxide for labor pain management. We also anticipate it will be of use to private sector organizations concerned with women's health, such as Childbirth Connection, the National Women's Health Network, and Our Bodies Ourselves.

Researchers can obtain a concise analysis of the current state of knowledge in this field. They will be poised to pursue further investigations that are needed to advance research methods, understand risk factors, develop options for labor pain management, and optimize the effectiveness and safety of clinical care for women in labor.

Methods

In this chapter, we document the procedures that the Vanderbilt Evidence-based Practice Center used to produce a systematic review on the use of nitrous oxide for the management of labor pain. We first describe the assistance provided by the technical expert panel (TEP) throughout the topic refinement and review process. We then present the Key Questions and analytic framework. We also discuss our strategy for identifying articles relevant to our five Key Questions, our inclusion and exclusion criteria, and the process we used to abstract pertinent information from the eligible articles and generate our evidence tables. In addition, we discuss our method for grading the quality of individual articles and for rating the strength of the evidence. Finally, we describe the applicability of this report.

Technical Expert Panel

We identified technical experts on the topic of the use of nitrous oxide for the management of labor pain in the fields of obstetrics and gynecology, anesthesiology, midwifery, nursing, pediatric care, primary care, and patient advocacy to provide assistance during the project. The TEP was expected to contribute to broader goals of the Agency for Healthcare Research and Quality (AHRQ), including (1) creating and maintaining science partnerships as well as public-private partnerships and (2) meeting the needs of an array of potential customers and users of its products. Thus, the TEP was both an additional resource and a sounding board during the project. The TEP included nine members serving as technical or clinical experts. To ensure robust scientifically relevant work, we called on the TEP to provide reactions to work in progress and advice on substantive issues or possibly overlooked areas of research. TEP members participated in conference calls and discussion through email to:

- Refine the analytic framework and Key Questions during topic refinement
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria
- Provide input on the information and domains included in evidence tables
- Develop a hierarchy of participant characteristics and outcomes to systematically assess
- Advise about the clinical availability and use of nitrous oxide for the management of labor pain in the United States

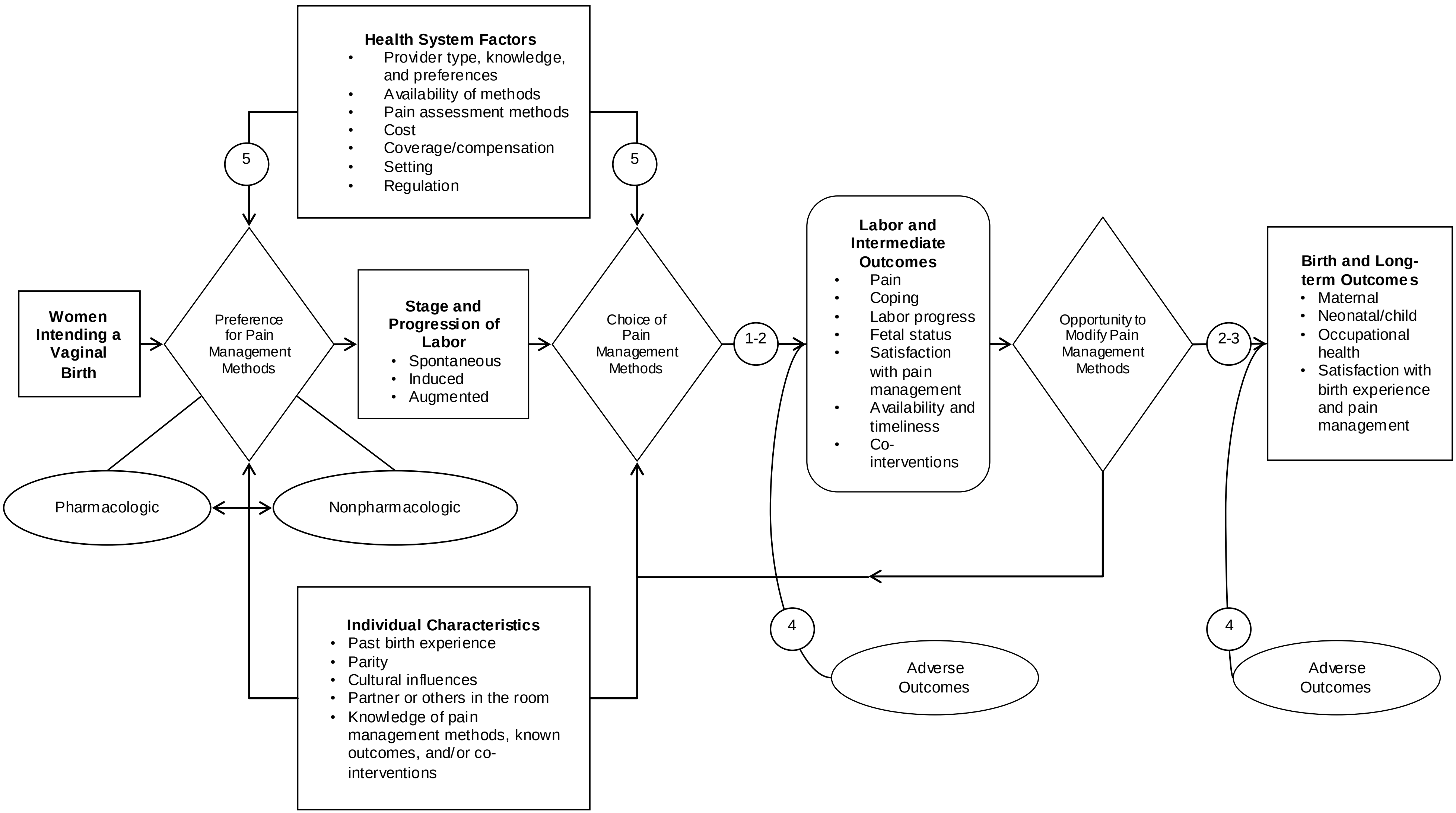
Because of their extensive knowledge of the literature, including numerous articles authored by TEP members themselves, and their active involvement in professional societies and trial networks, and as practitioners in the field, we also asked TEP members to participate in the external peer review of the draft report.

Analytic Framework for Nitrous Oxide for Labor Pain Management

The analytic framework in Figure 2 summarizes the conceptual model used to guide this systematic review by focusing the Key Questions on the critical health care related pathways and decision points. Our analytic framework emphasizes that care takes place at the interface of the health care system and the individual. The pathway through care is indicated in the boxes along the center line where the person and care meet. Each Key Question is indicated within the framework at the relevant point of influence in care. Each of the domains listed among individual and system factors, such as patient factors, use of cointerventions, provider factors and health system factors, has been shown to influence care trajectories and outcomes. Making these domains explicit as they influence the care pathway provides the framework in which the review team and technical expert panel conducted this review. To the degree that individuals or care settings vary in context-specific points of influence, this framework may or may not be applicable.

Overall, the figure represents the population of interest, women intending a vaginal birth, and the factors and decision points that influence the use of nitrous oxide for the management of labor pain. The initial preference for pain management methods, which is often determined prior to the onset of labor, can be shaped by past birth experience, cultural or familial influence, and knowledge of various pain management options. Women acquire knowledge about pain management options from a variety of sources including health care providers, childbirth educators, patient education books and other materials, popular media, friends, and family. Once labor begins, health system factors such as availability, setting, and provider preference may affect the utilization of the desired pain management methods (Key Question 5). The first two decision points reflect the initial preference for and actual implementation of pain management methods. A third decision point occurs after the onset of labor but prior to birth, at which point the woman in labor may opt to modify the pain management method. We sought to examine how the administration of nitrous oxide at various mixes, routes, and intervals affects outcomes that occur during labor, after birth, and in the long term (Key Questions 1–3). Adverse effects of treatment are examined in Key Question 4. Portions of the framework that are unexplored in the scientific literature are highlighted in the discussion of future research needs.

Figure 2. Analytic framework for nitrous oxide for the management of labor pain



Literature Review Methods

Literature Search and Retrieval Process

Databases

Our search included MEDLINE®, Embase, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Reviews conducted by the Cochrane Collaboration are indexed in the MEDLINE database and were also included in the search. We also hand-searched references of included articles to identify additional studies. We employed indexing terms within each database to exclude ineligible publication types and articles in languages other than English.

Search Terms

Controlled vocabulary terms served as the foundation of our search in each database, complemented by additional keyword phrases to represent the myriad ways in which nitrous oxide is referred to in the clinical literature. We limited the MEDLINE search strategy to exclude studies not relevant to human populations and non-English-language papers. We also used the search strategy to perform an initial exclusion of publications that lay beyond the scope of the review (letters, comments, case reports, reviews, news, editorials, historical articles, and meta-analyses), focusing on retaining items comprising primary data (prospective and retrospective studies).

We searched CINAHL and Embase to supplement the MEDLINE results with additional nursing and drug-focused results. Similarly, we used a combination of controlled vocabulary and keywords, limited to primary data, English-language reports, and human subjects. Our review process also allowed identification of additional articles which should be retained for hand searching of references. Appendix A outlines our search terms and results. Our searches were executed between July 2010 and July 2011 and were not limited by date.

Grey Literature

Grey literature was searched with a focus on background and regulatory material. Sources included websites and databases of the U.S. Food and Drug Administration (FDA), the Joint Commission, the Occupational Safety and Health Administration (OSHA), and the National Institute for Occupational Safety and Health (NIOSH); thesis/dissertation databases (ProQuest Dissertations and Theses A&I, Networked Digital Library of Theses & Dissertations, Index to Theses); New York Academy of Medicine's Grey Literature Report; PAIS International; Hazardous Substances Data Bank; legal resources (LexisNexis Academic, HeinOnline;, meeting/abstract databases (BIOSIS Previews, BioMed Central meeting abstracts); OpenDOAR open access repository; general web searching (Google, GoogleScholar, Scirus); and files posted to an email group focused on the use of nitrous oxide in labor (N2Oduringlabor Yahoo! Group).

Inclusion and Exclusion Criteria

Our inclusion and exclusion criteria and population, intervention, comparators, outcomes, timing, and setting (PICOTS) were developed in consultation with the TEP, to capture the literature most tightly related to the Key Questions. The PICOTS and criteria are summarized in Table 2.

Table 2. Inclusion and exclusion criteria

Category	Criteria
Study population	Pregnant women in first and second stages of labor (up to birth), other attendees and health care providers, and the fetus/neonate
Intervention	Nitrous oxide inhalation
Comparators	• No analgesic/anesthetic intervention, analgesia/anesthesia, other inhalational agents, and pharmacologic and nonpharmacologic pain management methods o Pharmacologic pain management methods include, but are not limited to, epidural analgesia, paracervical block, pudendal block, and parenteral opioids o Nonpharmacologic pain management methods include, but are not limited to, acupuncture, aromatherapy, continuous labor support, heat and cold, hydrotherapy, hypnosis, movement and positioning, music and audioanalgesia, patterned breathing and relaxation, sterile water injections, touch and massage, and transcutaneous electrical nerve stimulation (TENS)
Outcomes	• Primary outcomes: o Pain reduction o Satisfaction with pain management o Satisfaction with birth experience o Long-term maternal, child, and occupational health outcomes • Other outcomes: o Labor and intermediate outcomes – Pain – Coping – Labor progress – Satisfaction with pain management. – Satisfaction with birth experience – Availability and timeliness – Cointerventions associated with the use of nitrous oxide or other pain management methods o Birth and long-term outcomes – Maternal outcomes, including but not limited to route of birth and postpartum course – Child outcomes, including but not limited to Apgar scores, fetal cord blood gases, and neurobehavioral outcomes – Health care provider outcomes (occupational health) from exposure – Maternal satisfaction with pain management – Maternal satisfaction with birth experience o Adverse effects, including but not limited to: – Maternal adverse effects, such as nausea and vomiting, dreams, dizziness, and unconsciousness – Fetal/neonatal adverse effects, such as drug dependency – Childhood adverse effects, such as drug dependency and developmental complications. – Individuals present for labor adverse effects. – Health care provider adverse effects (occupational health)

Table 2. Inclusion and exclusion criteria (continued)

Category	Criteria
Timing	• Intermediate outcomes will include associated labor outcomes • Long-term outcomes will include associated birth outcomes • There will be no restriction on duration of follow-up
Setting	• All birth settings will be considered, including hospital, birth center, and home
Publication date	No limit
Publication languages	English only
Admissible evidence (study design and other criteria)	Admissible designs • Study size ≥ 20 pregnant women using nitrous oxide during labor and reporting outcomes • Addresses harms or occupational exposures Other criteria • Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results • Studies with mixed patient populations must include ≥ 20 pregnant women in labor or provide extractable information addressing harms or occupational outcomes • Studies must include at least one outcome measure of an outcome listed in the PICOTS • Relevant outcomes must be extractable from data presented in the papers

The study population includes pregnant women in labor, birth attendees or health care providers who may be exposed to nitrous oxide during labor, and the fetus/neonate. We did not restrict by parity or risk status. The initial study size was set at greater than or equal to 20 women using any intervention for labor pain management, provided that nitrous oxide was included in the study (i.e. studies with multiple arms that include nitrous oxide as an intervention for labor pain management would be included if the total N was greater than or equal to 20). However, once we completed the data abstraction, we determined that a meta-analysis would not be feasible given the heterogeneity among included studies in several key areas, most notably nitrous oxide mix, outcome assessment methods, and comparators. The study size inclusion criterion was then amended to specify that included studies must report outcomes on greater than or equal 20 women using nitrous oxide for labor pain management. Studies with fewer than 20 women reporting outcomes related to nitrous oxide use are too small to provide meaningful results in the absence of a meta-analysis. We excluded four studies based on the amended study size criterion.

We did not have translation services available to us to review non-English papers, and our TEP agreed that the vast majority of the relevant literature would be published in English. Furthermore, this review is intended to inform U.S. health care, and most research in the population of pregnant women in the United States is published in English language journals. Empirical evidence on the potential for bias created by excluding non-English studies also suggests little effect.[22]

Article Selection Process

Once we identified articles through the electronic database searches, review articles, and bibliographies, we examined abstracts of articles to determine whether studies met our criteria. Two reviewers separately evaluated the abstracts for inclusion or exclusion, using an Abstract

Review Form (Appendix B). If one reviewer concluded that the article could be eligible for the review based on the abstract, we retained it. Following abstract review, two reviewers independently assessed the full text of each included study using a standardized form (Appendix B) that included questions stemming from our inclusion/exclusion criteria. Disagreements between reviewers were resolved by a third-party adjudicator. The group of abstract and full text reviewers included three physicians (two obstetrician-gynecologists and an anesthesiologist), two certified nurse-midwives, two health services researchers, and two library scientists. Excluded studies, and the reasons for exclusion, are presented in Appendix E.

Literature Synthesis

Development of Evidence Tables and Data Abstraction Process

The staff members and clinical experts who conducted this review jointly developed the evidence tables. We designed the tables to provide sufficient information to enable readers to understand the studies and to determine their quality; we gave particular emphasis to essential information related to our Key Questions. We based the format of our evidence tables on successful designs used for prior systematic reviews.

The team was trained to abstract by abstracting several articles into evidence tables and then reconvening as a group to discuss the utility of the table design. We repeated this process through several iterations until we decided that the tables included the appropriate categories for gathering the information contained in the articles. All team members shared the task of initially entering information into the evidence tables. Another member of the team also reviewed the articles and edited all initial table entries for accuracy, completeness, and consistency. The two abstractors reconciled disagreements concerning the information reported in the evidence tables, the most common of which were study design and study setting. The full research team met regularly during the article abstraction period and discussed global issues related to the data abstraction process. In addition to outcomes related to intervention effectiveness, we abstracted all data available on harms. Harms encompass the full range of specific negative effects, including the narrower definition of adverse events.

The final evidence tables are presented in their entirety in Appendix C. Studies are presented in the evidence tables alphabetically by the last name of the first author. When possible, studies resulting from the same study population were grouped into a single evidence table. A list of abbreviations and acronyms used in the tables appears at the beginning of that appendix.

Rating Quality of Individual Studies

To assess the quality of individual studies, the team considered both novel and existing rating tools. Two existing, widely accepted tools were selected to account for the variety of potentially included study types (e.g. randomized controlled trials [RCTs] and cohorts); specifically the Cochrane Risk of Bias tool[23] and the Newcastle-Ottawa Quality Assessment Scale.[24] The Cochrane Risk of Bias tool is designed for the assessment of studies with experimental designs and randomized participants. As such, we employed the Cochrane Risk of Bias tool to assess the quality of RCTs. Fundamental domains include sequence generation, allocation concealment, blinding, completeness of outcome data, and selective reporting bias. The Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of nonrandomized studies (e.g. cohort and case-control studies). This scale assesses three broad perspectives: the selection of study groups, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. Both tools are presented in Appendix D.

Quality assessment of each study was conducted using the Distiller Systematic Review online reference manager (Evidence Partners Incorporated, Ottawa, Ontario). Web-based assessment forms were created using the tools provided in Appendix D as templates. Investigators did not rely on the study design as described by authors of individual papers; rather, the methods section of each paper was reviewed to determine which rating tool to employ. Four investigators independently assessed the quality of individual studies, with the Senior Scientist reviewing and resolving any discrepancies. Thresholds for converting the Cochrane Risk of Bias tool and Newcastle-Ottawa Quality Assessment Scale results to the AHRQ standard of "good," "fair," and "poor" quality designations are described in Appendix D.

Grading Strength of Evidence

We evaluated the overall strength of the evidence for the primary outcomes. We used the approach to strength of evidence described in the EPCs' Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[25] We graded available evidence for each key outcome for each of the following domains:

- Risk of bias (low, medium, or high)
- Consistency of findings (inconsistency not present, inconsistency present, or unknown or not applicable)
- Directness (direct comparison of influence on outcomes in RCT, or indirect information from observational research)
- Precision (precise or imprecise based on outcomes rates, size of the individual studies and the total number of women in the studies for the category of intervention)

We combined the grades of each domain to develop the strength of evidence for each key outcome. Possible grades for each domain were: low, moderate, or high risk of bias; consistent or inconsistent; direct or indirect; and precise or imprecise. We considered additional domains, including publication bias and large effect size, on a per-Key Question basis.

We graded the body of literature for effectiveness of nitrous oxide for the management of labor pain, women's satisfaction with their birth experience and pain management, effect of nitrous oxide on route of birth, and adverse effects associated with nitrous oxide. We present those ratings as part of the discussion in the final chapter of the report. The possible grades were:

High: High confidence that the evidence reflects the true effect. Further research is unlikely to change estimates.

Moderate: Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low: Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is also likely to change the estimate.

Insufficient: Evidence is either unavailable or does not permit a conclusion.

When no studies were available for an outcome or comparison of interest, we assessed the evidence as insufficient. Two reviewers independently graded the body of evidence; disagreements were resolved through discussion or a third reviewer adjudication.

Applicability

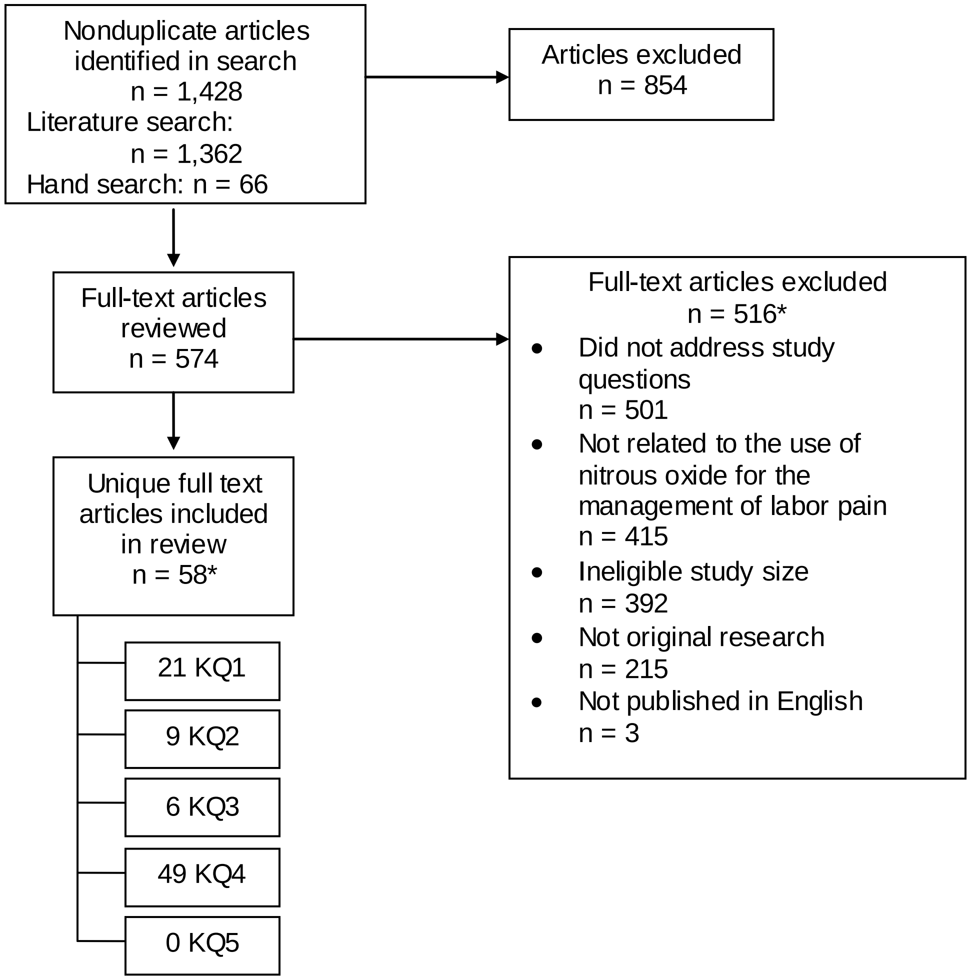
For decision makers to use this report to inform clinical care, they need information clarifying the degree to which findings of the included research might be expected to apply in the types of populations and settings in which intrapartum care is provided in the United States. Our assessment of applicability implemented the PICOTS framework, as described in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[25] Applicability tables depicting the similarity or lack of comparability of populations, interventions, comparison groups, outcomes, and settings represented in the available literature for each Key Question are presented in Appendix D.

Additionally, we used input from team and TEP members to identify study characteristics to be included in evidence tables and routinely abstracted. These characteristics were critical in highlighting limitations of current research, and in turn assessing applicability. We discuss applicability further in the Discussion chapter of the report.

Results

We identified 1,428 nonduplicate titles or abstracts, with 574 proceeding to full text review (Figure 3). Fifty-eight publications were included in the review, representing 59 distinct study populations: 13 randomized controlled trials (RCTs), seven crossover RCTs, four nonrandomized clinical trials, 14 prospective cohorts, one retrospective cohort, three case series, four case-control studies, 11 cross-sectional studies, and two trend studies. The most common reasons for exclusion were irrelevance to the topic and ineligible study size. Twenty-one articles pertain to Key Question (KQ) 1, nine articles to KQ2, six articles to KQ3, 49 articles to KQ4, and zero articles to KQ5. Tables 3, 4 and 5 provide summaries of the nitrous oxide interventions represented in this review. Studies are grouped by study type and displayed in reverse chronological order. Seven studies of occupational exposure to nitrous oxide,[26-32] three studies of addiction in offspring following nitrous oxide use during labor,[33-35] and one study of leukemia in offspring following nitrous oxide use during labor[36] are not included in the tables but are described in detail in the results of KQ4.

Figure 3. Disposition of articles identified by the search strategy



KQ = Key Question

*The number of articles addressing Key Questions and those excluded exceed the total number of articles in each category because some articles fit multiple exclusion categories or addressed more than one Key Question.

Table 3. Summary of nitrous oxide interventions, RCTs

Study Country Total N Study Type, Quality	Nitrous Oxide Mix and Administration Method	Comparator(s)
Talebi et al.,[37] 2009 Iran N = 523 RCT, poor	50%;self-administered via facemask	50% oxygen
Yeo et al.,[38] 2007 U.K. N = 32 Crossover RCT, poor	Entonox (50%); self-administered	0.8% sevoflurane
Einarsson et al.,[39] 1996 Sweden N = 24 RCT, poor	50%, 70%; administered via mouthpiece	The alternate nitrous oxide mixes were compared (50% vs. 70%)*
Abboud et al.,[40] 1995 U.S. N = 80 RCT, poor	30 - 60%; administered by an anesthesiologist	1 – 4.5% desflurane
Carstoniu et al.,[41] 1994 Canada N = 26 Crossover RCT, poor	50%; self-administered	Compressed air
Arora et al.,[42] 1992 U.K. N = 41 RCT, fair	Entonox (50%); administration method not reported	Entonox and isoflurane
Westling et al.,[43] 1992 Sweden N = 24 Crossover RCT, poor	40% and 70% (intermittent), 40% (continuous); administered via facemask	Intermittent oxygen, alternate nitrous oxide mixes, intermittent vs. continuous
Chia et al.,[44] 1990 Singapore N = 121 RCT, poor	Entonox (50%); administration method not reported	TENS
Abboud et al.,[45] 1989 U.S. N = 60 RCT, poor	30 - 60%	0.7% isoflurane
Constantine et al.,[46] 1989 U.K. N = 149 RCT, poor	Entonox (50%); administered via facemask, mouthpiece, or humidifier	The alternate administration methods were compared*
McLeod et al.,[47] 1985 U.K. N = 32 Crossover RCT, poor	Entonox (50%); administered via facemask	0.75% isoflurane
McGuinness and Rosen,[48] 1984 U.K. N = 20 Crossover RCT, poor	Entonox (50%); administered by an anesthesiologist via mouthpiece	1% enflurane

Table 3. Summary of nitrous oxide interventions, RCTs (continued)

Study Country Total N Study Type, Quality	Nitrous Oxide Mix and Administration Method	Comparator(s)
Abboud et al.,[49] 1981 U.S. N = 105 RCT, poor	30 - 60%; administered by an anesthesiologist	0.25 – 1.25% enflurane
Rosen et al.,[50] 1972 U.K. N = 250 RCT and prospective cohort, poor	Entonox (50%); administration method not reported	0.35% methoxyflurane
Bergsjo and Lindbaek,[51] 1971 Norway N = 63 Crossover RCT, poor	50%; administered via facemask	0.5 – 0.8% methoxyflurane
Phillips and Macdonald,[52] 1971 U.K. N = 152 RCT, poor	Entonox (50%); administration method not reported	Trichloroethylene and pethidine, pethidine only
NA,[12] 1970 U.K. N = 778 RCT, fair	50%, 70%; administration method not reported	The alternate nitrous oxide mixes were compared (50% vs. 70%)*
Jones et al.,[53] 1969 U.K. N = 50 RCT, poor	50%; administration method not reported	0.35% methoxyflurane
Jones et al.,[54] 1969 U.K. N = 50 RCT, poor	0 - 80%; administration method not reported	60% methoxyflurane

TENS = transcutaneous electrical nerve stimulation
*Studies that assessed nitrous oxide and no other pain management methods were only included in the harms KQ.

Table 4. Summary of nitrous oxide interventions, nonrandomized trials and cohort studies

Study Country Total N Study Type, Quality	Nitrous Oxide Mix and Administration Method	Comparator(s)
Stirk et al.,[55] 2002 U.K. N = 115 Prospective cohort, poor	Entonox (50%); administration method not reported	Diamorphine
Leong et al.,[56] 2000 Malaysia N = 118 Prospective cohort, good	Entonox (50%); administration method not reported	Epidural and bupivacine and/or fentanyl
Arfeen et al.,[57] 1994 U.K. N = 40 Prospective cohort, poor	Entonox (50%); administration method not reported	Epidural and bupivacine
Ranta et al.,[58] 1994 Finland N = 1,091 Prospective cohort, poor	50%; administered by an anesthesiologist	Epidural, water block, pethidine, multiple analgesics, no analgesia
Landon et al.,[59] 1992 U.K. N = 58 Prospective cohort, poor	Entonox (50%); administration method not reported	No nitrous oxide
Zelcer et al.,[60] 1989 Australia N = 75 Prospective cohort, poor	% not reported, administration method not reported	Epidural, pethidine
Deckardt et al.,[61] 1987 Germany N = 55 Prospective cohort, poor	50%; administration method not reported	Lumbar peridural anesthesia, no analgesic drugs
Harrison et al.,[62] 1987 Ireland N = 170 Prospective cohort, poor	Entonox (50%); self-administered	Epidural, TENS, pethidine and promazine
Harrison and Cullen[63] 1986 Ireland N = 110 Prospective cohort, poor	Entonox (50%); self-administered	Epidural, pethidine and promazine, TENS, TENS placebo, general anesthesia
Soyannwo,[64] 1985 Nigeria N = 150 Prospective cohort, poor	Entonox (50%); self-administered	Entonox and pethidine or pethilorphan
Murphy et al.,[65] 1984 U.K. N = 8,392 Retrospective cohort, poor	Entonox (50%); administration method not reported	Epidural, pethidine

Table 4. Summary of nitrous oxide interventions, nonrandomized trials and cohort studies (continued)

Study Country Total N Study Type, Quality	Nitrous Oxide Mix and Administration Method	Comparator(s)
Arthurs et al.,[16] 1979 U.K. N = 49 Prospective cohort, poor	Entonox (50%); self-administered intermittently via facemask, or continuously via nasal cannula	Facemask and nasal cannula vs. facemask only*
Rosen et al.,[66] 1969 U.K. N = 1,522 Nonrandomized trial, poor	Entonox (50%); administration method not reported	0.35%, 0.5% trichloroethylene; 0.35% methoxyflurane
Beppu,[67] 1968 Japan N = 667 Prospective cohort, poor	50 – 80%; administration method not reported	Trichloroethylene, halothane
Smith et al.,[68] 1968 U.S. N = 2,066 Nonrandomized trial, poor	25 – 50%; administration method not reported	0.2 – 0.5% methoxyflurane, 1 – 5% cyclopropane, pudendal, spinal
Clark et al.,[69] 1967 U.S. N = 94 Nonrandomized trial, fair	50% oxygen with nitrous oxide and methoxyflurane†; administered via inhaler	Methoxyflurane
McAneny and Doughty,[13] 1963 U.K. N = 501 Nonrandomized trial, poor	50%, 60%, 70%, 75%, 80%; self-administered	Alternate nitrous oxide mixes*

TENS = transcutaneous electrical nerve stimulation
*Studies that assessed nitrous oxide and no other pain management methods were only included in the harms KQ.
†Nitrous oxide concentration not reported.

Table 5. Summary of nitrous oxide interventions, other study designs

Study Country Total N Study Type, Quality	Nitrous Oxide Mix and Administration Method	Other Pain Management Method(s) Assessed
Waldenstrom and Irestedt,[70] 2006 Sweden N = 2,482 Trend, fair	% not reported; administration method not reported*	Epidural block , pethidine, paracervical bock, pudendal block
Henry and Nand,[71] 2004 Australia N = 496 Cross-sectional, poor	% not reported; administration method not reported†	Pethidine, epidural, local anesthesia, nonpharmacological methods
Peach,[72] 1999 Australia N = 1,000 Cross-sectional, fair	% not reported; administration method not reported†	Epidural, pethidine, nonpharmacological (alone and in combination)
Ross et al.,[73] 1999 U.K. N = 221 Case series, poor	Entonox (50%) with isoflurane; administration method not reported	None

Table 5. Summary of nitrous oxide interventions, other study designs (continued)

Study Country Total N Study Type, Quality	Nitrous Oxide Mix and Administration Method	Other Pain Management Method(s) Assessed
Waldenstrom,[74] 1999 Sweden N = 1,148 Cross-sectional, fair	Entonox (50%); administration method not reported	Epidural, pethidine
Waldenstrom et al.,[75] 1996 Sweden N = 385 Cross-sectional, fair	Entonox (50%); administration method not reported	Epidural, local anesthesia, acupuncture, bath, breathing techniques
Ranta et al.,[76] 1995 Finland N = 1,091 Cross-sectional, fair	50%; administered via facemask	Epidural, pethidine, paracervical block, bupivacaine
Reed et al.,[77] 1988 U.K. N = 41 Case series, poor	Entonox (50%); administration method not reported	Pethidine
Morgan et al.,[78] 1982 U.K. N = 1,000 Cross-sectional, poor	Entonox (50%); self-administered	Epidural, pethidine, pudendal block
Holdcroft and Morgan,[79] 1974 U.K. N = 705 Cross-sectional, poor	Entonox (50%); administration method not reported	Entonox and pethidine, pethidine only
Marx et al.,[80] 1970 U.S. N = 40 Case series, poor	50 – 70%; administered via facemask	None

*Survey of the prevalence of pain management methods; concentrations of nitrous oxide not reported

KQ1: Effectiveness of Nitrous Oxide for Labor Pain Management

Key Points

- The heterogeneous outcomes used to assess pain make synthesis of studies challenging.
- Epidural anesthesia provides more effective pain relief than nitrous oxide, but the quality of the studies is predominately poor.
- The strength of the evidence for the effectiveness of nitrous oxide to manage labor pain compared with other, nonepidural pain management methods is insufficient because the studies are predominately of poor quality, use heterogenous outcome measures, and have inconsistent findings.
- The strength of the evidence for the effectiveness of nitrous oxide to manage labor pain compared with epidurals was not assessed because the two interventions have different goals with the purpose of epidural to substantially block pain and the purpose of nitrous oxide to make pain manageable. A head to head comparison will always demonstrate greater effectiveness of epidural for reducing pain.

This section presents the results of the literature search and findings about the effectiveness of nitrous oxide as a labor analgesic compared with other pharmacologic and nonpharmacologic modalities. The pharmacologic modalities that were compared with nitrous oxide in the literature were other inhalational anesthetic gases, including methoxyflurane, isoflurane, enflurane, desflurane, sevoflurane, trichloroethylene, and cyclopropane; epidural anesthesia; the opioid pethidine/meperidine (Demerol®), which was sometimes used in conjunction with the antiemetic promazine; paracervical block; pudendal block; and varied combinations of the pharmacologic agents. Nonpharmacologic modalities included transcutaneous electrical nerve stimulation (TENS), hydrotherapy (bath or shower), sterile water papule blocks, acupuncture, and psychoprophylaxis.

Overview of the Literature

Twenty-one publications representing 22 studies of distinct populations addressed the effectiveness of nitrous oxide.[38, 40-41, 44-45, 47-49, 51, 53-54, 58, 62, 66, 68-70, 75-76, 78-79] Eight of these studies were conducted in the United Kingdom,[48 38, 47, 53-54, 66, 78-79] five in the United States,[40, 45, 49, 68-69] two in Sweden,[70, 75] two in Finland,[58, 76], two in Singapore,[44] and one each in Canada,[41] Ireland,[62] and Norway.[51] These studies included six RCTs,[40, 44-45, 49, 53-54] six crossover RCTs,[38, 41, 44, 47-48, 51] four cross-sectional studies,[75-76, 78-79] two nonrandomized clinical trials,[66, 68] two prospective cohort studies,[58, 62] one case series,[69] and one trend study.[70] One study included an RCT and a crossover RCT with two distinct populations.[44] Four studies were of fair quality,[69-70, 75-76] and 17 were of poor quality.[38, 40-41, 44-45, 47-49, 51, 53-54, 58, 62, 66, 68, 78-79]

Detailed Synthesis

Placebo

An RCT compared 50 percent nitrous oxide in oxygen with compressed air using a double-blind, crossover design.[41] Participants (n = 26) self-administered nitrous oxide or placebo for five consecutive contractions then were switched to the other option for the next five contractions. Visual analog scale (specific numerical values not reported) scores to rate pain were obtained after each contraction. No statistically significant differences in the mean visual analogue scores were found between the two groups.

Inhalational Anesthetic Gases

Twelve studies compared nitrous oxide with various other inhalational anesthetic gases not currently used for management of labor pain in the United States, including six with methoxyflurane;[51, 53-54, 66, 68-69] two with isoflurane;[45, 47] two with enflurane;[48-49] and one each with desflurane,[40] sevoflurane,[38] trichloroethylene,[66] and cyclopropane.[68] These studies are summarized in Table 6, with the exception of one study that did not contribute additional data.[69] Studies are displayed in reverse chronological order.

Table 6. Effectiveness of inhalational anesthetic gases

Author Year Study Type N	Interventions	Other Labor Pain Management Method(s)	Findings
Yeo et al.,[38] 2007 Crossover RCT N = 32	Entonox (nitrous oxide 50%) Sevoflurane 0.8%	None	• Women used both gases. • Visual analogue scales with 100 mm rulers were used to assess pain relief, pain intensity, and sedation. • Pain relief significantly better with sevoflurane than Entonox in the first ($p = 0.01$) and second ($p < 0.001$) crossovers. • Pain intensity significantly higher with Entonox than sevoflurane in the first crossover ($p = 0.04$) but not different in the second crossover. • Sedation significantly greater with sevoflurane than Entonox in both crossovers ($p < 0.001$). 97% of participants preferred sevoflurane over nitrous oxide ($p < 0.001$).
Abboud et al.,[40] 1995 RCT N = 80	Nitrous oxide 30% to 60%, usually 46% Desflurane 1% to 4.5%, usually 2%	Not reported	• Satisfactory analgesia scores were comparable among women, anesthesiologists, and obstetricians.
Abboud et al.,[45] 1989 RCT N = 60	Nitrous oxide 30%-60%, usually 33% Isoflurane 0.2%-0.7%, usually 0.4%	Local infiltration, pudendal block, epidural	• Proportion of satisfactory pain scores did not differ significantly between groups among mothers (87% for nitrous oxide, 83% for isoflurane), anesthesiologists (97% for nitrous oxide, 90% for isoflurane), and obstetricians (83% for nitrous oxide, 87% for isoflurane).
McLeod et al.,[47] 1985 Crossover RCT N = 32	Entonox (nitrous oxide 50%) Isoflurane 0.75%	None	• Pain was assessed with a linear analogue scale (0-100). Mean pain scores were 63.0 (range 24-92) with Entonox and 46.6 (range 19-86) with isoflurane ($p < 0.001$). • Drowsiness scores were higher with isoflurane than nitrous oxide. • When women asked which agent they preferred at the end of the study, 69% chose isoflurane, 25% chose Entonox, and 6% were undecided.

Table 6. Effectiveness of inhalational anesthetic gases (continued)

Author Year Study Type N	Interventions	Other Labor Pain Management Method(s)	Findings
McGuinness et al.,[48] 1984 Crossover RCT N = 20	Nitrous oxide 50% Enflurane 1%	Pethidine	• Women used both gases. • Pain assessed with linear analogue scores (0-100). Scores with enflurane (median 50, range 13-79) were significantly lower than the scores with nitrous oxide use (median 52, range 29-79, $p < 0.02$). • Drowsiness scores for enflurane were significantly higher that the scores for nitrous oxide ($p < 0.02$).
Abboud et al.,[49] 1981 RCT N = 105	Nitrous oxide 30% to 60%, usually 40% Enflurane 0.25% to 1.25%, usually 0.5%	Narcotic analgesia, local infiltration, pudendal block	• Most women had satisfactory analgesia according to scores from the women, anesthesiologists, and obstetricians. • The difference in satisfactory analgesia scores for the two gases was significant only for the obstetricians ($p < 0.05$).
Bergsjo et al.,[51] 1971 Crossover RCT N = 63	Nitrous oxide 50% Methoxyflurane 0.8%	None	• After using both, a higher proportion of mothers chose nitrous oxide (63%) than methoxyflurane (35%) with 2% undecided ($p < 0.05$). • Analgesic effect of nitrous oxide (rated by physician): excellent for 8%, good for 82%, moderate for 4%, and poor for none. • Analgesic effect of methoxyflurane (rated by physician): good for 95% and moderate for 5%.
Jones et al.,[54] 1969 RCT N = 48	Nitrous oxide calibrated in 5% steps from 20% to 100% oxygen Methoxyflurane with 40% oxygen	Pethidine	• Mean proportion of time the anesthetists assessed the women's reactions to contractions as satisfactory did not differ significantly between groups. • Most midwives and women reported pain relief was complete or considerable.
Jones et al.,[53] 1969 RCT N = 50	Nitrous oxide 50% Methoxyflurane 0.35%	Pethidine	• Mean proportion of time the anesthetists assessed the women's reactions to contractions as satisfactory was significantly ($p < 0.05$) higher for methoxyflurane (79.3 ± 20%) than nitrous oxide (62.3 ± 30%). • Most midwives and women reported pain relief was complete or considerable.

Table 6. Effectiveness of inhalational anesthetic gases (continued)

Author Year Study Type N	Interventions	Other Labor Pain Management Method(s)	Findings
Rosen et al.,[66] 1969 Prospective cohort N = 1257	Nitrous oxide 50%	Pethidine, morphine	• No significant difference between groups in the women's assessment of their pain relief in interviews immediately after the birth and two days later. • Midwives rated pain relief good or excellent more frequently with methoxyflurane (53%, $p < 0.01$) and trichloroethylene (49%, $p < 0.02$) than nitrous oxide (42%).
	Trichloroethylene 0.35% or 0.5%		
	Methoxyflurane 0.35%		
Smith et al.,[68] 1968 Prospective cohort N = 1616	Nitrous oxide 25% to 40%	Local or pudendal nerve block	• Participants and physician pain ratings did not differ significantly across groups.
	Methoxyflurane 0.2% to 0.5%		
	Cyclopropane 1% to 5%		

Transcutaneous Electric Nerve Stimulation

One publication comparing Entonox® with TENS reported two studies.[44] The first study was an RCT in which 101 women in early labor were randomized to Entonox or TENS as their initial pain management method. They could choose a different pain relief method if the initial method was inadequate, and the proportion of women who did this was comparable in the two groups (17% using Entonox vs. 19% using TENS, difference nonsignificant). On the first postpartum day, the woman rated her pain with Entonox or TENS on a scale of 0 to 10. The difference between groups was not statistically significant. The second study was a crossover RCT in which 20 nulliparous women undergoing induction of labor were randomized to Entonox or TENS for their first pain management method. When labor pain was no longer tolerable, the woman was asked to rate the pain relief as nil, partial, or complete then switched to the other method (Entonox or TENS). For their first method, women had more relief with TENS than Entonox, but this difference was not statistically significant and women in the Entonox group were having more frequent contractions. The difference in pain relief between groups was also nonsignificant for the second method used.

Observational Studies of Multiple Pain Management Methods

Two prospective cohort studies assessed the effectiveness of multiple pain management methods in women who chose their methods.[58, 62] The first study (n = 170) included women whose initial pain management method choice was Entonox, TENS, pethidine and promazine, or epidural.[62] Five-point scales were used to assess women's pain and midwives' evaluation of pain relief. Both groups rated epidural as providing the most pain relief, and pethidine and promazine as providing the least ($p < 0.001$ for participant and midwife ratings). Additional pain management methods were used by 5 percent of women in the nitrous group, 82 percent in the TENS group, 80 percent in the pethidine and promazine group, and none of the women in the epidural group. The second study (n = 833 with pain scores) included women who had 50 percent nitrous oxide, water blocks, pethidine, paracervical block, epidural, several methods, and no analgesia.[58] During labor, a visual pain scale (0–10) was used. Median pain scores decreased significantly ($p < 0.01$) from pre-analgesia values with epidural and paracervical block, and increased significantly ($p < 0.01$) after water block, nitrous oxide, and pethidine. On their third day postpartum, women were asked to rate the adequacy of analgesia. None of the women who had epidural rated it as poor ($p < 0.01$ for comparison with other groups) compared with 28 percent who used nitrous oxide.

Five cross-sectional studies retrospectively assessed the effectiveness of labor pain management methods.[70, 75-76, 78-79] In a study of 2,482 women, participants completed a questionnaire two months after their births that included assessment of their pain management methods as very effective, some effect, or no effect.[70] Epidural had the highest percentage of very effective responses (84% of primiparas, 72% of multiparas) followed by nitrous oxide (38%of primiparas, 49%of multiparas), psychoprophylaxis (39% of primiparas, 47% of multiparas), pethidine (41% of primiparas and multiparas), bath or shower (29% of primiparas, 35% of multiparas), and acupuncture (10% of primiparas, 23% of multiparas). In another study, 1,000 women were interviewed within 48 hours after giving birth and asked to identify how much pain they experienced using a 10 cm linear analogue scale graded between 0 and 100 mm.[78] Women who had epidurals had the lowest mean (± SD) pain score (29 ± 3.7) followed by pethidine plus epidural (30 ± 3.8), epidural plus Entonox (51 ± 4.2), pethidine plus Entonox (57 ± 3.4), pethidine (58 ± 3.1), Entonox (61 ± 3.1), pudendal block (68 ± 1.9), miscellaneous (69 ± 3.3), and no analgesia (70 ± 2.6). In one study, interviews were conducted 24 to 48 hours after birth in which women were asked to rate their pain relief with analgesia as complete, satisfactory, slight, or none.[79] When nitrous oxide ($n = 130$) was compared with pethidine ($n = 67$), more women had complete (4% vs. 0) or satisfactory (46% vs. 22%) pain relief with nitrous oxide. Nearly half of the women who used pethidine reported no pain relief compared with one-third of the women who used nitrous oxide. Two studies did not contribute additional data.[75-76]

KQ2: Effect of Nitrous Oxide on Women's Satisfaction

Key Points

- The measures used to assess women's satisfaction with their birth experience and pain management were unique to each study, which makes synthesis challenging.
- The strength of the evidence is low for equivalence or superiority of nitrous oxide compared with other pain management methods for women's satisfaction with their birth experience and pain management.

This section presents the results of the literature search and findings about women's satisfaction with nitrous oxide as a labor analgesic compared with other pharmacologic and nonpharmacologic modalities for labor pain management. The pharmacologic modalities that were compared with nitrous oxide in the literature were epidural anesthesia; the narcotic pethidine/meperidine, which was sometimes used in conjunction with the antiemetic promazine; other inhalational anesthetic gases, including isoflurane, enflurane, and desflurane; and paracervical block. Nonpharmacologic modalities included TENS and water blocks.

Overview of the Literature

Nine studies addressed the effectiveness of nitrous oxide on women's satisfaction.[40, 45, 49, 56, 58, 62, 71, 74, 79] Three of these studies were conducted in the United States,[40, 45, 49] and one each in

Australia,[71] the United Kingdom,[79] Malaysia,[56] Sweden,[74] Ireland,[62] and Finland.[58] These studies included three RCTs,[40, 45, 49] three prospective cohorts,[56, 58, 62] and three cross-sectional studies.[71, 74, 79] One study was of good quality,[56] one of fair quality,[74] and seven of poor quality.[40, 45, 49, 58, 62, 71, 79]

Women's Satisfaction with Their Birth Experience

Two studies assessed women's satisfaction with their birth experience.[62, 74] The first was a prospective cohort study in which 170 women who chose Entonox, epidural, pethidine and promazine, or TENS as their first choice of analgesia were asked in the first 24 hours if they would use the same method again.[62] The second was a cross-sectional study in which 1,111 women were asked about their birth experience at two months postpartum via questionnaire.[74] The results for these studies are grouped by comparator.

Epidural

Of the women in the prospective cohort study who chose Entonox, 80 percent (16 of 20) would request Entonox again, compared with 88 percent (44 of 50) of women who chose epidural.[62] In the postpartum survey, 57 percent of women who had nitrous oxide (n = 362) reported a positive or very positive birth experience compared with 34 percent of the women (n = 129) who had epidural analgesia.[74]

Pethidine

Eighty percent (16 of 20) of the women who chose Entonox in the prospective cohort study would request Entonox again compared with 38 percent (19 of 50) of women who chose pethidine and promazine.[62] Of 362 women who had nitrous oxide, 57 percent reported a positive or very positive birth experience at two months postpartum compared with 49 percent of 94 women who had pethidine.[74]

Transcutaneous Electric Nerve Stimulation

Women in the prospective cohort study who chose Entonox more frequently (16 of 20, 80%) reported they would choose it again compared with women who chose TENS (30 of 50, 60%).[62]

Women's Satisfaction with Their Pain Management

Epidural

Four studies compared women's satisfaction with pain management with nitrous oxide or epidural.[56, 58, 62, 71] In a prospective cohort study, only 5.5 percent (3 of 55) of women who had an epidural were not satisfied with the pain relief compared with 45.6 percent (31 of 68) of women who had Entonox and pethidine.[56] Of the women who chose Entonox in another prospective cohort study, 60 percent (12 of 20) reported that the pain relief was adequate, compared with 98 percent (49 of 50) of women who chose epidural analgesia.[62] In a third prospective cohort study, 33 percent (66 of 200) of women who chose Entonox rated the pain relief adequacy as good, compared with 94 percent (75 of 80) of those who chose an epidural.[58] A cross-sectional study found 30 percent (40 of 115) of women who chose nitrous oxide were very satisfied with the relief of pain, compared with 49 percent (58 of 118) of those who chose an epidural.[71]

Pethidine

Three studies compared women's satisfaction with the pain management of Entonox and pethidine. Of the women who chose Entonox in a prospective cohort study, 60 percent (12 of 20) reported that the pain relief was adequate, compared with 18 percent (9 of 50) of women who chose pethidine-promazine.[62] In another prospective cohort study, 33 percent (66 of 200) of women who chose Entonox rated the pain relief adequacy as good, compared with 60 percent (26 of 44) of those who chose pethidine.[58] Of the women in a cross-sectional study who received Entonox, 50 percent (65 of 130) reported satisfactory or complete pain relief, compared with 22 percent (15 of 67) of those receiving pethidine alone.[79]

Inhalational Anesthetic Gases

Three RCTs (total n = 245) compared women's satisfaction with pain management with use of nitrous oxide (30% to 60% mix) with use of other inhalational anesthetic gases. The proportion of women who were satisfied or very satisfied with nitrous oxide was not statistically different than enflurane (76% vs. 89%),[49] isoflurane (87% vs. 83%),[45] and desflurane (63% for both).[40]

Paracervical Block

In a prospective cohort study, a lower proportion of women who chose Entonox (33%, 66 of 200) reported good pain relief adequacy compared with women who chose to receive paracervical block (59%, 70 of 119).[58]

Transcutaneous Electric Nerve Stimulation

An equal proportion of women in a prospective cohort study who chose Entonox (80%, 12 of 20) and TENS (80%, 40 of 50) reported that their pain relief was adequate.[62]

Water Blocks

The proportion of women who rated their pain relief adequacy as good was lower with Entonox (33%, 66 of 200) than among those who chose to receive injections of water (water blocks) in their lower back (59%, 40/68) in one prospective cohort study.[58]

KQ3: Effect of Nitrous Oxide on the Route of Birth

Key Points

- The strength of the evidence is insufficient to determine the effect of nitrous oxide on the route of birth because the studies are predominately of poor quality, use heterogenous outcome measures, and have inconsistent findings.

This section presents the results of the literature search and findings about the route of birth in women who used nitrous oxide as a labor analgesic compared with other pharmacologic and nonpharmacologic modalities for labor pain management. The pharmacologic modalities that were compared with nitrous oxide in the literature were epidural anesthesia; the narcotic pethidine/meperidine, which was sometimes used in conjunction with the antiemetic promazine; other inhalational anesthetic gases, including methoxyflurane, desflurane, and trichloroethylene; and paracervical block. Nonpharmacologic modalities included TENS and water blocks.

Detailed Synthesis

Six studies compare the route of birth in women who used nitrous oxide with that in women who used other pain management methods.[40, 54, 56, 58, 62, 66] Two studies were conducted in the United Kingdom,[54, 66] one in Ireland,[62] one in Finland,[58] one in Malaysia,[56] and one in the United States.[40] Two studies are RCTs,[40, 54] three are prospective cohort studies,[56, 58, 62] and one is a nonrandomized clinical trial.[66] One study was of good q uality[56] and five were of poor quality.[40, 54, 58, 62, 66] Findings for route of birth are presented in Table 7. Studies are presented in reverse chronological order. Only two of the studies[56, 62] had statistically significant findings. In one prospective cohort study the proportion who had an assisted vaginal birth was lower with Entonox plus pethidine (13%) than epidural (40%).[56] Another prospective cohort study found the operative birth rate (which combined forceps-assisted, vacuum-assisted, cesarean, and breech births) was higher among women whose initial choice for pain management was epidural than those who chose nitrous oxide, TENS, or pethidine plus promazine.[62]

Table 7. Route of birth in women using nitrous oxide

Author Year Study Type	Intervention (N)	Vaginal Birth N (%)	Assisted Vaginal Birth N (%)	Cesarean Birth N (%)
Leong et al.,[56] 2000 Prospective cohort	Entonox plus IM pethidine (68)	56 (82.4)	9 (13.2)	3 (4.4)
	Bupivacaine epidural (55)	28 (50.9)	22 (40.1)*	5 (9.0)
Abboud et al.,[40] 1995 RCT	Nitrous oxide, 30-60% oxygen (40)	35 (87.5)	5 (12.5)	0^
	Desflurane 1-4.5% and oxygen (40)	31 (77.5)	9 (22.5)	0^
Ranta et al.,[58] 1994 Prospective cohort	Nitrous oxide 50% (210)	NR (95)	NR (2)	NR (3)
	Water blocks (69)	NR (90)	NR (3)	NR (7)
	Pethidine (50)	NR (91)	NR (2)	NR (7)
	Paracervical block (128)	NR (94)	NR (3)	NR (3)
	Epidural anesthesia (82)	NR (80)	NR (11)	NR (9)
	Several methods (339)	NR (86)	NR (7)	NR (7)
	No analgesia (213)	NR (94)	NR (1)	NR (5)

Table 7. Route of birth in women using nitrous oxide (continued)

Author Year Study Type	Intervention (N)	Vaginal Birth N (%)	Assisted Vaginal Birth N (%)	Cesarean Birth N (%)
Harrison et al.,[62] 1987 Prospective cohort	Entonox (20)†	12 (60.0)	7 (35.0)	0
	TENS (50)	32 (64.0)	14 (28.0)	4 (8.0)
	Pethidine plus promazine (50)	32 (64.0)	18 (36.0)	0
	Lumbar epidural (50)†	13 (26.0)	31 (62.0)[θ]	3 (6.0)[θ]
Rosen et al.,[66] 1969 Nonrandomized clinical trial	Nitrous oxide 50% (265)	235 (88.7)	30 (11.3)	0
	Trichloroethylene 0.35% or 0.5% (394)	345 (87.5)	46 (11.7)	3 (0.8)
	Methoxyflurane 0.35% (598)	525 (87.8)	68 (11.4)	5 (0.8)
Jones et al.,[54] 1969 Quasi-RCT	Nitrous oxide calibrated in 5% steps from 20% to 100% oxygen (24)	19 (79.2)	5 (20.8)	0^
	Methoxyflurane with 40% oxygen (24)	19 (79.2)	5 (20.8)	0^

NR = not reported; RCT = randomized controlled trial
*p < 0.01
^Study only included women with vaginal births.
†One woman in the Entonox group and three women in the lumbar epidural group had breech births that are not included in the table because the route of birth was not identified.
θThe operative birth rate (which included forceps- and vacuum-assisted births, cesarean births, and breech births) was higher for women whose initial choice was epidural than any of the other analgesia methods (p < 0.001).

KQ4: Adverse Effects of Nitrous Oxide for Labor Pain Management

Key Points

- When nitrous oxide was used as a sole agent, 0 to 28 percent of women experienced nausea and zero to 14 percent experienced vomiting.
- Three to 23 percent of women using nitrous oxide as a sole agent reported dizziness.
- Drowsiness occurred in 0 to 67 percent of women using nitrous oxide as a sole agent.
- 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.
- Limited data on occupational harms are available.

- The strength of evidence that adverse effects associated with nitrous oxide for labor pain management are primarily unpleasant side effects that affect tolerability is moderate.

In this section we present the results of the literature search and findings about maternal, fetal, neonatal, and occupational harms. Within each of these outcome categories we have organized the research findings by specific harms, with related or similar harms presented together.

Overview of the Literature

Forty-nine publications addressed maternal, fetal, neonatal and occupational harms related to nitrous oxide for labor.[12-13, 16, 26-30, 32-43, 45-61, 63-69, 72-73, 77, 80] Twenty-two of these studies were conducted in the United Kingdom,[12-13, 16, 26, 31-32, 38, 42, 46-48, 50, 52-55, 57, 59, 65-66, 73, 77] ten in Sweden,[27-30, 33-36, 39, 43] six in the United States,[40, 45, 49, 68-69, 80] two in Australia,[60, 72] and one each in Germany,[61] Canada,[41] Finland,[58] Iran,[37] Ireland,[63] Japan,[67] Malaysia,[56] Nigeria,[64] and Norway.[51] These studies include 12 RCTs,[12, 37, 39-40, 42, 45-46, 49-50, 52-54] six crossover RCTs,[38, 41, 43, 47-48, 51] four case-control studies,[33-36] four nonrandomized clinical trials,[13, 66, 68-69] 13 prospective cohorts,[16, 30, 32, 55-61, 63-64, 67] one retrospective cohort,[65] three case series,[73, 77, 80] five cross-sectional studies,[26-27, 29, 31, 72] and one trend study.[28] Two were of good quality,[36, 56] seven of fair quality,[26, 30-32, 42, 69, 72] and forty of poor quality.[12-13, 16, 27-29, 33-35, 37-41, 43, 45-55, 57-61, 63-68, 73, 77, 80]

Where appropriate to specific harms, these studies are grouped according to co-administered agents given. The 49 studies include twenty studies of nitrous oxide administered as a sole analgesic agent;[37-43, 45-48, 50, 55-60, 65, 72] seven studies of nitrous oxide administered with opioids;[16, 49, 52, 61, 64, 66, 77] one study of nitrous oxide administered with another anesthetic gas;[73] seven studies of nitrous oxide administered with opioids and sedatives or hypnotics;[12-13, 51, 53-54, 63, 68] two studies of opioids and sedatives or hypnotics, or combination thereof;[69, 80] and one of nitrous unspecified.[67] Seven studies evaluated nitrous oxide as an occupational agent.[26-32] Four case-control studies evaluated nitrous oxide use during labor as an independent risk factor.[33-36]

In the past, nitrous oxide for labor was co-administered with other analgesic, anesthetic, anxiolytic, and sedative agents in various combinations titrated to induce sedation and amnesia. These co-agents have a significant impact on the rate and degree of harms associated with nitrous oxide for labor analgesia. To maintain consistency with contemporary practice, thirteen studies published prior to 1980 in which nitrous oxide was given in combination with unspecified doses of narcotics, tranquilizers and sedatives are not included in the tables.[12-13, 16, 50-54, 66-69, 80]

Detailed Synthesis

Maternal Harms

Thirty-two studies reported maternal harms related to nitrous oxide. The most clinically significant and frequently reported maternal harms were nausea, vomiting, dizziness, and drowsiness. These side effects are presented in Table 8. Within the table, studies are grouped by agent(s) administered. Studies of nitrous oxide as a sole agent 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 agent designation, RCTs are listed first followed by nonrandomized clinical trials and observational studies, and each group of study type is in reverse chronological order.

In addition to the harms presented in Table 8, other infrequently reported maternal harms included restlessness,[12-13, 16, 53-54, 66] dreams,[12-13, 16, 53-54] dry mouth or nose,[16, 37, 46, 51] tingling or pins and needles,[37, 46] numbness,[51] paresthesias,[16] reduced awareness of experience,[72] mask phobia,[72] bothersome smell,[51, 54] euphoria,[51] and hiccups.[51]

Clinically relevant harms reported in included studies but not typically associated with nitrous oxide were backache and/or headache,[56, 72], shivering,[72] difficulty moving,[72] and renal dysfunction.[45, 49-50]

Other findings associated with nitrous oxide of unknown clinical significance include inactivation of methionine synthase[59] and effects on maternal circulation.[37, 43]

Nausea and Vomiting

Nausea and/or vomiting were reported in 17 studies,[12-13, 16, 37-38, 42-43, 46-49, 51, 53-54, 64, 66, 68-69, 72] ten of which are presented in Table 8. In these ten studies, rates of nausea ranged from zero to 45 percent.

Studies in women receiving nitrous oxide as a sole agent reported nausea rates from zero to 28 percent.[37-38, 42-43, 47-48, 64, 72] Three studies reported nausea data that include both nitrous oxide as a sole agent and an unmedicated control group.[37, 43, 72] Nausea rates with nitrous oxide ranged from zero to 13 percent with no incidence of nausea in control groups. Nausea was reported to be more common with nitrous oxide than sevoflurane in a crossover RCT[38] with a reported relative risk of 2.7 for nitrous oxide ($p = 0.004$). Nitrous oxide was associated with less nausea than enflurane in one study,[48] and a comparable rate of nausea to isoflurane in another study.[47] A cross-sectional study reported similar rates of nausea and vomiting with nitrous oxide (13%), epidural (14%), and pethidine (16%).[72]

Vomiting was reported in six studies presented in Table 8 with rates ranging from zero to 14 percent.[37-38, 43, 49, 64, 72] Four studies using nitrous oxide as a sole agent reported vomiting data, with rates of 0 to 14 percent.[37-38, 43, 72] Two studies addressed aspiration specifically.[13, 49] One RCT reported no aspiration with one episode of vomiting in a woman receiving nitrous oxide.[49] One nonrandomized trial reported no incidences of aspiration after vomiting in a series of 501 women receiving 50 to 80 percent nitrous oxide in conjunction with injected analgesics who had a combined nausea and vomiting rate of 15 to 22 percent across nitrous oxide concentrations.[13]

Dizziness and Lightheadedness

Dizziness was reported in seven studies,[37, 42, 46-47, 51, 54, 72] four of which are presented in Table 8. In these four studies, nitrous oxide was used as a sole agent with rates of dizziness from three to 23 percent. One RCT reported lightheadedness with Entonox and found it was more common with a mouthpiece compared with face mask.[46] Overall, 58 percent of women in the study had lightheadedness with Entonox, which some women were using in conjunction with pethidine.

Drowsiness and Sleepiness

Thirteen studies reported drowsiness,[12, 16, 37-38, 47-48, 51, 54, 61, 64, 66, 72-73] of which six have outcomes presented in Table 8. Four studies reported drowsiness incidence rates of zero to 67 percent with nitrous oxide used as a sole agent.[37-38, 64, 72] Two studies reported drowsiness data based upon a visual analog scale and do not report incidence rates.[47-48] Three studies compared drowsiness reported with nitrous oxide with other inhalational anesthetic gases and found drowsiness with nitrous oxide was equal to sevoflurane[38] and less than with isoflurane[47] or enflurane.[48] A cross-sectional study found nitrous oxide caused more drowsiness than epidural but less than pethidine.[72]

Sleepiness or sleep was reported as a side effect in older studies utilizing sedative analgesia.[12, 53-54, 66] No studies reported sleepiness as an outcome for nitrous oxide administered as a sole agent.

Table 8. Maternal adverse effects associated with nitrous oxide use during labor, side effects

Author Year Country Study Type	Intervention (N)	Nausea (%)	Vomiting (%)	Dizziness (%)	Drowsiness (%)
Talebi et al.,[37] 2009 Iran RCT	50% nitrous in oxygen (260)	8.4	2.3	23.0	8.3
	50% oxygen (249)	0.0	0.0	0	0.0
Arora et al.,[42] 1992 U.K. RCT	Entonox (39)	NR	NR	3.0	NR
	Entonox and 0.25% isoflurane (39)	5.0	NR	10.0	NR
Constantine et al.,[46] 1989 U.K. RCT	Entonox, via mask (49)†	45.0	NR	NR	NR
	Entonox, via mask and humidifier (36)†	25.0	NR	NR	NR
	Entonox, via mouthpiece (37)†	36.0	NR	NR	NR
	Entonox, via mouthpiece and humidifier (27)†	41.0	NR	NR	NR
Yeo et al.,[38] 2007 U.K. Crossover RCT	Entonox (22)	28.0	14.0	NR	0.0
	Sevoflurane (22)	3.0	0.0	NR	0.0
Westling et al.,[43] 1992 Sweden Crossover RCT	40% nitrous oxide in oxygen, intermittent (24)	0.0	0.0	NR	NR
	70% nitrous oxide in oxygen, intermittent (24)	0.0	0.0	NR	NR
	40% nitrous oxide in oxygen, continuous (24)	4.0	0.0	NR	NR
	Oxygen, intermittent (24)	0.0	0.0	NR	NR
McGuiness et al.,[48] 1984 U.K. Crossover RCT	50% nitrous in oxygen (20)	5.0	NR	NR	NR

Table 8. Maternal adverse effects associated with nitrous oxide use during labor, side effects (continued)

Author Year Country Study Type	Intervention (N)	Nausea (%)	Vomiting (%)	Dizziness (%)	Drowsiness (%)
Paech,[72] 1991 Australia Cross-sectional	Nitrous oxide (220)	13.0θ	13.0θ	5.0	4.0
	Epidural (112)	14.0θ	14.0θ	0.0	0.0
	Pethidine (83)	16.0θ	16.0θ	6.0	11.0
	Non-pharmacological (140)	0.0	0.0	0.0	0.0
	Enflurane in air (20)	15.0	NR	NR	NR
McLeod et al.,[47] 1985 U.K. Prospective cohort	50% nitrous oxide in oxygen (32)	3.0	NR	6.0	More drowsy with Entonox: 9.7
	0.75% Isoflurane in oxygen (32)	3.0	NR	0.0	More drowsy with isoflurane: 58.1
Abboud et al.,[49] 1981 U.S. RCT	30-60% nitrous in oxygen (50)*	NR	2.0	NR	NR
	0.25-1.25% Enflurane in oxygen (55)*	NR	0.0	NR	NR
Soyannwo,[64] 1985 Nigeria Prospective cohort	Entonox (114)	NR	4.0^	NR	Mild: 66.7 Moderate: 31.6 Severe: 1.7
	Entonox with 100mg pethidine or pethilorphan (36)	NR	4.0^	NR	Mild: 55.6 Moderate: 44.4 Severe: 0.0

NR = not reported, RCT= randomized clinical trial
Note: Studies published prior to 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.
*Some patients used additional narcotics (meperidine or alphaprodine).
^Results combined for entire study population.
†Some patients used pethidine.
θNausea and vomiting results combined.

Unconsciousness

Unconsciousness data were reported in eight studies, including one in which nitrous was the sole agent,[43] three with nitrous/opioid,[16, 64, 66] three with nitrous/opioid/sedatives,[12-13, 53] and one with nitrous/other anesthetic gas.[73] Studies published prior to 1980 report low rates (0-1%) of unconsciousness with sedative polypharmacy.[12-13, 53, 66, 73] In a study of 150 women, one woman became unconscious while breathing Entonox in conjunction with use of analgesics. No instances of unconsciousness were reported in a study of Entonox with and without continuous nitrous oxide supplement via nasal cannula,[16] and a study of women breathing up to 70 percent concentrations of nitrous oxide.[43]

Amnesia and Hazy Memory of Labor

Amnesia or hazy memory of labor or birth was addressed in nine studies.[12-13, 16, 40, 45, 49, 53-54, 68] Overall rates of amnesia ranged from zero to 16 percent.[40, 45, 49, 68] Studies published since 1980 reported low to nonexistent rates of amnesia. In an RCT published in 1981, 10 percent of women receiving 30 to 60 percent nitrous oxide with narcotics reported amnesia for birth.[49] In two subsequent RCTs, none of the women who used nitrous oxide reported amnesia.[40, 45]

Hazy memory of labor and birth was an outcome reported in older studies, and incidence ranged from eight to 60 percent.[12-13, 16, 53] Hazy memory of labor was not reported as an outcome in any studies published since 1980.

Hypoxia, Maternal Oxygen Saturation, and Diffusion Hypoxia

Hypoxia and/or maternal oxygen saturation was reported as an outcome in eight studies.[38-39, 41, 57, 60-61, 77] Hypoxia was not defined or inconsistently defined,[39, 41, 57, 77] and studies reporting oxygen saturation values were inconsistent in their reporting of mean, median, and average values. Where desaturations were reported, they occurred in all groups studied including control (no analgesia) and epidural.[57, 60, 77]

In a crossover placebo-controlled RCT, comparable rates of desaturation occurred in women receiving nitrous oxide and compressed air.[41] In another crossover RCT, there were no oxygen saturations less than 98 percent in women breathing Entonox or sevoflurane alone.[38] Hypoxic episodes exceeding 10 seconds to saturations less than 90 percent occurred at similar rates for all groups in a case series including women using nitrous oxide, nitrous oxide with pethidine, pethidine only, and epidural.[77] Maternal saturations did not differ between groups in an RCT comparing 50 and 70 percent nitrous oxide.[39] Median maternal oxygen saturation was not statistically different between Entonox and control in a prospective cohort study.[57] In another prospective cohort study, there were no significant difference in saturations between women using 50 percent nitrous oxide, epidural, pethidine, or no analgesia.[60] The same study found a significant decrease in maternal saturations in women breathing nitrous oxide 50 percent with co-administration of pethidine compared with women in the control group ($p < 0.05$). The difference in mean lowest oxygen saturations between women receiving nitrous oxide with meperidine compared with peridural anesthesia was significant for primiparous, but not multiparous, women.[61]

Three studies evaluated diffusion hypoxia.[16, 39, 41] Women who used nitrous oxide had no evidence of diffusion hypoxia when compared with a control group based upon analysis of end tidal nitrous oxide and carbon dioxide.[39] Maternal end tidal nitrous oxide levels were assessed in a study of women breathing Entonox with and without a continuous supplement of nitrous oxide 50 percent via nasal cannula. Mean end tidal nitrous oxide levels were 14.8 percent in between contractions, and mean maximum end tidal nitrous oxide concentrations were 44 percent for all women.[16] There was no evidence of diffusion hypoxia in a study of nitrous oxide compared with compressed air.[41]

Effects on Maternal Circulation

In a crossover RCT, nitrous oxide was reported to cause a clinically insignificant but statistically significant decrease in heart rate, cardiac output, and arterial pressure and increase in stroke volume ($p < 0.01$ for all) in laboring women while breathing nitrous oxide at 70 percent concentration compared with control (oxygen only).[43]

Biochemical Findings

Inhalational anesthetic gases have been associated with renal dysfunction. There was no significant difference in renal function indices in an RCT of women using methoxyflurane or nitrous oxide.[50] In another RCT comparing nitrous oxide with enflurane, serum electrolyte levels and renal function were not significantly affected.[49] Maternal and neonatal fluoride levels were assessed in an RCT comparing nitrous with isoflurane and were comparable.[45]

Inactivation of Methionine Synthase

The use of nitrous oxide by inhalation has been shown to inactivate methionine synthase activity (MSA) by binding to cobalamin, which is the central component of vitamin B12. Clinical implications of inactivation of methionine synthase have not been established. Landon measured methionine synthase in placental samples reporting a negative correlation between placental MSA and duration of exposure to nitrous oxide ($p = 0.01$).[59] There was a more rapid decrease in MSA in women with reduced B12 levels, although the regression coefficients were not significantly different.

Restlessness

Restlessness was reported in six studies, including two with nitrous/opioid[16, 66] and four with nitrous/opioid/sedatives.[12-13, 53-54] No studies reporting restlessness included a group receiving nitrous oxide as a sole agent. All studies reporting restlessness data were published prior to 1980. Reported rates of restlessness for nitrous oxide with opioids with or without sedatives ranged from 5 percent to 59 percent.

Dreams

Dreams were reported in five studies,[12-13, 16, 53-54] including four with nitrous/opioid/sedatives[12-13, 53-54] and one with nitrous/opioid.[16] All studies reporting dreams as a harm were published prior to 1980, and dreams were not reported in any studies of nitrous as a sole agent. Dreams were reported at rates of 10 percent to 26 percent of women breathing nitrous in combination with analgesic and sedative agents.

Other Maternal Side Effects

Dry mouth or nose was reported in four studies.[16, 37, 46, 51] One study of nitrous oxide as a sole agent reported a rate of 8.3 percent for dry mouth in women breathing nitrous oxide alone.[37] In one RCT dry mouth and nose were found to be more common with use of a mask compared with mouthpiece, and incidence was lowered by use of a humidifier.[46] Dry nose was reported by 75 percent of women breathing nitrous oxide via nasal cannula in one study.[16]

In a crossover RCT, women reported a rate of dry mouth of 10 percent while using nitrous oxide combined with narcotics and sedatives.[51]

Tingling or “pins and needles” was reported in two RCTs with rates of 4.1 percent[37] and 25 percent[46] in women using nitrous oxide. In a crossover RCT, 1.6 percent of women using nitrous oxide reported numbness. In a prospective cohort study, 40 percent of women breathing Entonox alone and 33 percent of women breathing Entonox with a continuous supplement of nitrous oxide 50 percent via nasal cannula experienced paresthesia.

In a cross-sectional study, reduced awareness of experience was more frequently reported as a disliked side effect for nitrous (18%) and pethidine (16%) than epidural (2%) and control (zero).[72]

Backache and/or headache were reported in two studies.[56, 72] In one prospective cohort study, women receiving epidural analgesia had a 3.6 percent incidence of spinal headache and 3.6 percent rate of persistent backache compared with zero incidence in women using nitrous oxide.[56] No women in a cross-sectional study who used nitrous oxide reported back pain compared with 14 percent of those with an epidural.

Shivering was not reported as a side effect by women using nitrous oxide compared with eight percent of women receiving an epidural in a cross-sectional study.[72]

Fourteen percent of women with epidural analgesia reported difficulty moving as a disliked side effect compared with none of the women using nitrous oxide.[72] Other side effects infrequently reported include mask phobia,[72] bothersome smell,[51, 54] euphoria,[51] and hiccups.[51]

Fetal and Neonatal Harms

Twenty-nine studies include outcomes on fetal and neonatal harms. The most clinically significant and frequently reported outcomes for fetal harms were umbilical cord gases and Apgar scores, which are presented in Tables 9, 10, and 11. Studies are presented in reverse chronological order. Additional fetal and neonatal outcomes reported include placental transfer of nitrous oxide, assessment of neurobehavioral status, neonatal fluoride levels, and long-term outcomes.

Neonatal intensive care unit (NICU) admission rates cannot be accurately reported because different countries vary in their definition of what constitutes a high acuity ward, and rates were not consistently reported. Three studies reported admission to a special care nursery[56, 73] or neonatal unit.[55] Other reported harms that suggest the need for NICU care included fetal resuscitation,[64, 73] asphyxia,[67] depressed babies,[49] sleepy babies,[67] prolonged time to sustained respiration,[80] and treatment for apnea.[73]

Umbilical Arterial and Venous Blood Gases

Umbilical cord blood gases were reported in eight studies. Three of these reported neonatal outcomes presented in Table 9.[45, 49, 61] The only significant finding was a lower mean umbilical artery pH in primiparous women who used nitrous oxide and meperidine compared with epidural ($p = 0.01$).[61] The remaining five studies were excluded from the table because they reported data prior to 1980 with unspecified co-administration of narcotics and sedatives in all groups[52, 68-69] or did not report actual cord blood gas values.[40, 58]

Table 9. Fetal adverse effects, cord blood gases*

Author Year Country Study Type	Intervention (N)	Umbilical pH, Arterial	Umbilical pH, Venous	Base Excess, Arterial	Base Excess, Venous
Abboud et al.,[45] 1989 U.S. RCT	30-60% nitrous oxide in oxygen (30)	7.27	7.33	-2.2	-2.8
	0.2-0.7% Isoflurane in oxygen (30)	7.28	7.34	-3.0	-3.0
Deckhart et al.,[61] 1987 Germany Prospective cohort	50% nitrous oxide in oxygen with meperidine (16 primip, 9 multip)	Primip:7.21^ Multip: 7.31	NR	Primip: -9.5 Multip: -5.1	NR
	Epidural (25 primip)	7.29^	NR	-6.4	NR
Abboud et al.,[49] 1981 U.S. RCT	30-60% nitrous oxide in oxygen (50)	7.27	7.27	-7.0	-5.6
	0.25-1.25% Enflurane in oxygen (55)	7.26	7.34	-6.3	-6.3

multip = multiparous, NR = not reported, primip - primiparous, RCT = randomized controlled trial
Note: Studies published prior to 1980 are not included in this table.
*Umbilical pH < 7 and base deficit ≥ 12 indicate metabolic acidosis. Arterial values are the most accurate.[81]
^Significant (p = 0.L01)

Apgar Scores

The Apgar score is used to assess the general condition of a newborn at 1 minute and 5 minutes after birth. A score of 0, 1, or 2 is given for each of five categories: heart rate, breathing effort, muscle tone, reflex response, and color. The highest possible score is 10, and a 5-minute score of 7 to 10 is considered normal.[82] Pharmacologic labor pain management methods can affect the Apgar score.

Twenty-five studies reported Apgar score data,[12-13, 16, 37, 40, 43, 45, 49, 51-56, 58-59, 61, 64-69, 73, 80] and 12 of these are presented in Tables 10 and 11. Studies that reported mean and/or median Apgar scores are presented in Table 10 while Table 11 presents studies that reported categorical Apgar scores (i.e., 8-10 and < 8). None of the studies reported in Tables 10 and 11 found significant differences in Apgar scores with nitrous oxide compared with other pain management methods or no labor analgesia. Apgar data were not included in table format for studies conducted prior to 1980 in which nitrous oxide was co-administered with unspecified and uncontrolled narcotics and/or sedatives. Two other studies were excluded from the table, one because neither treatment nor control group could be defined in terms of analgesia given[83] and the other because the timing of the Apgar scores was not defined.[64]

Table 10. Neonatal adverse effects, mean and median Apgar scores

Author Year Country Study Type	Intervention (N)	1 Min, Mean	5 Min, Mean	10 Min, Mean	1 Min, Median
Talebi et al.,[37] 2009 Iran RCT	50% nitrous oxide in oxygen (260)	8.5	9.5	NR	NR
	50% oxygen (249)	8.5	9.5	NR	NR
Stirk et al.,[55] 2002 U.K. Prospective cohort	Entonox (45)	8.2	9.6	NR	NR
	Morphine (70)	8.3	9.4	NR	NR
Ross et al.,[73] 1999 U.K. Case series	50% nitrous oxide in oxygen with 0.25% isoflurane (48)	NR	NR	NR	9.0
	50% nitrous oxide in oxygen with 0.25% isoflurane; narcotic given > 5 hours before delivery (85)	NR	NR	NR	9.0
	50% nitrous oxide in oxygen with 0.25% isoflurane, narcotic given < 5 hours before delivery (88)	NR	NR	NR	8.0
	Nitrous oxide stopped < 1 hour before delivery (174)	NR	NR	NR	9.0
	Nitrous oxide stopped > 1 hour before delivery (47)	NR	NR	NR	9.0
Westling et al.,[43] 1992 Sweden Crossover RCT	40% intermittent nitrous oxide in oxygen (24)	9.2 (all groups)	10.0 (all groups)	10.0 (all groups)	NR
	70% intermittent nitrous oxide in oxygen (24)				
	40% continuous nitrous oxide in oxygen (24)				
	Intermittent oxygen only (24)				
Landon et al.,[59] 1992 U.K. Prospective cohort	Entonox for vaginal delivery (45)	8.5	9.3	NR	NR
	Vaginal delivery without Entonox (13)	8.5	9.4	NR	NR
	Epidural for cesarean section (13)	8.1	9.0	NR	NR
	Cesarean section with general anesthesia and nitrous oxide (23)	7.5	9.3	NR	NR

Table 10. Neonatal adverse effects, mean and median Apgar scores (continued)

Author Year Country Study Type	Intervention (N)	1 Min, Mean	5 Min, Mean	10 Min, Mean	1 Min, Median
Deckardt et al.,[61] 1987 Germany Prospective cohort	50% nitrous oxide in oxygen with meperidine (25)	8.1	9.7	10.0	NR
	Epidural (25)	8.9	10.0	10.0	NR
Arthurs et al.,[16] 1979 U.K. Prospective cohort	50% nitrous oxide in oxygen intermittent with continuous nitrous 50% via nasal cannula* (24)	7.8	9.6	NR	NR
	50% nitrous oxide in oxygen, intermittent* (25)	7.7	9.3	NR	NR

NR = not reported, RCT = randomized controlled trial
Note: No studies reported 5 or 10 minute median Apgar scores.
*Some participants used pethidine and/or epidural

Table 11. Neonatal adverse effects, range of Apgar scores

Author Year Country Study Type	Intervention (N)	8-10, 1 Min (%)	<8, 1 Min (%)	8-10, 5 Min (%)	<8, 5 Min (%)
Leong et al.,[56] 2000 Malaysia Prospective cohort	Entonox with pethidine (68)	NR	NR	100	0
	Epidural (55)	NR	NR	100	0
Ross et al.,[73] 1999 U.K. Case series	50% nitrous oxide in oxygen with 0.25% isoflurane (48)	83*	17.6*	97.3	2.7
	50% nitrous oxide in oxygen with 0.25% isoflurane; narcotic given > 5 hours before delivery (85)	69	31	NR	NR
	50% nitrous oxide in oxygen with 0.25% isoflurane, narcotic given < 5 hours before delivery (88)	55	46	NR	NR
	Nitrous oxide stopped < 1 hour before delivery (174)	67	33	NR	NR
	Nitrous oxide stopped > 1 hour before delivery (47)	67*	36*	NR	NR
Abboud et al.,[40] 1995 U.S. RCT	30-60% nitrous oxide in oxygen (40)	92	8	100	0
	1-4.5% desflurane in oxygen (40)	87	13	100	0

Table 11. Neonatal adverse effects, range of Apgar scores (continued)

Author Year Country Study Type	Intervention (N)	8-10, 1 Min (%)	<8, 1 Min (%)	8-10, 5 Min (%)	<8, 5 Min (%)
Ranta et al.,[58] 1994 Finland Prospective cohort	50% nitrous oxide in oxygen (210)	93	7	99	1
	Water block (69)	90	10	97	3
	IM pethidine (50)	91	9	100	0
	Paracervical block (128)	97	3	97	3
	Epidural (82)	94	6	96	4
	Several forms of analgesia (339)	94	6	97	3
	No analgesia (213)	89	11	99	1
Abboud et al.,[45] 1989 U.S. RCT	30-60% nitrous oxide in oxygen (30)	93	7	100	0
	0.2-0.7% isoflurane in oxygen (30)	93	7	100	0
Murphy et al.,[65] 1984 U.K. Retrospective cohort	Entonox, born 1970-1974 (3,697)	87.8	12.3	NR	NR
	Entonox, born 1975-1979 (4,448)	89.9	10.1	NR	NR
	Entonox and pethidine, born 1970-1974 (12,084)	78.5	21.5	NR	NR
	Entonox and pethidine, born 1975-1979 (85,860)	78.8	21.2	NR	NR
	Pethidine, born 1970-1975 (2,770)	74.4	25.6	NR	NR
	Pethidine, born 1975-1979 (874)	80.3	19.7	NR	NR
	Epidural, born 1970-1974 (1,223)	74.5	25.4	NR	NR
	Epidural, born 1975-1979 (3,084)	82.0	18.0	NR	NR
	No analgesia, born 1970-1974 (1,508)	86.1	13.8	NR	NR
	No analgesia, born 1975-1979 (852)	90.0	10.0	NR	NR

Table 11. Neonatal adverse effects, range of Apgar scores (continued)

Author Year Country Study Type	Intervention (N)	8-10, 1 Min (%)	<8, 1 Min (%)	8-10, 5 Min (%)	<8, 5 Min (%)
Abboud et al.,[49] 1981 U.S. RCT	30-60% nitrous oxide in oxygen (50)	94	6	100	0
	0.25-1.25% enflurane in oxygen (55)	92	8	98	2

NR = not reported, RCT = randomized controlled trial
*As reported by publication; percentages do not tally to 100.

Assessment of Neonatal Neurobehavioral Status

Neurobehavioral status has been studied in four studies using a variety of assessment tools.[40, 45, 63, 67] Only one study compared newborns of women using nitrous oxide with a control group.[63] In this prospective cohort study, neonates of mothers receiving a variety of analgesic agents in labor were evaluated with the Neonatal Psychological Assessment profile. Neonatal scores with Entonox were comparable with all other methods, including epidural, pethidine, TENS, and no analgesia. Neonatal Adaptive Capacity Scores (NACS) at 2 and 24 hours did not differ significantly between newborns whose mothers used nitrous oxide and desflurane.[40] In another RCT, there were no significant differences in test item scores on the NACS between the nitrous oxide group and isoflurane group.[45] One study reported Perez and Moro reflexes became positive more rapidly in newborns after maternal administration of nitrous oxide compared with trichloroethylene and halothane (no test of statistical significance reported).[67]

Long-Term Harms

Long-term offspring outcomes were addressed in four studies.[33-36] All studies reporting long-term outcomes were retrospective; no prospective studies with regard to long-term harms were identified. Three poor-quality case-control studies from Sweden conducted by the same investigators with overlapping populations have investigated nitrous oxide use during labor and later addiction in offspring.[33-35] One of these studies reported a risk ratio of 5.6 (95% CI 1.6 to16.9, p = 0.005) for amphetamine addiction after greater than 4.5 hours of nitrous oxide exposure in utero compared with less than 0.25 hours; however, many participants had missing data and women used pure nitrous oxide rather than a mix with oxygen as is current practice.[35] The fourth case-control study investigated possible risk factors for childhood leukemia reporting an increased risk for all leukemias with in utero exposure to nitrous oxide (odds ratio 1.3, 95% CI 1.0 to 1.6), although the risk was not observed in all subgroups.[36]

Occupational Exposure

Occupational exposure in labor and birth settings was addressed in seven studies.[26-32] Three of these were Swedish studies that examined occupational exposure related harms in midwives.[27-29] One study focused on subfertility and found a decreased fecundability ratio in midwives who attended more than 30 births per month in which nitrous oxide was used (0.63, 95% CI 0.43 to 0.94).[28] Another study reported no increased risk of spontaneous abortion with nitrous oxide exposure.[29] In the third study, women exposed to nitrous oxide had newborns with reduced birth weight (-77 grams, 95% CI -129 to -24) and an increase in odds for small for gestational age (odds ratio 1.8, 95 % CI 1.1 to 2.8).[27]

The measurement of nitrous oxide exposure is addressed in four studies, which report nitrous oxide levels but not specific harms.[26, 30-32] A study in the United Kingdom collected data on midwives wearing exposure badges for 242 shifts in labor wards without scavenging and with standard room ventilation only.[32] Shifts ranged from 7.5 to 11 hours. Midwives had exposure greater than 100 ppm (the Swedish limit) during 23 percent of shifts and greater than 25 ppm (the U.S. limit) during 53 percent of shifts. An evaluation of scavenging systems in Swedish labor wards found a 4-fold reduction in nitrous oxide levels with use of efficient scavenging systems. Nitrous oxide concentrations in diffusive air samplers varied from 2.5 to 260 mg/m3, and mean 8-hour time-weighted averages were 17mg/m3 for midwives and 42mg/m3 for assistant midwives.[30] The 8-hour-time-weighted-averages exceeded the American Conference of Industrial Hygienists' average threshold limit value (50 ppm or 90 mg/m3) in 16 percent of midwives and 45 percent of assistant midwives. The authors attribute these differences to the fact that assistant midwives have a longer average exposure time and are also working more closely with women earlier in labor when nitrous oxide is used more frequently.[30] Another study in the United Kingdom correlated nitrous oxide exposure to urine nitrous oxide levels in a descriptive study of unscavenged and poorly-ventilated delivery suites.[26] Environmental levels exceeded 100 ppm over 8-hour time-weighted averages in 35 of 46 midwife shifts monitored. It is notable that in this study 22 of 46 midwives had nonzero baseline values of nitrous oxide in their urine, which the authors propose may indicate tissue clearance occurs over a longer time period than previously thought. Newton et al evaluated 8-hour time-weighted average nitrous oxide exposure (in ppm) for 15 midwives at a newly built English hospital with a ventilation system incorporating six to ten air changes per hour, comparing the results with historical data from an older building in which ventilation did not exist (Entonox machines were unscavenged in both hospitals).[31] Levels in the new hospital were significantly lower, and none of the 15 midwives in the new hospital was exposed to levels of nitrous oxide greater than 100 ppm. Six of the 15 midwives were exposed to levels of nitrous oxide greater than 25 ppm (the U.S. limit).

KQ5: Effects of Provider and Health System Factors

No studies addressed KQ5. It is discussed as a part of future research.

Grey Literature Search Results

Grey literature search methods are described in the Methods chapter of this review. No relevant articles were located.

Discussion

State of the Literature

We identified a total of 59 distinct studies reported in 58 publications: two of good quality; 11 fair; and 46 poor. Thirty-three percent of the studies identified were randomized clinical trials (RCTs), a smaller proportion were clinical trials without clear evidence of randomization (7%), and the balance are observational research.

Strength of Evidence

Overall the strength of evidence to answer the Key Questions (KQ) was insufficient for effectiveness in managing labor pain (KQ1), effect on route of birth (KQ3), and health system factors (KQ5); low for satisfaction (KQ2); and moderate for harms (KQ4) (Table 12). Deficiencies in the strength of evidence most often related to a preponderance of study designs with high risk of bias; inconsistent findings across studies and inconsistencies among outcomes that would be expected to show corresponding benefit; use of intermediate outcomes; and small studies with poor precision. In the summary below, we provide strength of evidence ratings by Key Question.

Table 12. Strength of evidence for nitrous oxide for the management of labor pain

Total Studies (Total Participants)	Domains Pertaining to Strength of Evidence				Strength of Evidence
	Risk of Bias	Consistency	Directness	Precision	
Effectiveness of Nitrous Oxide vs. Other, Nonepidural Labor Pain Management Methods for the Management of Labor Pain (KQ1)					
25 (15,991)	High	Inconsistent	Indirect	Imprecise	Insufficient; includes 6 RCTs; 5 studies of fair quality and 20 studies of poor quality total
Equivalence or Superiority of Nitrous Oxide vs. Other Labor Pain Management Methods for Women's Satisfaction With Their Birth Experience (KQ2)					
2 (1,303)	High	Consistent	Direct	Imprecise	Low; includes no RCTs; 1 study of fair quality and 1 study of poor quality total
Equivalence or Superiority of Nitrous Oxide vs. Other Labor Pain Management Methods for Women's Satisfaction With Their Pain Management (KQ2)					
8 (2,825)	High	Consistent	Direct	Imprecise	Low; includes 2 RCTs; 1 study of good quality and 7 studies of poor quality total
Effect of Nitrous Oxide for the Management of Labor Pain on Route of Birth (KQ3)					
6 (33,031)	High	Inconsistent	Direct	Imprecise	Insufficient; includes 2 RCTs; 1 study of good quality and 5 studies of poor quality total
Adverse Effects Associated With Nitrous Oxide for the Management of Labor Pain are Primarily Unpleasant Side Effects That Affect Tolerability (KQ4)					
48 (27,530)*	High	Consistent	Direct	Imprecise	Moderate; includes18 RCTS; 2 studies of good quality, 6 studies of fair quality, and 40 studies of poor quality total

RCT = randomized controlled trial
Note: Domains pertaining to SOE are taken from the AHRQ Methods Guide[25] and are explained in the Methods chapter
*One study did not provide an N and is not included in this calculation[32].

Principal Findings and Considerations

KQ1: Effectiveness of Nitrous Oxide for Labor Pain Management

Twenty-one studies addressed the effectiveness of nitrous oxide using some measurement of pain or pain relief.[38, 40-41, 44-45, 47-49, 51, 53-54, 58, 62, 66, 68-70, 75-76, 78-79] Four studies were of fair quality,[69-70, 75-76] and 17 were of poor quality.[38, 40-41, 44-45, 47-49, 51, 53-54, 58, 62, 66, 68, 78-79] There was considerable variation across studies in many aspects including the concentration of nitrous oxide and frequency (continuous vs. intermittent) administered, additional pain management methods used, and methods and persons (i.e., women, obstetricians, midwives, and anesthesia providers) assessing pain and pain relief. The substantial variation in timing of assessment may have affected the reported outcomes because women's opinions about pain relief change with time lapsed after birth.[53-54, 66]

The majority of the effectiveness studies (12 of 21) had as comparators other inhalational anesthetic gases that are not used to manage labor pain in the United States. Only one study compared nitrous oxide with placebo and found no significant difference in pain scores. As expected, epidurals provide more effective pain relief than nitrous oxide. It may be counterproductive to evaluate pain scores, which require focusing on the level of pain, in women using nitrous oxide, which is intended to produce dissociation from pain. What these studies are unable to demonstrate is whether nitrous provided adequate pain relief for women who knowingly accept less effective pain relief in exchange for increased mobility, less intervention and monitoring, and avoidance of potential complications associated with epidurals. Generally speaking, therefore, pain relief is likely to be an inadequate measure of effectiveness for nitrous oxide in the absence of other outcomes such as women's satisfaction.

KQ2: Effect of Nitrous Oxide on Women's Satisfaction

Nine studies addressed women's satisfaction with their birth experience or pain management.[40, 45, 49, 56, 58, 62, 71, 74, 79] One study was of good quality,[56] one of fair quality,[74] and seven of poor quality.[40, 45, 49, 58, 62, 71, 79] Measurements of satisfaction were not uniform making it impossible to synthesize studies. Satisfaction may be a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief.

KQ3: Effect of Nitrous Oxide on the Route of Birth

Six studies compare the route of birth in women who used nitrous oxide with women who used other pain management methods.[40, 54, 56, 58, 62, 66] Two of these only included women who had vaginal births,[40, 54] and five were of poor quality.[40, 54, 58, 62, 66] The strength of the evidence is insufficient to determine the effect of nitrous oxide on the route of birth.

KQ4: Adverse Effects of Nitrous Oxide for Labor Pain Management

Forty-nine studies addressed the maternal, fetal, neonatal, and occupational harms related to nitrous oxide use during labor.[12-13, 16, 26-30, 32-43, 45-61, 63-69, 72-73, 77, 80] Two were of good quality,[36, 56] seven of fair quality,[26, 30-32, 42, 69, 72] and forty of poor quality.[12-13, 16, 27-29, 33-35, 37-41, 43, 45-55, 57-61, 63-68, 73, 77, 80] Although these 49 studies report data from more than 27,000 women, only six of these studies were conducted in the United States (n = 2,445 women). In addition, one-third (16 of 49) of studies reporting harms were conducted prior to 1980 when nitrous oxide was often used in combination with sedatives, tranquilizers, and other inhaled anesthetics in labor, a practice that has largely been abandoned. 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 to be a positive outcome.

Most maternal harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness). Some maternal harms (e.g., nausea and oxygen desaturation) are common in all laboring women regardless of the type of analgesia used. Study sizes were inadequate to assess for unusual or rare harms that might be more serious in terms of morbidity.

Nitrous oxide is transmitted via the placenta and is rapidly eliminated by the neonate following birth once breathing begins. 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. Followup of newborns was short, most frequently lasting only to birth or discharge of the neonate from the hospital.

Limited data on occupational harms are available thus it is difficult to draw conclusions regarding potential occupational harms as a result of exposure to nitrous oxide. Evidence about occupational levels of nitrous oxide is limited, and some studies were conducted prior to the use of room ventilation systems or scavenging systems. The implementation of these systems in clinical practice has reduced occupational exposure, which should mitigate potential risks of exposure.

KQ5: Effects of Provider and Health System Factors

No studies addressed KQ5. It is discussed as a part of future research.

Applicability

Applicability describes the extent to which study populations and characteristics in the literature reviewed apply to the larger population. In this report, the study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.

Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox®. The 50/50 mix is available, although Entonox is not used in the United States and has not been reviewed by the U.S. Food and Drug Administration. In addition, mechanical equipment for administration of nitrous oxide in labor and delivery has very limited availability in the United States at the time of this writing. In the studies related to harms (Key Question 4), the intervention varied significantly in terms of dose, frequency, and duration. In many studies participants received unspecified amounts of narcotics and/or sedating agents. Studies prior to 1980 are not applicable to current guidelines for clinical use.

The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as transcutaneous electrical nerve stimulation (TENS). However, some comparators are not commonly used and/or available for laboring women, such as other inhalational anesthetic gases.

For KQ1, the most frequent outcome was an assessment of pain, generally during labor. Some studies retrospectively assessed pain in the immediate postpartum period and/or weeks to months after birth. The methods of pain assessment were heterogeneous. Those assessing outcomes included participants, obstetricians, midwives, and anesthesia providers. Satisfaction with pain management and the birth experience, as reported by the women were the outcome measures for KQ2. The outcomes for KQ3 were vaginal birth, assisted vaginal birth, and cesarean. None of the studies had a cesarean birth rate greater than 10 percent, which is much lower than the most recently reported U.S. rate of 32 percent.[1] For KQ4, the most frequent outcomes were assessments of nausea, vomiting, dizziness, drowsiness, hypoxia, oxygen saturation, Apgar scores, and cord blood gases.

Only six of 58 studies were conducted in the United States. The options for labor pain management in the United States are somewhat dissimilar to those in other countries because nitrous oxide for laboring women is widely available outside of the United States, whereas in this country its availability is extremely limited. While setting was not a criterion for inclusion or exclusion, all of the studies were conducted in hospitals. Thus the effectiveness, women's satisfaction, route of birth, and harms associated with nitrous oxide in birth centers and the home setting have not been reported.

Future Research

State of the Science

Nitrous oxide has been used for labor pain management since the 1930s, primarily outside the United States.[4] Much of the literature on this topic is older with nearly half of the studies in this review published prior to 1990 and one-quarter before 1980. Over the past decade, there has been growing interest in the use of nitrous oxide for laboring women in the United States. As use of nitrous oxide for labor pain management increases, continued research is warranted. Topics that would benefit from consideration include:

Methodologic Priorities

- Clearly documenting the mix of nitrous oxide used and the timing and mode of administration.
- Performing studies that use doses and equipment consistent with contemporary U.S. maternity care.
- Developing outcome measures that assess effectiveness as defined by women choosing nitrous oxide.
- Using standardized and validated outcome measures to assess pain and women's satisfaction.
- Including women's assessment of pain, rather than only providers', in all studies that report this outcome.
- Performing qualitative research in addition to quantitative studies.
- Conducting sequential analysis trials in which women can opt-in and opt-out of nitrous oxide.
- Conducting studies in out-of-hospital birth settings (i.e., freestanding birth centers and home births).
- Building consensus about critical maternal, fetal, neonatal, childhood, and occupational exposure outcomes, developing a minimal core data set for future research.
- Designing human studies that examine apoptosis, which has been observed in rodents exposed to high doses of systemic anesthetics.

- Developing electronic medical record approaches to long-term surveillance for adverse effects.

Content Priorities

- Exploring anti-anxiety effects of nitrous oxide during labor.
- Examining the influence of nitrous oxide on whether and when women choose to use other labor pain management methods.
- Investigating the impact of nitrous oxide on use of cointerventions, route of birth, maternal-newborn bonding, and breastfeeding.
- Assessing fetal/neonatal clearance of nitrous oxide.
- Determining optimal methods for minimizing occupational exposures, such as room ventilation and scavenging measures.
- Assessing potential occupational harms, including nitrous oxide abuse and addiction.
- Identifying health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization.
- Determining provider and patient education needed for nitrous oxide use in labor,
- Analyzing cost effectiveness of nitrous oxide and other labor pain management methods.

Current and Future Research

Recently completed and ongoing research includes the following:

Completed:

- One study on the effect of labor analgesia on babies' movement after birth, with nitrous oxide use or no analgesia as the control group.

Ongoing:

- Zero studies.

Planned:

- One study on the comparison of the effects of Entonox and TENS in labor pain.

Conclusions

The literature addressing nitrous oxide for the management of labor pain has few studies of good or fair quality. Synthesis of effectiveness and satisfaction studies was challenging because of heterogeneous interventions, comparators, and outcome measures. Satisfaction may be a more relevant measure of effectiveness than assessment of pain because nitrous oxide is not intended to provide complete pain relief. The strength of evidence for the effect of nitrous oxide on route of birth was insufficient. Most maternal harms reported in the literature were unpleasant side effects that affect tolerability (e.g., nausea, vomiting, dizziness, and drowsiness), and Apgar scores did not differ significantly across labor pain management methods. Data for occupational harms were limited. Research assessing nitrous oxide is needed across all of the Key Questions examined: effectiveness, women's satisfaction, route of birth, harms, and health system factors affecting use.

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Acronyms/Abbreviations/Symbols

±	plus or minus
≤	less than or equal to
≥	greater than or equal to
%	percent
ACGIH	American Conference of Governmental Industrial Hygienists
AE	adverse events
AHRQ	Agency for Healthcare Research and Quality
ANSI	American National Standard Institute
BUN	blood urea nitrogen
CGA	Compressed Gas Association
CI	confidence interval(s)
CINAHL	Cumulative Index to Nursing and Allied Health Literature
cm	centimeter
DHHS	Department of Health and Human Services
etc.	et cetera
EPA	United States Environmental Protection Agency
EPC	Evidence-based Practice Center
FDA	United States Food and Drug Administration
fl	fluid liter
g	gram(s)
g/dl	gram per decaliter
g/ml	grams per milliliter
Hb	hemoglobin
IM	intramuscular
Kg	kilogram
KQ	Key Question
mcM/L	micrometer per liter
mcmol/L	micromolar
mEq/L	milliequivalents per liter
Mg	milligram
mg/dl	milligrams per deciliter
min	minute(s)
ml	milliliter
mm	millimeter
mmHg	millimeters of mercury
mOsm/kg	milliosmoles per kilogram of water
mU/min	milliunits per minute
n, N	number
NACS	Neonatal Adaptive Capacity Scores
NFPA	National Fire Protection Association
NIOSH	National Institute for Occupational Health and Safety
NR	not reported

NS	not significant
N_2O	nitrous oxide
OSHA	Occupational Safety and Health Administration
O_2	oxygen
P, p	p value
pH	power of hydrogen
PICOTS	Population(s), Intervention(s), Comparator(s), Outcome(s), Timing, Setting(s)
PCO_2	partial pressure of carbon dioxide
PO_2	oxygen partial pressure
ppm	parts per million
pt	patient
RCT	randomized controlled trial
REL	recommended exposure limit
RR	relative risk
SD	standard deviation
SE	standard error
SGA	small for gestational age
TENS	transcutaneous electric nerve stimulation
TEP	technical expert panel
TLV	threshold limit value
torr	non-SI unit of pressure
TSCA	Toxic Substances Control Act
UCSF	University of California, San Francisco
U.S.	United States
USP	United States Pharmacopeia
VAS	visual analogue scale
vs.	versus
w/	with
wk(s)	week(s)
yr(s)	year(s)
µg/l	micrograms per liter

Appendix A. Exact Search Strings and Results

Table 1: Preliminary PubMed search strategies

Preliminary Search Terms		Preliminary Search Results
#1	"Nitrous Oxide"[Mesh] OR "nitrous oxide"[tw] OR "N2O"[tw] OR "laughing gas"[tw] OR "Entonox "[Substance Name] OR Entonox[tw] OR Equanox[tw] OR Kalinox[tw] OR Medimix[tw] OR "Dinitrogen Monoxide"[tw] OR Kalinox[tw] OR Medimix[tw] OR "Dinitrogen Monoxide"[tw]	19,052
#2	"Labor Pain"[Mesh] OR "Labor, Obstetric"[Mesh] OR labor[tw] OR "parturition"[MeSH Terms] OR "pregnancy"[MeSH Terms] OR "pregnancy"[tw] OR "Analgesia, Obstetrical"[mh] OR "obstetric"[tw] OR birth[tw] OR childbirth[tw] OR labour[tw] OR intrapartum[tw] OR delivery, obstetric[mh]	867,187
#3	#1 AND #2 AND eng[la] AND humans[mh]	646
#4	#3 AND letter[pt]	27
#5	#3 AND comment[pt]	14
#6	#3 AND case reports[pt]	50
#7	#3 AND review[pt]	72
#8	#3 AND news[pt]	2
#9	#3 AND editorial[pt]	5
#10	#3 AND historical article[pt]	6
#11	#3 AND meta-analysis[pt]	1
#12	#3 NOT (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	495*

Table 2: EMBASE search strategies

Preliminary Search Terms		Preliminary Search Results
#1	nitrous oxide.mp. or nitrous oxide/ or entonox.mp. or nitrous oxide plus oxygen/ or n20.mp. or laughing gas.mp. or equanox.mp. or kalinox.mp. or medimix.mp. or dinitrogen monoxide.mp.	30,451
#2	pregnancy/ or pregnancy.mp. or CHILDBIRTH/ or childbirth.mp. or labor pain.mp. or labor pain/ or obstetric analgesia.mp. or obstetric analgesia/ or delivery/ or delivery.mp. or INTRAPARTUM CARE/ or intrapartum.mp. or LABOR/ or labor.mp.	537,234
#3	#1 AND #2	1,789
#4	Limit #3 to (human and english language)	1,178
#5	Limit #4 to (editorial or letter or "review")	319
#6	#4 NOT #5	859*

Table 3: CINAHL search strategies

Preliminary Search Terms		Preliminary Search Results
#1	(MH "Nitrous Oxide") OR "nitrous oxide" OR "N2O" OR "laughing gas" OR Entonox OR Equanox OR Kalinox OR Medimix OR "Dinitrogen Monoxide"	925
#2	(MH "Pregnancy") OR (MH "Childbirth") OR (MH "Labor") OR (MH "Labor Pain") OR "labor pain" OR pregnancy OR childbirth OR birth OR labour OR intrapartum OR (MH "Analgesia, Obstetrical") OR (MH "Delivery")	100,226
#3	#1 AND #2	90
#4	#3 AND PT (Commentary OR Editorial OR Letter OR Review)	21
#5	#3 NOT #4	69

Appendix B. Sample Data Abstraction Forms

Nitrous Oxide for the Management of Labor Pain CER

Abstract Review Form

First Author, Year: ________________________________

EndNote Ref ID #: _______ Abstractor Initials: __ __ __

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude reviews, editorials, commentaries, letters to editor, etc.)	Yes	No	Cannot Determine
2. Study size ≥ 20 pregnant women in labor (record N if study size < 20: ____) OR addresses harms or occupational exposures	Yes	No	Cannot Determine
3. Relevant to CER topic If "No", select at least one of the following reasons: a. ___ Other pain management b. ___ Termination of pregnancy c. ___ Retained placenta and perineal repairs d. ___ Other________________________________	Yes	No	Cannot Determine
4. Study published in English	Yes	No	Cannot Determine

Retain for:

_____**BACKGROUND/DISCUSSION**

_____**REVIEW OF REFERENCES**

_____**OTHER**________________________________

COMMENTS:

Nitrous Oxide for the Management of Labor Pain Full-text Review Form

First Author, Year: ________________________________

EndNote Ref ID #: __________ Abstractor Initials: ____ ____ ____

Primary Inclusion/Exclusion Criteria		
5. Original research (exclude reviews, editorials, commentaries, letters to editor, etc.) If yes, record the following: Comparison group: ☐ Yes ☐ No ☐ Not reported Randomized (NA if no comparison group): ☐ Yes ☐ No ☐ Not reported/NA	Yes	No
6. Study size ≥ 20 pregnant women in labor (record N if study size < 20: ____) OR addresses harms or occupational exposure during labor	Yes	No
7. Relevant to CER topic If "No", select at least one of the following reasons: a. ___ Other pain management b. ___ Termination of pregnancy c. ___ Retained placenta and perineal repairs d. ___ Other________________________________	Yes	No
8. Study published in English	Yes	No
9. Does study answer any of the following key questions? (circle applicable questions)	Yes	No
KQ1. What is the effectiveness of nitrous oxide when compared to other methods for the management of labor pain among women intending a vaginal birth? **KQ2.** What is the comparative effectiveness of nitrous oxide on women's satisfaction with their birth experience and pain management? **KQ3.** What is the comparative effectiveness of nitrous oxide on the route of birth? **KQ4.** What is the nature and frequency of adverse effects associated with the use of nitrous oxide for the management of labor pain, including but not limited to: o Maternal adverse effects, such as nausea and vomiting, dreams, dizziness, unconsciousness, and postpartum complications. o Fetal/neonatal adverse effects, such as low Apgar scores and abnormal fetal cord blood gases. o Childhood adverse effects, such as drug dependency and developmental complications. o Adverse effects on health care providers and other individuals present for labor. **KQ5.** What are the health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization?		
10. If you answered YES to all questions, please review references and note relevant citation numbers below:		

Retain for: ___BACKGROUND/DISCUSSION ___REVIEW OF REFERENCES ___OTHER________________________

COMMENTS:

Appendix C. Evidence Tables

Tables are sorted by last name of first author.

Evidence Table 1: Nitrous oxide for management of labor pain

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Abboud et al., 1995 **Country:** U.S. **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************** **Inclusion criteria:** • Healthy parturients undergoing normal vaginal delivery **Exclusion criteria:** • Clinically significant history of gastro-intestinal, hepatic, renal, endocrine or respiratory disease, convulsive or neurological disorders • Fetal distress or any history of chronic alcohol or drug use	**Groups:** **G1:** N_2O in 30-60% O_2, mixed and administered by an anesthesiologist and initiated during the second stage of labor **G2:** Desflurane 1-4.5% and O_2, mixed and administered by an anesthesiologist and initiated during the second stage of labor **N at enrollment:** **G1:** 40 **G2:** 40 **N at followup:** (24 hours) **G1:** 40 **G2:** 40 **Age, mean yrs ± SD:** **G1:** 25.7 ± 5.7 **G2:** 26.3 ± 5.7 **Race/ethnicity:** NR **Parous, n (%):** **G1:** 27 (67.5) **G2:** 28 (70.0)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain, %:** (5 point scale from 0-4) Satisfactory (3 or 4):[1] Maternal report: **G1:** 63 **G2:** 63 Anesthesiologist report: **G1:** 63 **G2:** 58 Obstetrician report: **G1:** 55 **G2:** 50 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n (%):** Maternal: Birth amnesia: **G1:** 0 **G2:** 9 (22.5) **G1/G2:** $P < 0.05$ Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 35 (87.5) **G2:** 31 (77.5) Assisted:[2] **G1:** 5 (12.5) **G2:** 9 (22.5) Cesarean: **G1:** 0 **G2:** 0	**Satisfaction with pain management, %:** Participant would accept same treatment again: **G1:** 90 **G2:** 93 **Satisfaction with birth experience:** NR **Maternal status:** Blood loss, ml, mean: **G1:** 335 **G2:** 364 **Neonatal status, n (%):** Apgar score < 7: 1 minute: **G1:** 3 (8) **G2:** 5 (13) 5 minutes: **G1:** 0 **G2:** 0 NACS < 35: 2 hours: **G1:** 7 (18) **G2:** 4 (10) 24 hours: **G1:** 3 (8) **G2:** 0 **Adverse effects:** NR

Comments:

[1] Physician scale ranges from 0 (no demonstrable analgesia) to 4 (no observable signs of pain); patient scale ranges from 0 (none or worse) to 4 (absolutely no pain).

[2] Includes forceps and vacuum

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Abboud et al., 1989 **Country:** U.S. **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************ **Inclusion criteria:** • Women undergoing normal vaginal delivery **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O 30-60% in O_2 administered continuously by an anesthesiologist until moment of birth **G2:** Isoflurane 0.2-0.7% in O_2 administered continuously by an anesthesiologist until moment of birth **N at enrollment:** **G1:** 30 **G2:** 30 **N at followup:** **G1:** 30 **G2:** 30 **Age:** NR[1] **Race/ethnicity:** NR **Parous:** NR	Provider preferences: NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** **G1:** NR **G2:** 20 mg ketamine (for difficult forceps delivery) **Pain management, %:** No local anesthetic for delivery: **G1:** 53 **G2:** 47 Local infiltration: **G1:** 3 **G2:** 0 Pudendal nerve block: **G1:** 27 **G2:** 20 Epidural: **G1:** 7 **G2:** 7 Epidural and pudendal: **G1:** 10 **G2:** 26 Duration of prepartum analgesia, minutes, mean ± SD: **G1:** 14.7 ± 2.2 **G2:** 13 ± 2.4	**Pain, %:** (scale from 0 to 4)[2] Satisfactory (3 or 4): Mother: **G1:** 87 **G2:** 83 Anesthesiologist: **G1:** 97 **G2:** 90 Obstetrician: **G1:** 83 **G2:** 87 Labor progress: NR Fetal status: NR Timeliness: NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, %:**[3] Vaginal: **G1:** > 83 **G2:** > 83 Assisted: **G1:** < 17 **G2:** < 17 Cesarean: **G1:** 0 **G2:** 0	**Satisfaction with pain management, %:** Shortly after delivery, answered "yes" to "would you have the same agent again?": **G1:** 93 **G2:** 93 **Satisfaction with birth experience:** NR **Maternal status:** Blood loss estimated ml, mean ± SD: **G1:** 350 ± 22 **G2:** 320 ± 24 Hemoglobin, g/100 ml, mean ± SD: Antepartum: **G1:** 12.7 ± 0.2 **G2:** 13.2 ± 0.2 12-24 hours postpartum: **G1:** 11.0 ± 0.3 **G2:** 11.6 ± 0.2 Hematocrit, mean % ± SD: Antepartum: **G1:** 38.2 ± 0.6 **G2:** 39.3 ± 0.7 12-24 hours postpartum: **G1:** 33.1 ± 0.8 **G2:** 35.1 ± 0.7 Serum fluoride level < 5.6 mcmol/L, n (%): Before anesthesia, **G1:** 30 (100) **G2:** 30 (100) 12-24 houra postpartum: **G1:** 30 (100) **G2:** 30 (100) Urine fluoride level, mcmol/L, mean ± SD: Before anesthesia: **G1:** 38.9 ± 5.8 **G2:** 41.4 ± 4.6

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Abboud et al., 1989 (continued)				12-24 hours postpartum: **G1:** 23.62 ± 2.2 **G2:** 36.5 ± 3.1 **G1/G2:** $P < 0.05$ **Neonatal status:** Apgar score, 1 minute, %: 0-4: **G1:** 0 **G2:** 0 5-7: **G1:** 7 **G2:** 7 8-10: **G1:** 93 **G2:** 93 Apgar score, 5 minutes, %: 0-4: **G1:** 0 **G2:** 0 5-7: **G1:** 0 **G2:** 0 8-10: **G1:** 100 **G2:** 100 pH, mean ± SD: Umbilical vein: **G1:** 7.33 ± 0.01 **G2:** 7.34 ± 0.01 Umbilical artery: **G1:** 7.27 ± 0.01 **G2:** 7.28 ± 0.01 PCO_2 mmHg, mean ± SD: Umbilical vein: **G1:** 42.4 ± 1.2 **G2:** 41 ± 1.3 Umbilical artery: **G1:** 51.5 ± 1.5 **G2:** 50 ± 1.9 Base excess mEq/L, mean ± SD: Umbilical vein: **G1:** -2.8 ± 0.4 **G2:** -3 ± 0.3 Umbilical artery: **G1:** -2.2 ± 0.5 **G2:** -3 ± 0.5

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Abboud et al., 1989 (continued)				PO_2 mmHg, mean ± SD: Umbilical vein: **G1:** 32.1 ± 1.4 **G2:** 33 ± 1.4Umbilical artery: **G1:** 20.1 ± 1.1 **G2:** 20 ± 0.9 O_2 saturation, mean % ± SD: Umbilical vein: **G1:** 55.7 ± 2.4 **G2:** 58 ± 2.9 Umbilical artery: **G1:** 26.1 ± 2.2 **G2:** 26 ± 2.4 Urine fluoride levels from first voided urine < 5.6 mcmol/L, n (%): **G1:** 30 (100) **G2:** 30 (100) **Adverse effects:** Maternal: Partial amnesia, n: **G1:** 0 **G2:** 1[4] Neonatal: NR Childhood: NR Occupational: NR

Comments:

[1] Authors state maternal age was slightly higher in G1.

[2] Physician scale ranges from 0 (no demonstrable analgesia) to 4 (no observable signs of pain); patient scale ranges from 0 (none or worse) to 4 (absolutely no pain).

[3] Authors report that more than 83% of parturients in both groups had spontaneous vaginal deliveries; the rest were delivered by forceps.

[4] Parturient had difficult forceps delivery and 20 mg of ketamine.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Abboud et al., 1981 **Country:** U.S. **Participant source:** NR **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************* **Inclusion criteria:** • Normal vaginal delivery **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O, 30% to 60% and O_2 administered by anesthesiologist **G2:** Enflurane, 0.25% to 1.25% and O_2 **N at enrollment:** **G1:** 50 **G2:** 55 **N at followup:** **G1:** 50 **G2:** 55 **Age, mean yrs (SE):** **G1:** 25.1 (0.9) **G2:** 23.4 (0.7) **Race/ethnicity:** NR **Parous, %:** Primipara: **G1:** 38 **G2:** 51 Multipara: **G1:** 62 **G2:** 49	**Provider preferences:** NR **Provider specialty, %:** Obstetrician: **Total:** 100 **Cost of intervention:** NR **Other pain management methods available:** Single- or mutiple-dose meperidine intramuscular (IM), single-dose alpha-prodine subcutaneous (SC), local infiltration; pudendal block **Pain management, %:** Narcotic analgesia: < 1 hour before delivery: **G1:** 10 **G2:** 7 1-2 hours before delivery: **G1:** 12 **G2:** 14.5 > 2 hours before delivery: **G1:** 22 **G2:** 14.5 None: **G1:** 56 **G2:** 64 Single-dose meperidine IM: **G1:** 10 **G2:** 4 Multiple-dose meperidine IM: **G1:** 10 **G2:** 6 Single-dose alphaprodine SC:	**Pain:** (5 point scale 0-4)[1] Satisfactory (3 or 4), shortly after delivery, %: Mother: **G1:** 76 **G2:** 89 Anesthesiologist: **G1:** 70 **G2:** 80 Obstetrician: **G1:** 58 **G2:** 84 **G1/G2:** $P < 0.05$ **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: Estimated blood loss, ml, mean (SE): **G1:** 327 (13) **G2:** 321 (15) Neonatal: NR Occupational: NR **Route of birth, %:** Vaginal spontaneous: **G1:** 82 **G2:** 82 Assisted: Outlet forceps: **G1:** 10 **G2:** 14 Mid-forceps: **G1:** 2 **G2:** 2 Vacuum:	**Satisfaction with pain management:** (asked shortly after delivery) "Would you have the same agent again?", %: Yes: **G1:** 86 **G2:** 96 No: **G1:** 12 **G2:** 2 Maybe: **G1:** 2 **G2:** 2 **Satisfaction with birth experience:** NR **Maternal status:** Hemoglobin, g/100 ml, mean (SE): Antepartum: **G1:** 12.8 (0.2) G2: 12.9 (0.2) 12-24 hrs postpartum: **G1:** 12.0 (0.2) G2: 11.5 (0.2) Hematocrit, mean % (SE): Antepartum: **G1:** 38.0 (0.6) G2: 38.2 (0.5) 12-24 hrs postpartum: **G1:** 35.4 (0.6) G2: 34.4 (0.6) Blood sodium, meq/L, mean (SE): Before anesthesia: **G1:** 137 (0.3) G2: 137 (0.3) 12-24 hrs postpartum: **G1:** 138 (0.2) G2: 138 (0.3) Blood potassium, meq/L, mean

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
		G1: 24 **G2:** 27 Local anesthesia: None: **G1:** 56	**G1:** 6 **G2:** 2 Cesarean: Not applicable	(SE): Before anesthesia: **G1:** 4.0 (0.04) G2: 3.9 (0.04) 12-24 hrs postpartum: **G1:** 4.0 (0.1) G2: 4.0 (0.1)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Abboud et al., 1981 (continued)		**G2:** 51 Local infiltration: **G1:** 14 **G2:** 16 Pudendal block: **G1:** 30 **G2:** 33 Duration of prepartum analgesia, minutes, mean (SE): **G1:** 13.5 (1.5) **G2:** 14.7 (1.2)		Blood chloride, meq/L, mean (SE): Before anesthesia: **G1:** 103 (0.3) G2: 103 (0.3) 12-24 hrs postpartum: **G1:** 102 (0.2) G2: 103 (0.3) Blood bicarbonate, meq/L, mean (SE): Before anesthesia: **G1:** 17.7 (0.3) G2: 18.6 (0.3) G1/G2: $P < 0.05$ 12-24 hrs postpartum: **G1:** 22.7 (0.3) G2: 22.4 (0.3) Blood BUN, mg/100 ml, mean (SE): Before anesthesia: **G1:** 8.1 (0.4) G2: 8.2 (0.3) 12-24 hrs postpartum: **G1:** 8.1 (0.3) G2: 7.9 (0.3) Blood creatinine, mg/ 100 ml, mean (SE): Before anesthesia: **G1:** 0.7 (0.02) G2: 0.7 (0.01) 12-24 hrs postpartum: **G1:** 0.7 (0.01) G2: 0.7 (0.02) Blood uric acid, mg/ 100 ml, mean (SE): Before anesthesia: **G1:** 5.1 (0.1) G2: 5.3 (0.1) 12-24 hrs postpartum: **G1:** 5.3 (0.2) G2: 5.4 (0.1)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Blood osmolality, mOsm/kg, mean (SE): Before anesthesia: **G1:** 281 (0.8) G2: 280 (0.6) 12-24 hrs postpartum: **G1:** 284 (0.6) G2: 282 (0.6)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Abboud et al., 1981 (continued)				Serum fluoride, mcM/L, mean (SE): Before anesthesia: **G1:** 1.6 (0.1) G2: 1.4 (0.1) 12-24 hrs postpartum: **G1:** 1.5 (0.1) G2: 1.6 (0.1) Urine sodium, meq/L, mean (SE): Before anesthesia: **G1:** 142 (8.5) G2: 130 (6.8) 12-24 hrs postpartum: **G1:** 93.7 (7.7) G2: 88.2 (5.3) Blood potassium, meq/L, mean (SE): Before anesthesia: **G1:** 76.4 (6.5) G2: 83.7 (7.5) 12-24 hrs postpartum: **G1:** 39.3 (2.9) G2: 39.0 (3.4) Urine osmolality, mOsm/kg, mean (SE): Before anesthesia: **G1:** 599 (36.0) G2: 615 (32.7) 12-24 hrs postpartum: **G1:** 468 (28.8) G2: 480 (28.3) Urine fluoride, mcM/L, mean (SE): Before anesthesia: **G1:** 18.3 (2.2) G2: 20.0 (2.1) 12-24 hrs postpartum: **G1:** 15.9 (3.4) G2: 34.4 (4.0) G1/G2: $P < 0.05$

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Neonatal status: Birth weight, g, mean (SE): **G1:** 3,304 (61) G2: 3,461 (57)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Abboud et al., 1981 (continued)				Apgar score, 1 minute, %: 0-4: **G1:** 0 **G2:** 2 5-7: **G1:** 6 **G2:** 6 8-10: **G1:** 94 **G2:** 92 Apgar score, 5 minutes, %:0-4: **G1:** 0 **G2:** 0 5-7: **G1:** 6 **G2:** 6 8-10: **G1:** 94 **G2:** 92 Blood gases pH, mean (SE): Umbilical vein: **G1:** 7.34 (0.01) G2: 7.34 (0.01) Umbilical artery: **G1:** 7.27 (0.01) G2: 7.26 (0.01) Blood gases PCO_2, torr, mean (SE): Umbilical vein: **G1:** 35.6 (0.9) G2: 35.5 (0.7) Umbilical artery: **G1:** 42.5 (1.6) G2: 44.5 (1.1) Blood gases PO_2, torr, mean (SE): Umbilical vein: **G1:** 28.1 (0.9) G2: 30.5 (1.0) Umbilical artery: **G1:** 16.9 (0.7) G2: 17.9 (0.7) Blood gases base excess, meq/L, mean (SE): Umbilical vein: **G1:** -5.6 (0.4) G2: -6.3 (0.3) Umbilical artery: **G1:** -7.0 (0.6)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				G2: -6.3 (0.5)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Abboud et al., 1981 (continued)				Blood gases calculated O_2 saturation, mean %: Umbilical vein: **G1:** 63.5 G2: 69 Umbilical artery: **G1:** 28 G2: 31 Urine sodium, meq/L, mean (SE): **G1:** 17.9 (2.1) G2: 17.9 (2.0) Blood potassium, meq/L, mean (SE): **G1:** 23.3 (1.6) G2: 22.7 (1.7) Urine osmolality, mOsm/kg, mean (SE): **G1:** 167 (16.6) G2: 164 (19.9) Serum fluoride levels, umbilical cord, mcM/L, mean (SE): **G1:** 1.8 (0.1) **G2:** 2.4 (0.2) **G1/G2:** $P < 0.05$ Urine fluoride levels first voided urine, mcM/L, mean (SE): **G1:** 3.5 (0.3) G2: 4.0 (0.5) **Adverse effects:** Maternal: Complete amnesia for delivery, %: **G1:** 10 **G2:** 7 Neonatal: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Childhood: NR Occupational: NR

Comments:

[1] Physician scale ranges from 0 (no demonstrable analgesia) to 4 (no observable signs of pain); patient scale ranges from 0 (none or worse) to 4 (absolutely no pain).

Evidence Table 1: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Ahlborg et al., 1996 **Country:** Sweden **Participant source:** Community **Setting:** NR **Enrollment period:** 01/1989 to 12/1989 **Design:** Trend ************************ **Inclusion criteria:** • Women born in 1940 or after • Found in membership files of the Swedish Midwives Association in 1989 • Most recent pregnancy only **Exclusion criteria:** • Termination prior to 1983	**Groups:** **G1:** Midwives exposed to N_2O during deliveries **Ga:** > 30 N_2O deliveries per month **Gb:** 21-30 N_2O deliveries per month **Gc:** 11-20 N_2O deliveries per month. **Gd:** 1-10 N_2O deliveries per month **Ge:** 0 N_2O deliveries per month **N at enrollment:** (questionnaires returned) G1a: 41 G1b: 43 G1c: 136 G1d: 160 G1e: 346 **N at followup:** G1a: 41 G1b: 43 G1c: 136 G1d: 160 G1e: 346 **Age, yrs:** ≤ 29: Total: 196 30-34: Total: 386 ≥ 35: Total: 169 **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** Maternal: NR Neonatal: NR Childhood: NR Occupational: Became pregnant in first cycle, %: G1a: 14.6 G1b-d: 37.3 **G1e:** 42.8 Number of cycles to conception, women pregnant within 13 cycles, mean: G1a: 4.6 G1b: 3.1 G1c: 3.0 G1d: 2.8 **G1e:** 3.1 > 13 cycles to pregnancy, %: G1a: 29 G1b: 7 G1c: 8 G1d: 6 **G1e:** 10 Fecundability ratio, crude: G1a: 0.51 G1b: 1.10 G1c: 0.98 G1d: 1.10 **G1e:** 1.0 Fecundability ratio, adjusted

Evidence Table 1: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				(95% CI): G1a: 0.63 (0.43-0.94) G1b: 1.19 (0.89-1.59) G1c: 1.05 (0.86-1.28) G1d: 1.18 (0.98-1.41) G1e: 1.0

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Arfeen et al., 1994 **Country:** Scotland **Participant source:** NR **Setting:** NR **Enrollment period:** NR **Design:** Prospective cohort ************************ **Inclusion criteria:** • Healthy mothers • Normal medical and obstetric history • In first stage of labor • Cervical dilation > 2 cm **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Entonox. Breathed during contractions. **G2:** Epidural analgesia. Maintained with infusion of 20 ml/hr of 0.1% plain bupivacaine, bolus injections of 0.25% bupivacaine if needed. **N at enrollment:** (1st stage of labor) **G1:** 20 **G2:** 20 **N at followup:** (completed study) **G1:** 19 **G2:** 18 **Age, median yrs (range):** **G1:** 26.0 (20-36) **G2:** 27.5 (21-45) **Race/ethnicity:** NR **Parity, median (range):** **G1:** 1 (0-3) **G2:** 0 (0-4) **G1/G2:** *P* = 0.02[1]	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain, n:** **G1:** NR **G2:** 0 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: At least 1 desaturation, n (%): **G1:** 8 (42) **G2:** 6 (33) **G1/G2:** *P* = NS Total number of desaturations, n (% of time): **G1:** 74 (2.37) **G2:** 31 (1.08) **G1/G2:** *P* = 0.002[2] Hypoxic episodes, n: **G1:** 29 **G2:** 21 Duration of hypoxic episodes, seconds, mean: **G1:** 30.6 **G2:** 17.7 **G1/G2:** *P* = 0.002[1] Hypoxic episodes, median severity, % (range): **G1:** 88 (84-89) **G2:** 89 (86-89) **G1/G2:** *P* = 0.03[1] Neonatal: NR Occupational: NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** Median SpO_2 (range): **G1:** 96.0 (84-100) **G2:** 95.0 (86-99) **G1/G2:** *P* = NS **Neonatal status:** NR **Adverse effects:** NR

Comments:

[1] Mann-Whitney test.

[2] Chi-squared test.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Arora et al., 1992 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************* **Inclusion criteria:** • Normal labor with regular painful uterine contractions • Required inhalational analgesia **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Participants received Entonox or Entonox-isoflurane for five contractions, room air for one contraction, then the other agent for five contractions **G1a:** Received Entonox first **G1b:** Received Entonox-isoflurane first **N at enrollment:** (In labor) G1: 41 **N at followup:** G1: 39 **G1a:** 19 G1b: 20 **Age, mean yrs:** G1: 28.7 **Race/ethnicity:** NR **Parous, n (%):** G1: 16 (41.0)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Oxytocin, diamorphine, epidural **Pain management, n (%):** Oxytocin: G1:13 (33.3) Diamorphine: G1:19 (48.7) Epidural: G1:2 (5.1)	**Pain, mean ± SD (median):** Linear visual analog scale G1a: 5.8 ± 1.5 (5.0) G1b: 7.0 ± 1.5 (7.0) Entonox-isoflurane provided significantly more pain relief **G1a/G1b:** *P* = 0.001 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal, n (%): Dizziness: **G1:** 5 (12.8) **G1a:** 1 (5.2) **G1b:** 4 (20.0) Unpleasant or nauseating odor: **G1a:** NR **G1b:** 6 (30.0) Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: G1: 25 (64.1) Assisted: G1: 9 (23.1) Cesarean: G1: 5 (12.8)	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects, n (%):** Maternal: NR Neonatal: Agpar-minus-color score < 8: G1: 20 (51.3) Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Arthurs et al., 1979 **Country:** United Kingdom **Participant source:** NR **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** • Women in labor who chose to use nitrous oxide **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O mix 50/50 administered inter-mittently by mask plus continuous N_2O mix 50/50 via nasal cannula **G2:** N_2O 50/50 administered inter-mittently by mask **N at enrollment:** **G1:** 24 **G2:** 25 **N at followup:** **G1:** 22 **G2:** 22 **Age :** NR **Race/ethnicity:** NR **Parous, n:** **G1:** 13 **G2:** 10	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Pethidine, epidural **Pain management, n (%):** Pethidine: **G1:** 19 (79) **G2:** 22 (88) Epidural: **G1:** 3 (NR) **G2:** 4 (NR)	**Pain:** (0% to 100%)[1] Linear analogue score, mean increase ± SD: After 2 contractions: **G1:** 0.3 ± 16.2 **G2:** 11.5 ± 14.6 After 4 contractions: **G1:** 5.7 ± 17.0 **G2:** 17.9 ± 12.1 Pain relief, after 4 contractions, n (%): Pain had increased: **G1:** 21 (84) **G2:** 4 (17) No change: **G1:** 4 (16) **G2:** 7 (29) Pain had decreased: **G1:** 0 **G2:** 13 (54) **G1/G2:** $P < 0.0005$ Pain relief, midwife report: Complete: **G1:** 7 (29) **G2:** 1 (4) Considerable: **G1:** 15 (63) **G2:** 15 (60) Slight: **G1:** 2 (8) **G2:** 9 (36) **G1/G2:** $P = 0.02$ None: **G1:** 0 **G2:** 0 **Labor progress:** Duration of labor, hours:minutes, mean (SE): **G1:** 7:54 (0:48) **G2:** 8:42 (1:07) **Fetal status:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status, n (%):** Too drowsy, midwife report: **G1:** 2 (8) **G2:** 2 (8) Restless, midwife report: **G1:** 2 (8) **G2:** 8 (32) Noncooperative, midwife report: **G1:** 0 **G2:** 1 (4) **Neonatal status:** Apgar score, mean ± SD: 1 minute: **G1:** 7.8 ± 1.9 **G2:** 7.7 ± 1.9 5 minutes: **G1:** 9.6 ± 0.7 **G2:** 9.3 ± 1.1 **Adverse effects:** Maternal: Hazy memory of labor: **G1:** 13 (54) **G2:** 7 (28) Memory of delivery: Hazy: **G1:** 2 (8) **G2:** 4 (16) None: **G1:** 1 (4) **G2:** 0 Neonatal: NR Childhood: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Timeliness: NR **Labor co-interventions:** NR	Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Arthurs et al., 1979 (continued)			**Adverse effects, n (%):** Maternal: Nausea during labor: **G1:** 8 (33) **G2:** 9 (36) Vomiting during labor: **G1:** 6 (25) **G2:** 11 (44) Dreams: **G1:** 6 (25) **G2:** 7(28) Paraesthesia: **G1:** 8 (33) **G2:** 10 (40) Neonatal: NR Occupational: NR **Route of birth:** Vaginal: NR Assisted: NR Cesarean: **G1:** 1 **G2:** 1	

Comments:

[1] 0% = no pain, 100% = max pain

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Axelsson et al., 1996 **Country:** Sweden **Participant source:** Community **Setting:** NR **Enrollment period:** 01/1989 to 12/1989 **Design:** Cross-sectional ************************* **Inclusion criteria:** • Female members of Swedish midwives association • Born 1940 or later • Worked more than half the time during first trimester • Information on background variables was complete **Exclusion criteria:** • Ongoing pregnancy at time of questionnaire • Pregnancies before 1980 • Ectopic pregnancies • Women with five or more spontaneous abortions	**Groups:** **G1:** Midwives exposed to N_2O during deliveries **G1a:** Midwives using N_2O for > 50% of deliveries **G1b:** Midwives using N_2O for ≤ 50% of deliveries **G2:** Midwives not using N_2O **N at enrollment:** NR **N at followup, n (%):** **G1a:** 705 **G1b:** 538 **G2:** 1,262 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n (%):** Maternal: NR Neonatal: NR Occupational: Spontaneous abortions: **G1a:** 111/705 (15.7) **G1b:** 71/538 (13.2) **G2:** 168/1,262 (13.3) Spontaneous abortions, women who worked as a midwife during the first trimester:[1] **G1a:** 98/624 (15.7) **G1b:** 65/495 (13.1) **G2:** 89/598 (14.8) **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** Maternal: NR Neonatal: NR Childhood: NR Occupational: Spontaneous abortion, nitrous oxide exposure odds ratio, crude: **G1a:** 1.22 **G1b:** 0.99 G2: 1.0 Spontaneous abortion, nitrous oxide exposure odds ratio, adjusted (95% CI): **G1a:** 1.17 (0.84-1.62) **G1b:** 0.95 (0.66-1.35) G2: 1.0 Spontaneous abortions, women who worked as a midwife during the first trimester, n:[1] All: **G1a:** 98 **G1b:** 65 **G2:** 89 Early: **G1a:** 77 **G1b:** 50 **G2:** 73 Late: **G1a:** 21 **G1b:** 15 **G2:** 19

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Axelsson et al., 1996 (continued)				Spontaneous abortion, nitrous oxide exposure odds ratio, women who worked as a midwife during the first trimester, crude:* All: **G1a:** 1.07 **G1b:** 0.86 **G2:** 1.0 Early: **G1a:** 1.02 **G1b:** 0.81 **G2:** 1.0 Late: **G1a:** 1.27 **G1b:** 1.11 **G2:** 1.0 Spontaneous abortion, nitrous oxide exposure odds ratio, women who worked as a midwife during the first trimester, adjusted (95% CI):[1] All: **G1a:** 0.95 (0.62-1.47) **G1b:** 0.75 (0.48-1.19) **G2:** 1.0 Early: **G1a:** 0.94 (0.58-1.53) **G1b:** 0.70 (0.42-1.17) **G2:** 1.0 Late: **G1a:** 1.05 (0.44-2.52) **G1b:** 1.02 (0.41-2.53) **G2:** 1.0

Comments:

[1] About a third of the pregnancies occurred when the woman had an occupation other than midwife (e.g., nurse).

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Beppu, 1968 **Country:** Japan **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************ **Inclusion criteria:** • Fit volunteers in normal labor • Uncomplicated pregnancies and onset of labor between the 38th and 42nd weeks **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O (50-80%) and O_2, delivery method NR **G1a:** Vaginal delivery **G1b:** Caesarean delivery **N at enrollment:** **G1:** 26 **G1a:** 20 **G1**b**:** 6 **N at followup:** **G1:** 26 **G1a:** 20 **G1**b**:** 6 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** **G1a:** NR **G1b:** 0.5 mg atropine, 50 mg meperidine for premedication of anesthesia; halothane **Pain management:** Inhalation time, minutes, mean (range): **G1a:** 28 (4-108) **G1b:** 24 (18-36)	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n (%):** Vaginal: **G1:** 20 (76.9) Assisted: NR Cesarean: **G1:** 6 (23.1)	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** Nitrous oxide concentration, mg/dl, mean ± SD: Cubital artery: **G1a:** 23.82 ± 14.55 **G1b:** 26.25 ± 13.40 Cubital vein: **G1a:** 16.85 ± 10.60 **G1b:** 25.76 ± 10.70 **Neonatal status:** Nitrous oxide concentration, mg/dl, mean ± SD: Intravillous space: **G1a:** NR **G1b:** 24.50 ± 8.90 Umbilical artery: **G1a:** 7.51 ± 3.67 **G1b:** 18.43 ± 3.46 Umbilical vein: **G1a:** 11.02 ± 7.25 **G1b:** 18.50 ± 6.00 Apgar score, mean (range): **G1a:** 8.8 (6-9) **G1b:** 8.8 (6-9) **Adverse effects:** Maternal: NR Neonatal, n: Asphyxia: **G1a:** 0 **G1a:** 0 Sleepy baby: **G1a:** 2 **G1a:** 0 Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Beppu, 1968 **Country:** Japan **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** NR **Exclusion criteria:** NR	**Groups:** **G1:** Infant of mother who received N_2O mix (% and delivery method NR) **G2:** Infant of mother who received trichloroethylene **G3:** Infant of mother who received halothane **N at enrollment:** **G1:** 148 **G2:** 210 **G3:** 283 **N at followup:** **G1:** 148 **G2:** 210 **G3:** 283 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status, n (%):** Asphyxia, Cazean's classification: None: **G1:** 141 (95.27) **G2:** 199 (94.76) **G3:** 267 (95.06) First degree: **G1:** 5 (3.38) **G2:** 8 (3.81) **G3:** 10 (3.53) Second degree: **G1:** 2 (1.35) **G2:** 3 (1.43) **G3:** 4 (1.41) Asphyxia, Flagg's classification: None: **G1:** 139 (93.91) **G2:** 196 (93.34) **G3:** 267 (94.36) First degree: **G1:** 6 (4.05) **G2:** 10 (4.76) **G3:** 10 (3.53) Second degree: **G1:** 2 (1.35) **G2:** 2 (0.95) **G3:** 4 (1.41) Third degree: **G1:** 1 (0.69) **G2:** 2 (0.95) **G3:** 2 (0.70) Asphyxia, Lund's classification: None: **G1:** 138 (93.24) **G2:** 196 (93.34) **G3:** 265 (93.64) Slight: **G1:** 7 (4.72) **G2:** 10 (4.76) **G3:** 12 (4.24) :

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Beppu, 1968 (continued)				Moderate **G1:** 2 (1.35) **G2:** 2 (0.95) **G3:** 3 (1.06) Severe: **G1:** 1 (0.69) **G2:** 2 (0.95) **G3:** 3 (1.06) Asphyxia, Silverman's classification: 0 point: **G1:** 128 (86.50) **G2:** 190 (90.49) **G3:** 269 (91.53) 1 point: **G1:** 12 (8.10) **G2:** 14 (6.66) **G3:** 17 (6.00) 2 points: **G1:** 6 (4.05) **G2:** 4 (1.90) **G3:** 4 (1.41) ≥ 3 points: **G1:** 2 (1.35) **G2:** 2 (0.95) **G3:** 3 (1.06) **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Bergsjo and Lindbaek, 1971 **Country:** Norway **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Crossover RCT ************************* **Inclusion criteria:** • Women with established labor with obvious pain • Delivery was expected to be normal **Exclusion criteria:** • Women with a history of liver and kidney disease • Anticipated difficult delivery	**Groups:** **G1:** N_2O 50% /O_2 50% (Entonox) inhaled through face mask working by demand flow used first **G2:** Methoxyflurane used first **Ga:** N_2O chosen as preferred drug **Gb:** Methoxyflurane chosen as preferred drug **Gc:** Undecided on drug preference All patients tried both N_2O and methoxy-flurane, the order decided at random; patients then selected the preferred agent to use during labor. **N at enrollment:** **G1:** 26 **G2:** 37 **N at followup:** **G1:** 26 **G1a:** 14 **G1b:** 12 **G1c:** 0 **G2:** 37 **G2a:** 26 **G2b:** 10 **G2c:** 1 **Age, n (%):** < 20: **G1:** 0 **G2:** 4 (10.8) 20-29:	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Diazepam 10 mg intramuscularly (IM) or pethidine 100 mg IM **Pain management, n:** Diazepam < 30 min after trial start: **Ga:** 1 **Gb:** 1 **Gc:** NR Diazepam ≥ 30 min after trial start: **Ga:** 1 **Gb:** 4 **Gc:** NR Pethidine < 30 min after trial start: **Ga:** 8 **Gb:** 0 **Gc:** NR Pethidine ≥ 30 min after trial start: **Ga:** 6 **Gb:** 3 **Gc:** NR Diazepam and/or pethidine < 30 min after trial start: **Ga:** 9 **Gb:** 1 **Gc:** NR Diazepam and/or pethidine ≥ 30 min after trial start: **Ga:** 7 **Gb:** 6 **Gc:** NR	**Pain:** NR Labor progress: Dilation of cervix at start of trial, n (%): 1-2 cm: **G1:** 7 (26.9) **G2:** 9 (24.3) 3 cm: **G1:** 7 (26.9) **G2:** 10 (27.1) 4 cm: **G1:** 6 (23.1) **G2:** 10 (27.1) 5 cm: **G1:** 2 (7.7) **G2:** 3 (8.0) ≥ 6 cm: **G1:** 4 (15.4) **G2:** 4 (10.8) Not stated: **G1:** 0 **G2:** 1 (2.7) Duration of labor, n: ≤ 6 hours: **Ga:** 19 **Gb:** 5 > 6 hours: **Ga:** 21 **Gb:** 17 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	**Satisfaction with pain management:** Satisfaction with preferred drug, n: Excellent: **Ga:** 3 **Gb:** 0 **Gc:** 0 Good: **Ga:** 33 **Gb:** 21 **Gc:** 1 Moderate: **Ga:** 4 **Gb:** 1 **Gc:** 0 Poor: **Ga:** 0 **Gb:** 0 **Gc:** 0 **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Apgar score, patients who continued with preferred drug, n: ≤ 4: **Ga:** 0 **Gb:** 0 5: **Ga:** 1 **Gb:** 1 6: **Ga:** 0 **Gb:** 0 7: **Ga:** 2 **Gb:** 3 8: **Ga:** 5 **Gb:** 2 9: **Ga:** 21 **Gb:** 12 10: **Ga:** 4 **Gb:** 2 **Adverse effects, n:**[1] Maternal, patient

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	G1: 16 (61.5) **G2:** 27 (73.0) ≥ 30: **G1:** 10 (38.5) **G2:** 6 (16.2) **Race/ethnicity:** NR **Parous, n (%):** Primigravidae: **G1:** 16 (61.5) **G2:** 23 (62.2)	No additional drugs: **Ga:** 17 **Gb:** 12 **Gc:** NR		report:

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Bergsjo and Lindbaek, 1971 (continued)	Multiparae: **G1:** 10 (38.5) **G2:** 14 (37.8)			Nausea, by cause: N_2O: **Total:** 4 Methoxyflurane: **Total:** 2 Dizziness and similar sensations, by cause: N_2O: **Total:** 11 Methoxyflurane: **Total:** 11 Dry mouth, mask unpleasant, by cause: N_2O: **Total:** 6 Methoxyflurane: **Total:** 0 Bad smell or taste, by cause: N_2O: **Total:** 0 Methoxyflurane: **Total:** 9 Numbness, by cause: N_2O: **Total:** 1 Methoxyflurane: **Total:** 0 No reported side effect, by cause: N_2O: **Total:** 42 Methoxyflurane: **Total:** 44 Maternal, objective/ observed: Drowsiness, by cause: N_2O: **Total:** 7 Methoxyflurane: **Total:** 8 Euphoria, by cause: N_2O:

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Total: 4 Methoxyflurane: **Total:** 0 Hiccups, by cause: N_2O: **Total:** 1 Methoxyflurane: **Total:** 0 Vomiting, by cause:

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Bergsjo and Lindbaek, 1971 (continued)				N_2O: **Total:** 3 Methoxyflurane: **Total:** 1 Neonatal: NR Childhood: NR Occupational: NR

Comments:

[1] Adverse effect numbers may exceed total number as some patients reported more than one side effect.

Evidence Table 1: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Bodin et al., 1999 **Country:** Swedeb **Participant source:** Community **Setting:** Other **Enrollment period:** 01/1989 to 12/1989 **Design:** Cross-sectional ************************* **Inclusion criteria:** • Members of Swedish Midwives Association • Born in 1940 or later • In second trimester between 1980 and 1987 that ended as single birth in the Swedish Medical Birth Register • Working more than half time (greater than 20 hours per week) **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O used at assisted deliveries **G1a:** N_2O used in ≥ 50% of all deliveries **G1b:** N_2O used in < 50% of all deliveries **G2:** Did not work with N_2O **N at enrollment:** **Total:** 1,781[1] **N at followup:** **G1a:** 454 **G1b:** 357 **G2:** 931 **Age, yrs:** ≤ 29: **Total:** 960 30-34: **Total:** 642 ≥ 35: **Total:** 179 **Race/ethnicity:** NR **Parous, n (%):** 1: **Total:** 694 (38.9) 2: **Total:** 679 (38.1) 3: **Total:** 320 (17.9) 4: **Total:** 72 (4.0) ≥ 5: **Total:** 16 (0.8)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: NR Neonatal: NR Preterm birth rate, %: **G1a:** 4.2 **G1b:** 4.2 **G2:** 4.2 Occupational: NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Birth weight, grams, mean ± SD: **G1a:** 3,516 ± 534 **G1b:** 3,524 ± 527 **G2:** 3,588 ± 519 Birth weight in term births, adjusted difference (95% CI): **G1/G2:** -77 (-112,-8) Birth weight, linear regression effect differences, adjusted (95% CI): **G1/G2:** -102 (-183, -22) Low birth weight (LBW) rate, %: **G1a:** 3.5 **G1b:** 3.1 **G2:** 1.9 Low birth weight odds ratio, adjusted (95% CI): **G1:** 1.5 (0.7,3.3) **G2:** 1.0 Low birth weight,

Evidence Table 1: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				logistic regression effect difference, adjusted (95% CI): **G1:** 3.4 (0.9,13.4) Gestational age at delivery, weeks, mean ± SD: **G1a:** 39.7 ± 1.9 **G1b:** 39.6 ± 1.8 **G2:** 39.7 ± 1.9 Gestational age in term births, adjusted difference (95% CI): **G1/G2:** 0.02 (-0.20, 0.23)

Evidence Table 1: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Bodin et al., 1999 (continued)				Gestational age, linear regression effect difference, adjusted (95% CI): G1: 0.30 (-0.03,0.63) Small for gestational age (SGA) rate, %: **G1a:** 13.4 **G1b:** 11.5 **G2:** 9.7 SGA odds ratio, adjusted (95% CI): **G1:** 1.8 (1.1,2.8) G2: 1.0 Logistic regression effect differences of SGA, adjusted (95% CI): **G1:** 3.0 (1.2,7.2) **Adverse effects:** NR

Comments:

[1] 1,781 pregnancies linked to 1,302 women.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Carstoniu et al., 1994 **Country:** Canada **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Crossover RCTs ************************ **Inclusion criteria:** • Admitted in labor and delivery suite at Toronto Hospital **Exclusion criteria:** • Age < 18 yrs • Maternal cardiorespiratory disease • Evidence of fetal distress or abnormal heart rate pattern • Any condition affecting accuracy of pulse oximetry • Use of opioid or analgesia	**Groups:** **G1:** NC (cross-over) **G2:** CN (cross-over) **Ga:** 50% N_2O in O_2 (N) **Gb:** Compressed air (C) **N at enrollment:** (admission to labor and delivery) **Total:** 29 **N at followup:** G1: 14 G2: 12 **Age, mean yrs ± SD:** **G1:** 31.1 ± 5.8 **G2:** 28.4 ± 5.0 **Race/ethnicity:** NR **Parrous, n:** Primipara: **G1:** 7 **G2:** 7 Multipara: **G1:** 7 **G2:** 5	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** VAS score, baseline, mean ± SD: Contraction 1: **G1:** 5.6 ± 2.1 **G2:** 4.9 ± 2.5 Contraction 2: **G1:** 5.2 ± 2.2 **G2:** 5.8 ± 2.7 VAS score, trial, mean: Contraction 1: **Ga:** 5.1 **Gb:** 4.9 Contraction 2: **Ga:** 5.2 **Gb:** 5.2 Contraction 3: **Ga:** 5.7 **Gb:** 6.1 Contraction 4: **Ga:** 5.2 **Gb:** 5.6 Contraction 5: **Ga:** 5.6 **Gb:** 5.7 **Ga/Gb:** *P* = NS SpO_2, baseline, mean % ± SD: Contraction 1: **G1:** 97 ± 2.0 **G2:** 97 ± 2.0 Contraction 2: **G1:** 97 ± 2.0 **G2:** 96 ± 2.0 SpO_2, trial, mean %: Contraction 1: **Ga:** 97 **Gb:** 97 Contraction 2: **Ga:** 97 **Gb:** 96 Contraction 3: **Ga:** 97	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Gb: 96 Contraction 4: **Ga:** 97 **Gb:** 96 Contraction 5: **Ga:** 97 **Gb:** 96 **Ga/Gb:** $P < 0.05$	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Carstoniu et al., 1994 (continued)			**Labor progress:** Cervical dilation, cm, mean ± SD: **G1:** 3 ± 1.4 **G2:** 3 ± 1.3 Duration of labor, hours, mean ± SD: **G1:** 7.9 ± 3.8 **G2:** 7.6 ± 4.9 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Chia et al., 1990 **Country:** Singapore **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** 2 RCTs ************************* **Inclusion criteria:** • Patients admitted in the morning to labor suite in early labor or for induction of labor • Consented to use TENS or Entonox for pain relief **Exclusion criteria:** • Expressed desire for epidural analgesia • Admitted in advanced labor • Previously given other forms of analgesia • For groups G3 and G4, delivered without requesting further anesthesia	**Groups:** **G1:** Entonox (50% N_2O in O_2) as first method pain relief in patients in early labor, instructed by midwife on breathing technique on admission to labor ward. **G2:** Transcutaneous electric nerve stimulation (TENS). Patient controlled flow of current using control box after demonstration of equipment. **G3:** Entonox (50% N_2O in O_2) in nulliparous patients scheduled for surgical induction. Patients switched to TENS when Entonox was not sufficient for pain relief. Same administration method as above for G1. **G4:** TENS at a first method in patients scheduled for surgical induction. Patients switched to	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** **G1+G2:** Pethidine alone, pethidine combined with TENS or Entonox, or epidural **G3:** TENS (at first switch), if inadequate then combined Entonox and either TENS or 75 mg IM pethidine **G4:** Entonox (at first switch), if inadequate then combined TENS and either Entonox or 75 mg IM pethidine **Pain management, additional methods, n (%):** No additional relief: **G1:** 9 (17) **G2:** 9 (18.8) **G3:** NR **G4:** NR Pethidine: **G1:** 38 (71.7) **G2:** 28 (58.3) **G3:** NR **G4:** NR Other modalities: **G1:** 6 (11.3) **G2:** 11 (22.9) **G3:** NR **G4:** NR	**Pain, n (%):** (patient described intensity on 1-10 scale the day after delivery) 1-5: **G1:** 2 (3.2) **G2:** 4 (8.3) 6-10: **G1:** 51 (96.2) **G2:** 44 (91.7) Description of pain, time of request for pain relief in early labor: Mild: **G3:** 3 (30) **G4:** 7 (78) **G3/G4:** P = NS Moderate: **G3:** 4 (40) **G4:** 0 **G3/G4:** P = NS Severe: **G3:** 3 (30) **G4:** 2 (22) **G3/G4:** P = NS Type of relief from first method of pain relief: Nil: **G3:** 5 (50) **G4:** 1 (11) **G3/G4:** P = NS Partial: **G3:** 5 (50) **G4:** 8 (89) **G3/G4:** P = NS Complete: **G3:** 3 (30) **G4:** 0 **G3/G4:** P = NS After switching to second method: Mild: **G3:** 0 **G4:** 0 **G3/G4:** P = NS Moderate: **G3:** 5 (56) **G4:** 4 (40) **G3/G4:** P = NS Severe:	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	Entonox when TENS was not sufficient for pain relief. Same methods as listed above for G2. **N at enrollment:** (admitted in early labor or for surgical induction) **G1:** 53 **G2:** 48 **G3:** 10 **G4:** 10 **N at followup:** **G1:** 53 **G2:** 48 **G3:** 9[1] **G4:** 10 **Age, mean yrs ± SD:** **G1:** 28.3 ± 4.3 **G2:** 28.4 ± 4.2 **G3:** NR		**G3:** 4 (44) **G4:** 5 (50)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Chia et al., 1990 (continued)	**G4:** NR **Race/ethnicity:** NR **Parous, n (%):** Nulliparous: **G1:** 33 (62.3) **G2:** 26 (54.2) **G3:** 9 (100) **G4:** 10 (100)		**G3/G4:** *P* = NS Type of relief with second method, n: Same as before: **G3:** 4 **G4:** 1 **G3/G4:** *P* = NS Worse than before: **G3:** 6 **G4:** 2 **G3/G4:** *P* = NS Partial: **G3:** 4 **G4:** 6 **G3/G4:** *P* = NS Complete: **G3:** 0 **G4:** 0 **G3/G4:** *P* = NS **Labor progress, n (%):** Observed length of first stage of labor: ≤ 8 hours: **G1:** 30 (56.6) **G2:** 35 (72.9) **G1/G2:** *P* = NS > 8 hours: **G1:** 23 (43.4) **G2:** 13 (27.1) **G1/G2:** *P* = NS Length of labor, hours:minutes, mean: **G1b:** 6:16 **G2b:** 4:48 **G1/G2:** *P* = NS **Fetal status:** NR **Timeliness:** NR **Labor co-interventions, n (%):** Augmented or induced: **G1:** 16 (30.2) **G2:** 23 (47.9) **G3:** 9 (100)	

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G4: 10 (100) **Adverse effects:** NR **Route of birth:** NR	

Comments:
[1] One patient in G3 did not switch to TENS.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Clark et al., 1967 **Country:** U.S. **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Nonrandomized trial ************************* **Inclusion criteria:** NR **Exclusion criteria:** NR	**Groups:** **G1:** Methoxyflurane analgesia with the inhaler and anesthesia with N_2O and methoxyflurane **G2:** Anesthesia with N_2O and methoxyflurane **G3:** Methoxyflurane analgesia with the inhaler or some type of regional block **N at enrollment:** **G1:** 42 **G2:** 11 **G3:** 41 **N at followup:** (infant blood gas and pH obtained) **G1:** 17 **G2:** 0 **G3:** 4 **Age, mean yrs:** **G1:** 24.5 **G2:** 18.6 **G3:** 26.4 **Race/ethnicity:** NR **Parous, n (%*):** **G1:** 9 (21.4) **G2:** 5 (45.4) **G3:** 6 (14.6)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** **G1:** Meperidine **G2:** Meperidine, oxytocin (after delivery) **G3:** Meperidine, conduction anesthesia (epidural) **Pain management, n (%):** Meperidine: **G1:** 7 (16.6*) **G2:** 1 (9.0*) **G3:** 5 (12.1*) Oxytocin (after delivery): **G2:** 11 (100) Conduction anesthesia (epidural): **G3:** 11 (26.8)	**Pain, %:**[1] Excellent: **G1:** 20 **G2:** NR **G3:** 14 Good: **G1:** 37 **G2:** NR **G3:** 46 Fair: **G1:** 32 **G2:** NR **G3:** 24 Poor: **G1:** 11 **G2:** NR **G3:** 16 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:–** Apgar score < 7, 1 minute, n: **G1:** 14/42 **G2:** 4/11[2] **G3:** 2/42 Umbilical artery pH, mean (range): **G1:** 7.27 (7.17-7.38) **G2:** NR **G3:** 7.29 (7.25-7.33) Umbilical artery pO_2, mean (range): **G1:** 29.0 (13.40-52.6) **G2:** NR **G3:** 26.40 (21.7-31.2) Umbilical artery pCO_2, mean (range): **G1:** 56.7 (34.0-90.0) **G2:** NR **G3:** 43.33 (40-50) Umbilical artery Neg BE, mean (range): **G1:** -3.07 (-11.0,0.80) **G2:** NR **G3:** -6.06 (-9.8,-2.1) Femoral vein pH, 1 hour, mean (range): **G1:** 7.31 (7.19-7.39) **G2:** NR **G3:** 7.27 (7.23-7.34) Femoral vein pO_2, 1 hour, mean (range): **G1:** 42.8 (22.9-80.7) **G2:** NR **G3:** 41.87 (32.8-60.2) Femoral vein pCO_2, 1 hour, mean (range): **G1:** 42.5 (26.0-58) **G2:** NR **G3:** 53.87 (45-75)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Clark et al., 1967 (continued)				Femoral Vein Neg BE, 1 hour, mean (range): **G1:** -5.2 (-11.4,-2.0) **G2:** NR **G3:** -3.82 (-9.0,-0.10) **Adverse effects, n (%):** Maternal: Nausea and vomiting: **G1:** 6 (14.2)[3] **G2:** 0 **G3:** 2 (4.8) Neonatal: Stillborn: **G1:** 0 **G2:** 0 **G3:** 1 (2.4) Pneumonitis: **Total:** 3 Apneic spells: **Total:** 1 Ocular discharge: **Total:** 1 Respiratory distress syndrome: **Total:** 1 Diarrhea: **Total:** 1 Childhood: NR Occupational: NR

Comments:
* Calculated by reviewer.
[1] Pain Relief Scale: Excellent — patient lay quietly during contractions in a tranquil state; Good — appreciable relief of pain, but still some discomfort; Fair — some, but not satisfactory relief of pain; Poor — little or no relief of pain.
[2] All breech

[3] Six in this group had nausea and/or vomiting during or after the analgesia and anesthesia. In addition, two additional participants vomited during labor, before the inhaler was started.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Constantine et al., 1989 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************ **Inclusion criteria:** • Pregnant women using Entonox either alone or in combination with pethidine during labor **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Entonox ($50\%\ O_2$, $50\%\ N_2O$) **Ga:** Mask alone **Gb:** Mask with humidifier **Gc:** Mouthpiece alone **Gd:** Mouthpiece with humidifier **N at enrollment:** **G1:** 149 **G1a:** 49 **G1b:** 36 **G1c:** 37 **G1d:** 27 **N at followup:** **G1:** 149 **G1a:** 49 **G1b:** 36 **G1c:** 37 **G1d:** 27 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, %:** Required further analgesia: **G1:** 52 Length of nitrous use, hours, mean ± SD: G1a-b: 3.3 ± 2.5 G1c-d: 3.3 ± 2.1	**Pain, n (%):** Rated good: **G1:** 80 (53) G1a-b: 43 (50.5) G1c-d: 37 (57.8) Rated moderate: **G1:** 42 (28) G1a-b: 25 (29.4) G1c-d: 17 (26.5) Rated poor: **G1:** 20 (14) G1a-b: 11 (12.9) G1c-d: 9 (14.1) Rated useless: **G1:** 7 (5) G1a-b: 6 (7.0) G1c-d: 1 (1.5) **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n (%):** Maternal: Nausea: **G1:** 55 (37) **G1a:** 22 (45) **G1b:** 9 (25) **G1c:** 13 (36) **G1d:** 11 (41) Dry nose: **G1:** 23 (15) **G1a:** 11 (31) **G1b:** 5 (18) **G1c:** 6 (17) **G1d:** 1 (4)	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Dry mouth: **G1:** 116 (78) **G1a:** 37 (75) **G1b:** 26 (72) **G1c:** 31 (86) **G1d:** 22 (81) Light headed: **G1:** 87 (58) **G1a:** 16 (33) **G1b:** 20 (56)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Constantine et al., 1989 (continued)			**G1c:** 28 (76) **G1d:** 23 (85) **G1c/G1a:** *P* < 0.05 **G1c-d/G1a-b:** *P* < 0.01 Tingling: **G1:** 37 (25) **G1a:** 15 (31) **G1b:** 5 (18) **G1c:** 11 (31) **G1d:** 6 (22) Neonatal: NR Occupational: NR **Route of birth:** NR	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Deckardt et al., 1987 **Country:** (West) Germany **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort • Patients assigned to pain managements according to their own request ************************* **Inclusion criteria:** • Healthy pregnant women • Singleton pregnancy • Received training in prepared childbirth **Exclusion criteria:** • Patients with premature rupture of membranes	**Groups:**[1] **G1:** N_2O with O_2 1:1 breathed at irregular intervals and meperidine 50-100 mg intra-muscularly 2-4 hours before delivery **G2:** Patients received lumbar peridural anesthesia (9-12 ml bupivacaine 0.25%) **G3:** No analgesic drugs **G4:** Control/women at term but not in labor **Ga:** Primiparas **Gb:** Multiparas **N at enrollment:** (admitted to study as soon as true labor had began and progress-sive dilation to 3-4 cm was ascertained) **G1:** 25 **G1a:** 16 **G1b:** 9 **G2:** 15 **G2a:** 15 **G2b:** 0 **G3:** 6 **G3a:** 0 **G3b:** 6 **G4:** 9 **N at followup:** **G1:** 25 **G1a:** 16 **G1b:** 9 **G2:** 15 **G2a:** 15 **G2b:** 0	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** **G1:** Lumbar peridural anesthesia **G2:** N_2O and meperidine **G3:** Lumbar peridural anesthesia, N_2O, and meperidine **Pain management:** NR	**Pain, mean ± SD (range):** (VAS 0-10): **G1a:** 7.1 ± 1.2 (5-9) **G2a:** 3.5 ± 2.0 (1-8) **Gb:** 4.9 ± 1.7 (NR) **G1a/G2a:** $P < 0.001$ Labor progress: Labor duration, hours, mean ± SD: **G1a:** 3.3 ± 1.7 **G2a:** 4.5 ± 1.5 **Gb:** NR **G1a/G2a:** $P < 0.05$ Uterine contraction rate during labor, mean ± SD: **G1a:** 21.8 ± 4.13 **G2a:** 20.2 ± 4.27 **Gb:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions, n (%):** Oxytocin stimulation (infusion rate 1-3.6 mU/min): **G1a:** 11 (68.7) **G2b:** 11 (73.3) **Gb:** NR **Adverse effects:** NR **Arterial oxygen saturation, % mean ± SD (range):** **G1a:** 88.8 ± 3.9 (74-100) **G2a:** 94.3 ± 1.3 (85-100) **Gb:** 93.9 ± 2.0 (NR) **G4:** 96 (NR) **Route of birth, n (%):**	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Umbilical artery pH, mean ± SD: **G1a:** 7.21 ± 0.10 **G2a:** 7.29 ± 0.06 **Gb:** 7.31 ± 0.05 **G1a/G2a:** $P = 0.01$ Umbilical artery base excess, mean ± SD: **G1a:** -9.5 ± 4.5 **G2a:** -6.4 ± 2.2 **Gb:** -5.1 ± 3.5 Apgar score, 1 minute, mean ± SD: **G1a:** 8.1 ± 0.9 **G2a:** 8.5 ± 0.7 **Gb:** NR Apgar score, 5 minutes, mean ± SD: **G1a:** 9.7 ± 0.5 **G2a:** 10.0 ± 0 **Gb:** NR Apgar score, 10 minutes, mean ± SD: **G1a:** 10.0 ± 0 **G2a:** 10.0 ± 0 **Gb:** NR Birth weight, g, mean ± SD: **G1a:** 3,424 ± 395 **G2a:** 3,256 ± 726 **Gb:** 3,358 ± 361 Gestational age, weeks, mean ± SD: **G1a:** 39.7 ± 0.68 **G2a:** 39.3 ± 1.23 **Gb:** 239.7 ± 0.70 **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	G3: 6 **G3a:** 0 **G3b:** 6 **G4:** 9 **Age, mean yrs ± SD:** **G1a:** 24.3 ± 4.40 **G1b:** NR **G2a:** 27.4 ± 4.85 **G3:** NR **Gb:** 27.6 ± 3.62 **G4:** NR		Vaginal spontaneous: **Total:** 40 Assisted forceps: **Total:** 5 Cesarean: **Total:** 1	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Deckardt et al., 1987 (continued)	**Race/ethnicity:** NR **Parous, n (%):** **G1:** 9 (36) **G2:** 0 **G3:** 6 (100) **G4:** NR			

Comments:

[1] Results are reported for groups G1a, G2a and Gb, but not separately for groups G1b and G3b.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Einarsson et al., 1996 **Country:** Sweden **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************* **Inclusion criteria:** • Women undergoing vaginal delivery **Exclusion criteria:** • Maternal cardiorespiratory disease • Pre-eclampsia • Evidence of fetal distress • Used opioids • Used regional analgesia	**Groups:** **G1:** 70% N_2O in O_2[1] **G2:** 50% N_2O in O_2[1] **N at enrollment:** **G1:** 12 **G2:** 12 **N at followup:** **G1:** 12 **G2:** 12 **Age, median yrs (range):** **G1:** 28 (19-41) **G2:** 29 (21-37) **Race/ethnicity:** NR **Parous, n (%):** Primiparous: **G1:** 6 (50) **G2:** 8 (66.7) Multiparous: **G1:** 6 (50) **G2:** 4 (33.3)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** Cervical dilation at time of study, cm, median (range): **G1:** 4.5 (3.0-8.0) **G2:** 5.0 (4.0-7.0) **Fetal status, n (%):** Decline in fetal heart rate: **G1:** 0 G2: 1 (8.3)* **Timeliness:** NR **Labor co-interventions:** NR **End-tidal CO_2, median %:** Before N_2O inhalation: **G1:** 3.7 **G2:** 3.5 At end of N_2O inhalation: **G1:** 3.6 **G2:** 3.6 30 seconds after N_2O: **G1:** 3.6 **G2:** 3.5 60 seconds after N_2O: **G1:** 3.8 **G2:** 3.5 120 seconds after N_2O: **G1:** 3.8 **G2:** 3.8 **End-tidal O_2, median %:** Before N_2O inhalation: **G1:** 16.0 **G2:** 16.2 At end of N_2O inhalation:	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G1: 25.4 **G2:** 43.7 30 seconds after N_2O: **G1:** 17.5 **G2:** 18.4 **G1/G2:** $P < 0.05$	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Einarsson et al., 1996 (continued)			60 seconds after N_2O: **G1:** 16.3 **G2:** 16.9 **G1/G2:** *P* = NS 120 seconds after N_2O: **G1:** 15.4 **G2:** 15.4 **G1/G2:** *P* = NS **Oxygen saturation, median %:** Before N_2O inhalation: **G1:** 96.3 **G2:** 97.0 At end of N_2O inhalation: **G1:** 98.0 **G2:** 98.8 **G1/BL:** *P* < 0.01 **G1/BL:** *P* < 0.01 **G1/G2:** *P* = NS 30 seconds after N_2O: **G1:** 97.5 **G2:** 98.0 **G1/BL:** *P* < 0.01 **G1/BL:** *P* < 0.01 **G1/G2:** *P* = NS 60 seconds after N_2O: **G1:** 97.0 **G2:** 97.0 120 seconds after N_2O: **G1:** 97.0 **G2:** 97.0 **Expiratory ventilation volume, L/min, median:** Before N_2O inhalation: **G1:** 13.7 **G2:** 11.1 At end of N_2O inhalation: **G1:** 13.9 **G2:** 11.3 30 seconds after N_2O: **G1:** 12.2 **G2:** 11.0 60 seconds after N_2O: **G1:** 10.8 **G2:** 9.9	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			120 seconds after N_2O: **G1:** 8.7 **G2:** 9.8	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Einarsson et al., 1996 (continued)			**Nitrous inhalation time per contraction, seconds, median:** **G1:** 33 **G2:** 58 **G1/G2:** *P* = 0.01 **Uterine contraction time, seconds, median:** **G1:** 87 **G2:** 90 **Adverse effects, n (%):** Maternal: Hypoxemia: **G1:** 1 (8.3) **G2:** 1 (8.3) Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 12 (100) **G2:** 12 (100) Assisted: NR Cesarean: Not applicable	

Comments:

[1] For all participants, administered via a nonrebreathing system with a demand valve; parturients breathed through mouthpiece while using a nose clip and switched on or off as desired.

* Calculated by reviewer

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Harrison et al., 1987 **Country:** Ireland **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 06/1983 to 12/1983 **Design:** Prospective cohort • Patients selected at random ************************* **Inclusion criteria:** • Primigravid • Initial choice of analgesia was transcutaneous electrical nerve stimulation, Entonox, pethidine and promazine, or lumbar epidural • Admitted to main labor ward **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Entonox: 50% N_2O, 50% O_2 self-administered, usually towards the end of first stage of labor and during second stage **G2:** Transcutaneous electrical nerve stimulation (TENS) **G3:** Pethidine and promazine 50 mg each combined when deemed necessary by mutual consent **G4:** Lumbar epidural **N at enrollment:** **G1:** 20 **G2:** 50 **G3:** 50 **G4:** 50 **N at followup:** **G1:** 20 **G2:** 50 **G3:** 50 **G4:** 50 **Age:** NR **Race/ethnicity:** NR **Parous, n:** **Total:** 0	**Provider preferences:** NR **Provider specialty, %:** Midwives and medical personnel: 100 **Cost of intervention:** NR **Other pain management methods available:** **G1:** TENS, pethidine and promazine, epidural **G2:** Entonox, pethidine and promazine, epidural **G3:** Entonox, TENS, epidural **G4:** Entonox, TENS, pethidine and promazine **Pain management, n (%):** Initial choice alone: **G1:** 19 (95) **G2:** 9 (18) **G3:** 10 (20) **G4:** 50 (100) Initial choice + Entonox: **G1:** NA **G2:** 15 (30) **G3:** 25 (50) **G4:** 0 Initial choice + pethidine and promazine: **G1:** 1 (5) **G2:** 8 (16) **G3:** NA **G4:** 0 Initial choice + epidural: **G1:** 0 **G2:** 8 (16)	**Pain, n (%):** (5 point scale 0-4)[1] Degree of pain relief: Nil (pain score 4): **G1:** 2 (10) **G2:** 2 (4) **G3:** 23 (46) **G4:** 0 Partial (score 1-3): **G1:** 18 (90) **G2:** 48 (96) **G3:** 27 (54) **G4:** 6 (12) Complete (score 0): **G1:** 0 **G2:** 0 **G3:** 0 **G4:** 44 (88) Degree of pain relief, midwife report: Nil: **G1:** 0 **G2:** 1 (2) **G3:** 16 (32) **G4:** 0 Poor: **G1:** 4 (20) **G2:** 1 (2) **G3:** 10 (20) **G4:** 0 Fair: **G1:** 9 (45) **G2:** 14 (28) **G3:** 21 (42) **G4:** 1 (2) Good: **G1:** 7 (35) **G2:** 34 (68) **G3:** 3 (6) **G4:** 8 (16) Excellent: **G1:** 0 **G2:** 0 **G3:** 0 **G4:** 41 (82)	**Satisfaction with pain management, n (%):** Positive comments, 1 hour after delivery: **G1:** 18 (90) **G2:** 46 (92) **G3:** 26 (52) **G4:** 50 (100) Efficacy was yes, 24 hours after delivery: **G1:** 16 (80) **G2:** 46 (92) **G3:** 24 (48) **G4:** 49 (98) Adequacy was yes, 24 hours after delivery: **G1:** 12 (60) **G2:** 40 (80) **G3:** 9 (18) **G4:** 49 (98) **Satisfaction with birth experience, n (%):** (1-24 hours after delivery) Would request same analgesia again: Yes: **G1:** 16 (80) **G2:** 30 (60) **G3:** 19 (38) **G4:** 44 (88) Qualified yes: **G1:** 0 **G2:** 7 (14) **G3:** 0 **G4:** 0 No: **G1:** 3 (15) **G2:** 10 (20) **G3:** 24 (48) **G4:** 1 (2) Don't know: **G1:** 1 (5) **G2:** 3 (6) **G3:** 7 (14) **G4:** 5 (10) **Maternal status:** NR **Neonatal status:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
		G3: 15 (30) **G4:** NA Initial choice + pethidine and	**Labor progress:** Hours in labor, mean ± SD: Initial choice alone: **G1:** 5.2 ± 1.7 (n=19) **G2:** 6.3 ± 2.4 (n=9) **G3:** 6.2 ± 1.4 (n=10) **G4:** 7.7 ± 2.4 (n=50)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Harrison et al., 1987 (continued)		promazine + Entonox: **G1:** NA **G2:** 7 (14) **G3:** NA **G4:** 0 Initial choice + pethidine and promazine + epidural: **G1:** 0 **G2:** 3 (6) **G3:** NA **G4:** NA	Including other analgesia: **G1:** 5.4 ± 1.7 (n=1) **G2:** 8.2 ± 3.0 (n=41) **G3:** 7.7 ± 2.8 (n=40) **G4:** NA **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n (%):** Vaginal (normal): **G1:** 12 (60) **G2:** 32 (64) **G3:** 32 (64) **G4:** 13 (26) Assisted (forceps and vacuum): **G1:** 7 (35) **G2:** 14 (28) **G3:** 18 (36) **G4:** 31 (62) Cesarean: **G1:** 0 **G2:** 4 (8) **G3:** 0 **G4:** 3 (6) Breech: **G1:** 1 (5) **G2:** 0 **G3:** 0 **G4:** 3 (6)	**Adverse effects:** NR

Comments:

[1] 0 (no pain) to 4 (very severe pain)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Harrison and Cullen, 1986 **Country:** Ireland **Participant source:** Community **Setting:** Hospital **Enrollment period:** 08/1983 to 12/1983 **Design:** Prospective cohort ************************* **Inclusion criteria:** • Born at selected hospital between August and December 1983 • Mothers had taken part in study evaluating different forms of analgesia in labor • Birth weight between 2.65 kg and 4.66 kg • ≥ 36 weeks gestation **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Babies whose mothers received one or more forms of analgesia during labor **Ga:** N_2O 50% and O_2 50% (Entonox) self administered as required by patient **Gb:** Pethidine/ promazine **Gc:** Epidural **Gd:** Transcutaneous electrical nerve stimulation (TENS) **Ge:** TENS placebo **Gf:** General anesthesia **N at enrollment:** (3-5 days postdelivery) **G1:** 110 **G1a:** 46 **G1b:** 46 **G1c:** 48 **G1d:** 27 **G1e:** 31 **G1f:** 4 **N at followup:** **G1:** 110 **Age:** NR **Race/ethnicity:** NR **Parous:** NR[1]	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, n:** Initial analgesic choice: Entonox: **G1:** 7 Pethidine/promazine: **G1:** 45 Epidural: **G1:** 26 TENS: **G1:** 15 TENS placebo: **G1:** 17 General anesthesia: **G1:** 0	Pain: NR Labor progress: Duration of labor, hours, mean (range): **G1:** 6 (2-12) Fetal status: NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n:** Vaginal: **G1:** 65 Assisted: **G1:** 38[2] Cesarean: **G1:** 7	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Birth weight, kg, mean (range): **G1:** 3.488 (2.65-4.66) Gestational age, weeks, mean (range): **G1:** 40.2 (36-43) Neonatal Psychological Assessment Profile raw scores, mean:[3] Habituation to light: **G1a:** 2.92 **G1b:** 2.95 **G1c:** 3.15 **G1d:** 3.41 **G1e:** 3.11 **G1f:** 3.50 Habituation to sound: **G1a:** 3.29 **G1b:** 2.86 **G1c:** 3.03 **G1d:** 2.64 **G1e:** 3.35 **G1f:** 3.75 Auditory inanimate orientation: **G1a:** 2.53 **G1b:** 2.43 **G1c:** 2.15 **G1d:** 2.37 **G1e:** 2.48 **G1f:** 2.00 Visual inanimate orientation: **G1a:** 1.65 **G1b:** 1.58 **G1c:** 1.68 **G1d:** 1.56 **G1e:** 1.59 **G1f:** 1.00

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Harrison and Cullen, 1986 (continued)				Auditory animate: orientation **G1a:** 2.57 **G1b:** 2.62 **G1c:** 2.23 **G1d:** 2.35 **G1e:** 2.44 **G1f:** 1.00 Visual animate orientation: **G1a:** 2.45 **G1b:** 2.34 **G1c:** 2.22 **G1d:** 2.29 **G1e:** 2.45 **G1f:** 2.00 Auditory and visual animate orientation: **G1a:** 2.80 **G1b:** 2.61 **G1c:** 2.66 **G1d:** 2.61 **G1e:** 2.83 **G1f:** 2.00 Alertness: **G1a:** 2.37 **G1b:** 2.13 **G1c:** 2.08 **G1d:** 2.00 **G1e:** 2.29 **G1f:** 1.00 Peak of excitement: **G1a:** 3.23 **G1b:** 3.44 **G1c:** 3.17 **G1d:** 3.11 **G1e:** 3.12 **G1f:** 1.50 Irritability: **G1a:** 2.21 **G1b:** 2.37 **G1c:** 2.23 **G1d:** 2.33 **G1e:** 2.51 **G1f:** 1.50 Consolability: **G1a:** 2.84 **G1b:** 2.97 **G1C:** 2.91 **G1D:** 2.77 **G1E:** 3.38 **G1F:** 1.75

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Harrison and Cullen, 1986 (continued)				Cuddliness: **G1a:** 2.60 **G1b:** 2.40 **G1c:** 2.47 **G1d:** 2.44 **G1e:** 2.50 **G1f:** 2.50 Self-quieting activity: **G1a:** 2.00 **G1b:** 1.40 **G1c:** 2.20 **G1d:** 2.00 **G1e:** 1.50 **G1f:** 1.00 Suckling time, %: 1 minute: **G1a:** 67.58 **G1b:** 62.00 **G1c:** 64.45 **G1d:** 66.13 **G1e:** 64.92 **G1f:** NR 5 minutes: **G1a:** 70.63 **G1b:** 65.83 **G1c:** 77.46 **G1d:** 68.25 **G1e:** 77.14 **G1f:** NR **Adverse effects:** NR

Comments:

[1] The authors state mothers were either primigravid or women of the second parity.

[2] 34 forceps, 3 vacuum, 1 assisted breech

[3] Babies were assessed with the Neonatal Psychological Assessment Profile, which combines sections from the Neonatal Behavioural Assessment Scale, items from the Neurological Assessment of preterm and full-term infants, and two measures of suckling behaviors. The scale ranges from 1-5.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Henderson et al., 2003 **Country:** United Kingdom **Participant source:** Academic multiple sites **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** NR **Exclusion criteria:** NR	**Groups:** **G1:** Midwives exposed to N_2O mix as delivery attendants. Midwives wore passive sampling tube for the first four hours (first half) of their shift, placed on lapel "within the breathing zone." They also completed questionnaires and provided urine samples. **N at enrollment:** **G1:** 46[1] **N at followup:** **G1:** 50 shifts of data[1] **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty, n (%):** Midwives: **G1:** 46 (100) **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** All were exposed to N_2O, concentration not noted.	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n:** Maternal: NR Neonatal: NR Occupational: Time-weighted average of nitrous exposure, n: 10 times the occupa-tional exposure limits: **G1:** 5/46 5 times the occupa-tional exposure limits: **G1:** 5/46 2 times the occupa-tional exposure limits: **G1:** 13/46 Below the occupa-tional exposure limits: **G1:** 13/46 Interindividual environmental concentrations, ppm, mean ± SD	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** Maternal: NR Neonatal: NR Childhood: NR Occupational: See labor and immediate outcomes.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			(range): **G1:** 313 ± 358 (2.4-1300) No nitrous oxide present in urine after 4 hours: **G1:** 3 Nonzero values of nitrous oxide in baseline urine prior to starting shift: **G1:** 22	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Henderson et al., 2002 (continued)			Nonzero baseline urinary concentrations of nitrous oxide, μg/l, mean ± SD (range): **G1:** 44 ± 51 (3-174) (n=22) Urinary nitrous oxide concentrations in excess of 27 μg/l (biological exposure limit in Italy) before starting their shift: **G1:** 12 Urinary nitrous oxide concentrations, second sample, μg/l, mean ± SD (range): G1: 114 ± 191 (0-1103) **Route of birth:** NR	

Comments:

[1] All shifts where midwives were monitored (shifts were 4 hours in length); some participants were monitored more than once. In hospital 1, 15 midwife shifts were monitored, 2 of which were on the same midwife. In hospital 2, 35 midwife shifts were monitored, with 20 monitored only on one shift, and 4 monitored on 2 shifts, 1 on 3 shifts, and 1

on 4 shifts. Text variously describes 46 midwives and 46 shifts, although some midwives were monitored more than once.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Henry et al., 2004 **Country:** Australia **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 10/2002 to 01/2003 **Design:** Cross-sectional ************************ **Inclusion criteria:** • Women in labor **Exclusion criteria:** • Age < 17 years • Non-English speaking • Women undergoing elective or urgent cesarean where no labor occurred • Women with stillbirth/neonatal deaths, major congenital anomaly/major neonatal morbidity • Homebirths • Active psychiatric illness at time of labor	**Groups:**[1] **G1:** N_2O **G2:** Pethidine **G3:** Epidural anesthesia **G4:** Local anesthesia (infiltration of the perineum) **G5:** "Natural" methods which included massage, hot pack, bath/shower, or any other nonpharmacologic method **G6:** No N_2O **N at enrollment:** (survey given in the first 24 hours postpartum, completed within 1st postpartum week) Total: 496 **N at followup, n (%):** (included surveys) **G1:** 268 (54) **G2:** 132 (27) **G3:** 217 (44) **G4:** 190 (38) **G5:** 367 (74) **G6:** 228 (46) Total: 496 **Age, mean yrs (range):** **Total:** 32 (18-44) **Race/ethnicity:** NR **Parous, %:** Nulliparous: **Total:** 56	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, n (%):** N_2O: **Total:** 268 (54) Pethidine: **Total:** 132 (27) Epidural anesthesia: **Total:** 217 (44) Local anesthesia: **Total:** 190 (38) "Natural" methods: **Total:** 367 (74) "Natural" methods only: **Total:** 46 (9.3) Number of pain management methods used, %: At least one: **Total:** 93 Two methods: **Total:** 24 Three methods: **Total:** 33 Pain management, normal vaginal deliveries, %: N_2O: **Total:** 49 Pethidine: **Total:** 22 Epidural anesthesia: **Total:** 26	**Pain:** NR[2] **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Effect of place of "booking in" vs. place of delivery, %:** Booked and gave birth in delivery suite or operating theatre (n = 398): **G1:** 59 **G2:** 29 **G3:** 49 **G4:** NR **G5:** 70 Booked into birth center, but gave birth in delivery suite or operating theatre (n=44): **G1:** 43 **G2:** 27 **G3:** 46 **G4:** NR **G5:** 93 Booked and gave birth in birth center (n=51): **G1:** 20 **G2:** 5 **G3:** 0 **G4:** NR **G5:** 86 **Labor co-interventions:** NR	**Satisfaction with pain management:** (survey given in the first 24 hours postpartum, to be completed within 1st postpartum week) Very satisfied, %: **G1:** 35 **G6:** 57 **G1/G6:** $P < 0.01$ Pain management method, probably or definitely would use again, %: **G1:** 65 **G2:** 49 **G3:** 82 **G4:** NR **G5:** 79 **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
		Local anesthesia: **Total:** NR "Natural methods": **Total:** 72 Any pharmacologic: **Total:** 75	**Adverse effects:** NR **Route of birth:** NR	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Henry et al., 2004 (continued)		Pain management, "other" deliveries, %: N_2O: **Total:** 66 Pethidine: **Total:** 40 Epidural anesthesia: **Total:** 92 Local anesthesia: **Total:** NR "Natural" methods: **Total:** 80 Any pharmacologic: **Total:** 99		

Comments:

[1] Groups are not exclusive.

[2] Utility of pain management methods only displayed graphically. Epidural analgesia recieved the highest utility scores, with 194/217 (89) rating it 'very useful' in relieving their pain.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Holdcroft and Morgan, 1974 **Country:** United Kingdom **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 7 month period **Design:** Cross-sectional ************************* **Inclusion criteria:** • See exclusion criteria **Exclusion criteria:** • Those receiving epidurals • Having a cesarean • Non-English speaking	**Groups:** **G1:** Entonox alone (50% mixture of N_2O and O_2) **G2:** Entonox and pethidine **G3:** Pethidine alone **G4:** No analgesia **N at enrollment:** (interviewed) **G1:** 130 **G2:** 466 **G3:** 67 **G4:** 42 **N at followup:** (24-48 hours after delivery) **G1:** 130 **G2:** 466 **G3:** 67 **G4:** 42 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain, n (%):** (scale developed by investigators) Pain relief from Entonox: None: **G1:** 39 (30.0) **G2:** 157 (33.7) Slight analgesia: **G1:** 23 (17.7) **G2:** 80 (17.2) Satisfactory analgesia: **G1:** 60 (46.2) **G2:** 212 (45.5) Complete analgesia: **G1:** 5 (3.8) **G2:** 8 (1.7) Amnesia: **G1:** 1 (0.8) **G2:** 5 (1.1) No pain to relieve: **G1:** 2 (1.5) **G2:** 4 (0.9) Pain relief from Entonox by duration of labor, primagravid: Less than 4 hours: None: **G1+G2:** 9 (30) Slight: **G1+G2:** 4 (13.3) Satisfactory: **G1+G2:** 14 (46.6) Complete: **G1+G2:** 0 Amnesia: **G1+G2:** 1 (3.3) No pain to relieve: **G1+G2:** 2 (6.7) 4 to 12 hours: None: **G1+G2:** 72 (38.9) Slight: **G1+G2:** 29 (15.7) Satisfactory: **G1+G2:** 75 (40.5) Complete: **G1+G2:** 4 (2.2) Amnesia: **G1+G2:** 2 (1.1) No pain to relieve: **G1+G2:** 3 (1.6)	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Holdcroft and Morgan, 1974 (continued)			More than 12 hours: None: **G1+G2:** 32 (38.6) Slight: **G1+G2:** 15 (18.1) Satisfactory: **G1+G2:** 35 (42.2) Complete: **G1+G2:** 0 Amnesia: **G1+G2:** 1 (1.2) No pain to relieve: **G1+G2:** 0 Pain relief from Entonox by duration of labor, multipara: Less than 4 hours: None: **G1+G2:** 27 (30.3) Slight: **G1+G2:** 13 (14.6) Satisfactory: **G1+G2:** 45 (50.6) Complete: **G1+G2:** 3 (3.4) Amnesia: **G1+G2:** 0 No pain to relieve: **G1+G2:** 1 (1.1) 4 to 12 hours: None: **G1+G2:** 51 (29.1) Slight: **G1+G2:** 33 (18.8) Satisfactory: **G1+G2:** 84 (48.0) Complete: **G1+G2:** 5 (2.9) Amnesia: **G1+G2:** 2 (1.1) No pain to relieve: **G1+G2:** 0 More than 12 hours: None: **G1+G2:** 5 (14.7) Slight: **G1+G2:** 9 (26.5) Satisfactory: **G1+G2:** 19 (55.9) Complete: **G1+G2:** 1 (2.9) Amnesia: **G1+G2:** 0 No pain to relieve:	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G1+G2: 0	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Holdcroft and Morgan, 1974 (continued)			Pain relief from pethidine: No analgesia: **G2:** 224 (48.1) **G3:** 32 (47.7) Slight analgesia: **G2:** 163 (35.0) **G3:** 15 (22.4) Satisfactory analgesia: **G2:** 65 (13.9) **G3:** 15 (22.4) Complete analgesia: **G2:** 5 (1.1) **G3:** 0 Amnesia: **G2:** 5 (1.1) **G3:** 4 (6.0) No pain to relieve: **G2:** 4 (0.9) **G3:** 1 (1.5) **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n:** Maternal: Vomiting: **Total:** 22[1] Altered consciousness: **Total:** 27 Loss of control: **Total:** 7 Neonatal: NR Occupational: NR **Route of birth:** NR	

Comments:

[1] Ascribed to pethidine in 10 patients.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Jacobson et al., 1990 **Country:** Sweden **Participant source:** Community **Setting:** Review of data for addicts from county jail, forensic medicine institute, and hospital **Enrollment period:** Addicts born from 1945 to 1966 **Design:** Case control ************************* **Inclusion criteria:** • Opiate addict and siblings from one of three sources • Birth records available **Exclusion criteria:** • Siblings who were also drug addicts or brought up outside family	**Groups:**[1] **G1a:** Opiate addicts whose mothers received N_2O during labor **G1b:** Nonaddict siblings of addicts, whose mothers may also have received N_2O during labor **G2a**[2]**:** Addicts whose mothers may have received opiates and/or barbiturates during labor **G2b**[2]**:** Nonaddict siblings of addicts, whose mothers may have received opiates and/or barbiturates during labor. **N at enrollment:** **G1a:** 145 **G1b:** 174 **G2a:** 200 **G2b:** 230 **N at followup:** **G1a:** 145 **G1b:** 174 **G2a:** 200 **G2b:** 230 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** Maternal: NR Neonatal: NR Childhood: Duration of N_2O exposure of mothers during labor, hours, n (%): $\leq$ 0.25 hours: **G1a:** 22 (15.2) **G1b:** 44 (25.3) > 0.25 to $\leq$ 1 hour: **G1a:** 30 (20.7) **G1b:** 46 (26.4) > 1.0 to < 2.5 hours: **G1a:** 32 (22.1) **G1b:** 32 (18.4) $\geq$ 2.5 to < 4.5 hours: **G1a:** 30 (20.7) **G1b:** 30 (17.2) $\geq$ 4.5 hours: **G1a:** 31 (21.4) **G1b:** 22 (12.6) Opiate addiction in offspring, relative risk for N_2O exposure of > 1 to < 2.5

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				hours (95% CI): Matched: **G1a/G1b:** 1.6 (0.95, 2.6) Unmatched: **G1a/G1b:** 1.7 (1.2, 2.3)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Jacobson et al., 1990 (continued)				Time between last administration of opiates and/or barbiturates and delivery, hours, n (%): ≤ 0.5 hours: **G2a:** 1 (0.5) **G2b:** 2 (0.9) > 0.5 to ≤ 1.5 hours: **G2a:** 6 (3) **G2b:** 2 (0.9) > 1.5 to ≤ 4.5 hours: **G2a:** 23 (11.5) **G2b:** 16 (7) > 4.5 to ≤ 10 hours: **G2a:** 13 (6.5) **G2b:** 6 (2.6) > 10 hours: **G2a:** 18 (9) **G2b:** 16 (7) No administration, n (%): **G2a:** 150 (75) **G2b:** 194 (84.3) Opiate addiction in offspring, relative risk for single dose of opiates, (95% CI): Matched: **G2a/G2b:** 1.6 (0.75, 3.6) Unmatched: **G2a/G2b:** 1.8 (0.94, 3.5) Opiate addiction in offspring, relative risk for single dose of barbituates, (95% CI): Matched: **G2a/G2b:** 1.7 (0.97, 3.0)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Unmatched: **G2a/G2b:** 1.6 (0.97, 2.6) Occupational: NR

Comments:

[1] Those subjects in G2 not in G1 were missing data for administration of nitrous oxide.

[2] Opiate doses were 0.01-0.02g morphine or 0.05-0.1 g pethidine hydrochloride, barbiturates doses as 0.05-2g phenobarbitone (and some other barbiturates not described)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Jacobson et al., 1988 **Country:** Sweden **Participant source:** Community **Setting:** Other (custody center for arrests) **Enrollment period:** 11/1986 to 09/1987 **Design:** Case control ************************* Inclusion criteria: • Adult amphetamine addicts born between 1945 and 1966 • Born in any of the seven largest hospitals in Stockholm • Brought up at home by biological mother **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Addicts whose mothers were given N_2O during delivery (mix and administration NR) **G2:** Nonaddicted siblings as controls **N at enrollment:** **G1:** 200 **G2:** 195 **N at followup:** NR **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, %:** Duration of nitrous oxide analgesia: ≥ 4.5 hours: **G1:** 18.4 G2: 7.1 ≥ 2.5 to < 4.5 hours: **G1:** 21.3 **G2:** 20.8 > 1 to < 2.5 hours: **G1:** 19.9 **G2:** 16.9 > 0.25 to ≤ 1 hour: **G1:** 23.4 **G2:** 27.3 ≤ 0.25 hour: **G1:** 17.0 **G2:** 27.9	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n:** Vaginal: NR Assisted: NR Cesarean: **G1:** 0 **G2:** 0	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Adverse effects:** Maternal: NR Neonatal: NR Childhood: Amphetamine addiction in offspring, relative risk for N_2O exposure ≥ 4.5 hours (95% CI): Males: **G1/G2:** 8.2 (1.2, 55.2) Females: **G1/G2:** 3.6 (0.96,15.8) Amphetamine addiction in offspring, relative risk for N_2O exposure: ≥ 4.5 hours: **G1/G2:** 5.6[1] ≥ 2.5 to < 4.5 hours: **G1/G2:** NR[1] > 1 to < 2.5 hours: **G1/G2:** NR[1] > 0.25 to ≤ 1 hour: **G1/G2:** NR[1] ≤ 0.25 hour: **G1/G2:** 1.0 Occupational: NR

Comments:

[1] Data only displayed graphically. Observed relative risks for all exposure levels fall within the 95% confidence intervals of estimated risks determined from logistic regression analysis.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Jones et al., 1969 **Country:** United Kingdom **Participant source:** NR **Setting:** Hospital **Enrollment period:** 05/1962 to 11/1967 **Design:** RCT ************************* **Inclusion criteria:** • Normal delivery **Exclusion criteria:** • Those who had received instruction in psychoprophylaxis or hypnosis	**Groups:** **G1:** N_2O in O_2 (calibrated in 5% steps from 20% to 100% O_2 and checked at continuous flows up to 40 liters/ minute) **G2:** Methoxyflurane in O_2 enriched air (40% O_2 with a flow of about 30 liters/minute) Both administered by observer **N at enrollment:** **G1:** 24 **G2:** 24 **Age, mean yrs ± SD:** **G1:** 25.0 ± 5.0 **G2:** 24.4 ± 5.9 **Race/ethnicity:** NR **Parous, n (%*):** **G1:** 13 (54) **G2:** 13 (54)	**Provider preferences:** NR **Provider specialty, %:** Midwife: **Total:** 100 **Cost of intervention:** NR **Other pain management methods available:** Pethidine given within 4 hours of inhalation **Pain management, n (%*):** Pethidine: **G1:** 11 (45.8) **G2:** 14 (58.3) Duration of inhalation, minutes, mean ± SD: **G1:** 83 ± 66.3 **G2:** 82.5 ± 72.8	**Pain:** Anesthetist's assessment of analgesia, mean % of time satisfactory ± SD: All factors: **G1:** 70.9 ± 17.6 **G2:** 73.8 ± 26.3 All factors, pethidine within 4 hours of inhalation: **G1:** 72.9 ± 19.0 **G2:** 67.5 ± 29.6 All factors, no pethidine: **G1:** 69.3 ± 16.0 **G2:** 82.6 ± 18.8 Reactions to contractions: **G1:** 77.2 ± 14.7 **G2:** 81.4 ± 22.3 Level of consciousness: **G1:** 94.5 ± 7.2 **G2:** 94.0 ± 8.7 Restlessness: **G1:** 97.2 ± 6.4 **G2:** 92.1 ± 14.7 Anesthetist's assessment of analgesia, all factors, mean % of time satisfactory, n (%): 0-59: **G1:** 2 (8) **G2:** 3 (13) 60-69: **G1:** 4 (17) **G2:** 3 (13) 70-79: **G1:** 8 (33) **G2:** 2 (8) 80-89: **G1:** 5 (21) **G2:** 4 (16) 90-100: **G1:** 5 (21) **G2:** 12 (50) **G1/G2:** *P* < 0.05	**Satisfaction with pain management, n (%):** Midwife report: Complete pain relief: **G1:** 2 (9) **G2:** 9 (38) **G1/G2:** *P* < 0.05 Complete or considerable pain relief: **G1:** 15 (65) **G2:** 20 (83) Maternal report, immediately after delivery: Complete pain relief: **G1:** 4 (18) **G2:** 7 (29) Considerable pain relief: **G1:** 15 (68) **G2:** 12 (50) Slight pain relief: **G1:** 3 (14) **G2:** 4 (17) No pain relief: **G1:** 0 **G2:** 1 (4) Pain relief complete or considerable, 48 hours post delivery: **G1:** 19 (83) **G2:** 22 (92) **Satisfaction with birth experience, n (%):** Better than previous labour, multiparae: **G1:** 6 (46) **G2:** 8 (62) **Neonatal status:** Apgar score, 1 minute: **G1:** NR **G2:** NR **G1/G2:** *P* = NS

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Adverse effects: Maternal: Too drowsy, midwife report, n (%*) **G1:** 3 (12.5) **G2:** 3 (12.5)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Jones et al., 1969 (continued)			Anesthetist's assess-ment of analgesia, all factors, mean % of time satisfactory: First stage: **G1:** 71.2 **G2:** 73.8 Second stage: **G1:** 73.8 **G2:** 71.2 Third stage: **G1:** 67.5 **G2:** 62.0 30 minutes before delivery: **G1:** 66.7 **G2:** 73.1 **Labor progress:** Duration of second stage labor, minutes, mean ± SD: **G1**: 32.0 ± 23.4 **G2**: 36.7 ± 25.3 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n (%):** Vaginal: **G1:** 19 (79) **G2:** 19 (79) Assisted: **G1:** 5 (21) **G2:** 5 (21) Cesarean: **G1:** 0 **G2:** 0	Blood loss, midwife estimate, ml, mean (range): **G1:** 160 (25-500) **G2:** 176 (30-500) Vomiting, n (%): During labor (asses-sed immediately after delivery): **G1:** 4 (17) **G2:** 0 At some point during labor or in succeeding 24 hours (assessed 36-48 hours after delivery): **G1:** 6 (25) **G2:** 4 (17) Nausea, n (%): During labor (asses-sed immediately after delivery): **G1:** 8 (35) **G2:** 2 (8) At some point during labor or in succeeding 24 hours (assessed 36-48 hours after delivery): **G1:** 13 (54) **G2:** 5 (21) **G1/G2:** $P < 0.05$ Memory of labor and delivery (assessed 36-48 hours after delivery): **G1:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				G2: NR **G1/G2:** *P* = NS Neonatal, n: Fetal distress: **G1:** 1 **G2:** 0 Neonatal deaths: **Total:** 2 Childhood: NR Occupational: NR

Comments:

* Calculated by reviewer.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Jones et al., 1969 **Country:** United Kingdom **Participant source:** NR **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************ **Inclusion criteria:** • Normal delivery **Exclusion criteria:** • Received instruction in psychoprophylaxis or hypnosis	**Groups:** **G1:** N_2O in O_2 (50%/50%) **G2:** Methoxyflurane (0.35%) in air Both self-administered intermittently. **N at enrollment:** **G1:** 25 **G2:** 25 **N at followup:** NR **Age, mean yrs ± SD:** **G1:** 26.5 ± 7.2 **G2:** 24.1 ± 5.1 **Race/ethnicity:** NR **Primiparous, n (%):** **G1:** 9 (36) **G2:** 11 (44)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Other analgesic (pethidine) or sedative drugs were given by the midwife on her usual indications. **Pain management n (%*):** Pethidine: **G1:** 17 (68) **G2:** 16 (64) Mean duration of inhalation, minutes, mean ± SD: **G1:** 66.1 ± 39.2 **G2:** 90.1 ± 67.5 **G1/G2:** *P* = NS	**Pain, n:** Anesthetist's assessment of analgesia, mean % of time satisfactory ± SD: All factors: **G1:** 61.5 ± 29.9 **G2:** 78.1 ± 20.1 **G1/G2:** $P < 0.05$ All factors, pethidine within 4 hours of inhalation: **G1:** 61.3 ± 30.8 **G2:** 85.4 ± 12.8 **G1/G2:** $P < 0.01$ All factors, no pethidine: **G1:** 60.5 ± 32.7 **G2:** 65.1 ± 24.6 **G1/G2:** *P* = NS Reactions to contractions: **G1:** 62.3 ± 30 **G2:** 79.3 ± 20 **G1/G2:** $P < 0.05$ Level of consciousness: **G1:** 98.9 ± 2.2 **G2:** 98.7 ± 3.7 Restlessness: **G1:** 98.5 ± 4.2 **G2:** 99.4 ± 1.4 Anesthetist's assessment of analgesia, all factors, mean % of time satisfactory, n (%): 0-59: **G1:** 11(44) **G2:** 4 (16) 60-69: **G1:** 2 (8) **G2:** 4 (16) 70-79: **G1:** 2 (8) **G2:** 2 (8) 80-89: **G1:** 6 (24) **G2:** 5 (20) 90-100: **G1:** 4 (15) **G2:** 10 (40) **Labor progress:**	**Satisfaction with pain management, n (%):** Midwife report: Complete pain relief: **G1:** 2 (8) **G2:** 4 (16) Complete or considerable pain relief: **G1:** 18 (72) **G2:** 21 (84) Adequately cooperative: **G1:** 24 (96) **G2:** 24 (96) Satisfactory (restless assessment): **G1:** 15 (60) **G2:** 17 (68) Maternal report, immediately after delivery: Complete pain relief: **G1:** 4 (16) **G2:** 7 (28) Considerable pain relief: **G1:** 16 (64) **G2:** 14 (56) Slight pain relief: **G1:** 5 (20) **G2:** 4 (16) No pain relief: **G1:** 0 **G2:** 0 Labor worse than expected, n (%): (36 to 48 hours after delivery) Time 1: **G1**: 10 (40) **G2**: 4 (16) **G1/G2:** *P* = NS Time 2: **G1:** 9 (36) **G2:** 2 (8) **G1/G2:** $P < 0.05$

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G1: NR[1] **G2:** NR[1]	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Jones et al., 1969 (continued)			Fetal status: NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	**Labor better than previous labors, multiparae, n (%):** (36 to 48 hours after delivery) Time 1: **G1:** 4 (25) **G2:** 9 (64) **G1/G2:** *P* = NS Time 2: **G1:** 12 (86) **G2:** 5 (31) **G1/G2:** *P* < 0.01 **Maternal Status, n (%):** Remembered labor clearly (vs. hazily): **G1:** 17 (68) **G2:** 17 (68) Remembered actual delivery clearly: **G1:** 10 (40) **G2:** 17 (68) Thought they had fallen asleep during inhalation: **G1:** 8 (32) **G2:** 4 (16) Smell noted with inhalation: **G1:** 4 (16) **G2:** 25 (100) Dreams experienced: **G1:** 6 (24) **G2:** 4 (16) Other sensations: **G1:** 9 (36) **G2:** 2 (8) **G1/G2:** *P* < 0.05 **Neonatal status:** Apgar scores, 1-10 minutes after delivery: **G1:** NR[2] **G2:** NR[2]

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Jones et al., 1969 (continued)				**Adverse effects:** Maternal: Blood loss, midwife estimate, ml, mean ± SD: **G1:** 144.0 ± 149 **G2:** 186.7 ± 101 Vomiting during labor (assessed immediately after delivery), n (%): **G1:** 2 (8) **G2:** 0 Nausea during labor (assessed immediately after delivery), n (%): **G1:** 8 (32) **G2:** 0 **G1/G2:** *P* < 0.01 Nausea or vomiting at some point during labor (assessed subsequently), n (%): **G1:** 8 (32) **G2:** 4 (16) **G1/G2:** *P* = NS Neonatal: NR Childhood: NR Occupational: NR

Comments:

* Calculated by reviewer.

[1] The progress of labor in the two groups was similar, though the first stage of labor was shorter in G1.

[2] There were no differences between the agents as demonstrated by the Apgar scores at 1, 2, 5, or 10 minutes.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Landon et al., 1992 **Country:** United Kingdom **Participant source:** NR **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** • Healthy • Uncomplicated pregnancy **Exclusion criteria:** • Preeclampsia • Metabolic or haematological disease • IUGR • Abnormalities of the placenta • Pregnancy did not progress normally to full-term delivery	**Groups:** **G1:** Vaginal birth and Entonox **G2:** Vaginal birth without N_2O **N at enrollment:** **G1:** 45 **G2:** 13 **N at followup:** **G1:** 45 **G2:** 13 **Age, mean yrs:** **G1:** 27.5 **G2:** 29.4 **Race/ethnicity, n:** Asian: **G1:** 16 **G2:** 3 **Parous, n:** **G1:** 21 **G2:** 8	**Provider preferences:** NR **Provider specialty:** NR Cost of intervention: NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress,** Duration of labor, hours, mean ± SD: **G1:** 6.2 ± 2.8 **G2:** 5.5 ± 3.0 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n (%):** Vaginal: **G1:** 45 (100) **G2:** 13 (100) Assisted: **G1:** 0 **G2:** 0 Cesarean: **G1:** 0 **G2:** 0	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** Hb, g/dl, mean ± SD: **G1:** 12.8 ± 1.2 **G2:** 12.7 ± 0.67 Mean cell volume, fl, mean ± SD: **G1:** 86.8 ± 14.5 **G2:** 90.4 ± 3.1 **Neonatal status:** Birth weight, kg, mean ± SD: **G1:** 3.3 ± 0.45 **G2:** 3.1 ± 0.45 Apgar score, mean ± SD: 1 minute: **G1:** 8.5 ± 1.1 **G2:** 8.5 ± 0.9 5 minutes: **G1:** 9.3 ± 0.5 **G2:** 9.4 ± 0.5 **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Leong et al., 2000 **Country:** Malaysia **Participant source:** Academic single setting **Setting:** Hospital **Enrollment period:** NR Design: Prospective cohort[1] ************************* **Inclusion criteria:** • Randomly selected healthy primigravid women at term (37-41 weeks) • Cervical dilation not exceeding 4 cm • Cephalic presentation • Presenting to labor between 0800 and 1000 hours **Exclusion criteria:** • Complications such as previous uterine surgery • Pre-existing illness • Hypertension • Abnormal admission cardiotocography • Contraindictions to an epidural	**Groups:** **G1:** Inhalational Entonox (nitrous) and IM pethidine routine; 75-100 mg IM pethidine every 4-6 hours with Entonox (these patients declined an epidural) **G2:** Epidural with initial dose of 4-6 ml of 0.25% bupivacaine followed by mainten-ance dose of 6-10 ml/hour of 0.125% bupivacaine with 0.0002% fentanyl (selected by patients) **N at enrollment:** (enrolled in labor between 0800 and 1000 hours) **G1:** 68 **G2:** 55 **N at followup:** **G1:** 68 **G2:** 50 **Age, mean yrs:** **G1:** 24.9 **G2:** 25.5 **Race/ethnicity, %:** Chinese: **G1:** 20.6 **G2:** 30.9 Indian: **G1:** 11.8 **G2:** 14.6 Malay: **G1:** 67.7 **G2:** 54.6 **Parous:**	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress, mean duration of labor, min, mean:** First stage: **G1:** 483.4 (n=65) **G2:** 565.8 **G1/G2:** $P < 0.02$ Second stage: **G1:** 36.3 (n=65) **G2:** 60.2 **G1/G2:** $P < 0.03$ Third stage: **G1:** 5.8 (n=65) **G2:** 6.3 **G1/G2:** P = NS Total duration of labor: **G1:** 525.5 (n=65) **G2:** 631.6 **G1/G2:** $P < 0.03$ **Fetal status:** NR **Timeliness:** NR **Labor co-interventions, n (%):** Oxytocin augmentation: **G1:** 38 (55.9) **G2:** 48 (87.3) G1/G2: $P < 0.01$ Continuous cardiotocography: **G1:** 68 (100) **G2:** 55 (100) **Adverse effects, n (%):**	**Satisfaction with pain management, n (%):** (day after birth) Happy with method and would repeat in next pregnancy: **G1:** NR (35.3) **G2:** NR (69) Unhappy and unsatisfied with pain method: **G1:** 31 (45.6) **G2:** 3 (5.5) **Satisfaction with birth experience:** NR **Maternal status:** NR[2] **Neonatal status:** NR[3] **Adverse effects, n:** Maternal: Voiding difficulties requiring repeat catheterization: **G1:** 0 **G2:** 2 Neonatal: NR Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	NR		Maternal: Ascension of epidural block to T3/T4: **G1:** 0 (NR) **G2:** 1 (NR) Spinal headache requiring blood patch: **G1:** 0 **G2:** 2 (3.6) Backache requiring oral analgesics: **G1:** 0 **G2:** 2 (3.6)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Leong et al., 2000 (continued)			Neonatal: Occipito-transverse position in second stage of labor: **G1:** 0 **G2:** 8 (1.8) Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 56 (82.4) **G2:** 28 (50.9) Forceps assisted: **G1:** 5 (7.3) **G2:** 13 (23.6) Vacuum assisted: **G1:** 4 (5.9) **G2:** 9 (16.5) Cesarean: **G1:** 3 (4.4) **G2:** 5 (9.0) G1/G2: P = NS Total instrumental delivery rate: **G1:** NR (13.2) **G2:** NR (40.1) G1/G2: $P < 0.01$	

Comments:

[1] Patients were randomly selected from those meeting inclusion criteria, but chose whether to be in epidural group.

[2] No significant difference in time to full ambulation or time to spontaneously void urine.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Marx et al., 1970 **Country:** U.S. **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** • Parturients with unremarkable prenatal courses **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Vaginal delivery **G2:** Elective repeat cesarean section **N at enrollment:** **G1:** 26 **G2:** 14 **N at followup:** **G1:** 26 **G2:** 14 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** **G1:** N_2O (ranging from 50-70%) and O_2 by mask in a semiclosed system with circle absorber plus local anesthesia **G2:** Anesthetized with 150-250 mg thiopental followed by N_2O-O_2 via endotracheal tube and 0.1% succinyl-choline by IV infusion	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n:** Vaginal: **G1:** 16 **G2:** 0 Assisted, forceps: **G1:** 10 **G2:** 0 Cesarean: **G1:** 0 **G2:** 14	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Umbilical vein blood N_2O levels, vol % range: **Total:** 11.2-28.8 Apgar score < 6, 1 minute, n: 6 or less: **G1:** 3 **G2:** 1 Apgar score 9-10, 5 minutes, n (%): **Total:** 40 (100) **Adverse effects:** Maternal: NR Neonatal, n: Severe fetal acidosis: **G1:** 3 **G2:** 0 High fetal N_2O level with normal acid-base values: **G1:** 0 **G2:** 1 Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: McAneny and Doughty 1963 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** Nonrandomized trial ************************* **Inclusion criteria:** • English speaking women in labor **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** 50% N_2O in O_2 **G2:** 60% N_2O in O_2 **G3:** 70% N_2O in O_2 **G4:** 75% N_2O in O_2 **G5:** 80% N_2O in O_2 **N at enrollment:** **G1:** 101 **G2:** 101 **G3:** 100 **G4:** 101 **G5:** 98 **Total:** 501 **N at followup:** **G1:** 101 **G2:** 101 **G3:** 100 **G4:** 101 **G5:** 98 **Age:** NR **Race/ethnicity:** NR **Parous, n (%):** Primigravidae: **Total:** 342 (68.3) Multigravidae: **Total:** 159 (31.7)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, %:** Multiple analgesics by injection: **G1:** 30.0 **G2:** 26.0 **G3:** 22.0 **G4:** 29.0 **G5:** 33.0	**Pain, %:** Considerable and complete relief, mothers report: **G1:** 52.0 **G2:** 64.0 **G3:** 74.0 **G4:** 76.0 **G5:** 75.5 **G1/G3:** $P < 0.01$ First stage, midwife report: Complete relief: **G1:** 8.0 **G2:** 6.0 **G3:** 14.0 **G4:** 12.0 **G5:** 7.0 Complete or adequate relief: **G1:** 92.0 **G2:** 92.0 **G3:** 90.0 **G4:** 88.0 **G5:** 92.0 Second stage, midwife report: Complete relief: **G1:** 18.0 **G2:** 10.0 **G3:** 12.0 **G4:** 9.0 **G5:** 11.0 Complete or adequate relief: **G1:** 94.0 **G2:** 92.0 **G3:** 94.0 **G4:** 92.0 **G5:** 93.0 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR	**Satisfaction with pain management:** One day after labor: Only 2 mothers reported no pain during labor About 40% of mothers reported that the pain was worse than expected **Satisfaction with birth experience, %:** One day after labor: Would tolerate the same labor again: **G1:** 82.0 **G2:** 81.0 **G3:** 89.0 **G4:** 87.0 **G5:** 75.5 **G3/G5:** $P < 0.02$ Were comfortable late in 1st stage of labor: **G1:** 55.0 **G2:** 66.0 **G3:** 63.0 **G4:** 56.0 **G5:** 60.0 Were comfortable while pushing in 2nd stage: **G1:** 72.0 **G2:** 74.0 **G3:** 74.0 **G4:** 73.0 **G5:** 74.0 Were comfortable at the actual birth: **G1:** 76.0 **G2:** 82.0 **G3:** 86.0 **G4:** 88.0 **G5:** 83.0 **Maternal status:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Adverse effects: Maternal, (%):	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
McAneny and Doughty 1963 (continued)			Unconsciousness: **G1:** 1.0 **G2:** 3.0 **G3:** 1.0 **G4:** 5.0 **G5:** 5.0 Restless or noisy: **G1:** 21.0 **G2:** 14.0 **G3:** 15.0 **G4:** 16.0 **G5:** 23.0 Any complications: **G1:** 25 .0 **G2:** 27.0 **G3:** 20.0 **G4:** 19.0 **G5:** 24.5 Hemorrhage: **G1:** 8.5 **G2:** 8.5 **G3:** 6.5 **G4:** 4.0 **G5:** 5.0 Hazy or no memory of labor: **G1:** 43.0 **G2:** 53.0 **G3:** 57.0 **G4:** 53.0 **G5:** 49.0 Hazy or no memory of birth: **G1:** 15.0 **G2:** 25.0 **G3:** 26.0 **G4:** 31.0 **G5:** 26.0 **G1/G4:** $P < 0.02$ Dreamed while breathing gas: **G1:** 8.0 **G2:** 12.0 **G3:** 18.0 **G4:** 21.0 **G5:** 26.0 **G1/G5:** $P < 0.001$ Nausea or vomiting: **G1:** 16.0 **G2:** 15.0 **G3:** 22.0 **G4:** 22.0 **G5:** 18.5 Neonatal: NR	**Neonatal status:** Mean Apgar score: **G1:** 9.1 **G2:** 8.6 **G3:** 8.9 **G4:** 8.6 **G5:** 8.9 **Adverse effects:** Maternal: NR Neonatal: Death: **G1:** One neonatal death 9 hours after delivery Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Occupational: NR	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
McAneny and Doughty 1963 (continued)			**Route of birth, %:** Vaginal: NR Assisted:[1] **G1:** 15.0 **G2:** 18.0 **G3:** 11.5 **G4:** 10.5 **G5:** 17.0 Cesarean: NR	

Comments:

[1] Forceps

Evidence Table1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: McGuiness and Rosen, 1984 **Country:** United Kingdom **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Crossover RCT At onset of regular uterine contractions, each participant was randomly dministered one agent during 3 consecutive uterine contractions, followed by the other agent for 3 further contractions (the agent was concealed to the operator). ************************* **Inclusion criteria:** • Fit women • Age 20 to 33 • Early normal labor **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Women delivered two gas mixtures via the same tubing and mouthpiece **Ga:** Entonox (50% N_2O in O_2) **Gb:** Enflurane 1% in air (delivered from a low resistance drawover Cyprane vaporizer) **Gc:** No analgesia **N at enrollment:** (during early normal labor) **G1:** 20 **N at followup:** **G1:** 20 **Age, range yrs:** **G1:** 20-33 **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** Linear analog score, median (range): **G1a:** 52 (29-79) **G1b:** 50 (13-79) **G1c:** 61 (47-87) **G1a/G1b**: $P < 0.02$ **G1a/G1c:** P = NR[1] **G1b/G1c:** P = NR[1] Linear analog score, n (%): 0-20: **G1a:** 0 **G1b:** 1 (5.0) **G1c:** 0 20-40: **G1a:** 4 (20.0) **G1b:** 7 (35.0) **G1c:** 0 40-60: **G1a:** 10 (50.0) **G1b:** 6 (30.0) **G1c:** 10 (50.0) 60-80: **G1a:** 6 (30.0) **G1b:** 6 (30.0) **G1c:** 6 (30.0) 80-100: **G1a:** 0 **G1b:** 0 **G1c:** 4 (20.0) **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:**	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Maternal: Drowsiness, linear analog score, median (range): **G1a:** 26 (0-68) **G1b:** 38 (0-88) **G1a/G1b:** *P* < 0.02 Slightly nauseous, n (%): **G1a:** 1 (5.0) **G1b:** 3 (15.0)	

Evidence Table1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
McGuiness and Rosen, 1984 (continued)			Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 15 (75.0) Assisted, forceps: **G1:** 2 (10.0) Cesarean: **G1:** 3 (15.0)	

Comments:

[1] The authors state that the difference is significant, but do not report the significance level used.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: McLeod et al., 1985 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** Crossover RCT ************************* **Inclusion criteria:** • Women aged18-38 • ASA group I • Normal labor **Exclusion criteria:** • Use of any other analgesic or sedative agent during labor	**Groups:** **G1:** Women given both agents in random sequence during 5 consecutive uterine contractions, with a break of 2 contrac-tions to allow for elimination of first agent **Ga:** Entonox (50% N_2O in O_2) **Gb:** Isoflurane (0.75% in O_2) Both self-administered using separate facemasks **N at enrollment:** (in established labor) **G1:** 32 **N at followup:** (end of trial) **G1:** 32 **Age, range yrs:** **G1:** 18-38 **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** Linear analog scores, mean (range): Prior to analgesia: **G1:** 75.4 (44-99) Post analgesia: **G1a:** 63.0 (24-92) **G1b:** 46.6 (19-86) **G1a/G1b:** *P* < 0.001 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n (%):** Maternal:[1] Drowsiness, assessed by midwife and patient: More drowsy when using Entonox: **G1:** 3 (9.7) More drowsy when using isoflurane: **G1:** 18 (58.1) Equal between agents: **G1:** 10 (32.2) Nausea, n: **G1a:** 1 **G1b:** 1 Dizziness, n: **G1a:** 2 **G1b:** 0 Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 32 (100)	**Satisfaction with pain management, n (%):** Preference at the end of the trial: Entonox: **G1:** 8 (25.0) Isoflurane: **G1:** 22 (68.8) No preference: **G1:** 2 (6.3) **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Assisted: **G1:** 0 Cesarean: **G1:** 0	

Comments:
[1] Results of 31 participants included.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Mills et al., 1996 **Country:** United Kingdom **Participant source:** Multisite **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** • Midwives working in labor wards in one of two selected UK hospitals **Exclusion criteria:** • See inclusion criteria	**Groups:** Midwives working in labor wards at one of two hospitals (DRI and BDGH) and wearing N_2O personal sampling devices **N at enrollment:** DRI: 5 midwives/shift BDGH: 4 midwives/shift **N at followup:** 242 total shifts analyzed **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty, %:** Midwives: 100 **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: NR Neonatal: NR Occupational: N_2O exposure, mean ppm (range): **DRI:** 45 (0-413) **BDGH:** 124 (0-1638) **Total:** 86 (0-1638) In 111 shifts worked in rooms where Entonox was not used: Mean ppm (range): **Total:** 22 (0-233) Exceed exposure level, n (%): > 100 ppm: **Total:** 4 (3.6) > 25 ppm: **Total:** 21 (18.9) **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Morgan et al., 1982 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** Cross-sectional ************************* **Inclusion criteria:** • Vaginal delivery of a live child **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Entonox, self administered **G2:** 100 mg Pethidine and 25 mg promethazine IM **G3:** Entonox and pethidine **G4:** Pudendal block **G5:** Epidural **G6:** Epidural and Entonox **G7:** Epidural and pethidine **G8:** Miscellaneous (ineffective epidural blocks or other analgesia, various IM and IV opiates, and regional blocks) **G9:** None **N at enrollment:** **Total:** 1,000 **G1:** 128 **G2:** 120 **G3:** 88 **G4:** 24 **G5:** 423 **G6:** 38 **G7:** 47 **G8**: 52 **G9:** 80 **N at followup:** (within 48 hours of delivery) **Total:** 1,000 **Age, mean yrs ± SD:** **Total:** 28 ± 4.8	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, n (%):** Entonox: **Total:** 128 (12.8) Pethidine: **Total:** 120 (12.0) Entonox and pethidine: **Total:** 88 (8.8) Pudendal block: **Total:** 24 (2.4) Epidural: **Total:** 423 (42.3) Epidural and Entonox: **Total:** 38 (3.8) Epidural and pethidine: **Total:** 47 (4.7) Miscellaneous: **Total:** 52 (5.2) None: **Total:** 80 (8.0)	**Pain:** (linear analogue scale 0-100 mm)[1] Linear analogue score, mean ± SD: **G1:** 61 ± 3.1 **G2:** 58 ± 3.1 **G3:** 57 ± 3.4 **G4:** 68 ± 1.9 **G5:** 29 ± 3.7 **G6:** 51 ± 4.2 **G7:** 30 ± 3.8 **G8:** 69 ± 3.3 **G9:** 70 ± 2.6 Painless labor, n (%): **G1:** 15 (11.7) **G2:** 15 (12.5) **G3:** 16 (18.2) **G4:** 2 (8.3) **G5:** 251 (59.3) **G6:** 13 (34.2) **G7:** 29 (61.7) **G8:** 7 (13.5) **G9:** 6 (7.5) Duration of pain, minutes, mean: **G1:** 47 **G2:** 66 **G3:** 71 **G4:** 73 **G5:** 35 **G6:** 66 **G7:** 56 **G8:** 75 **G9:** 50 **Labor progress, n (%):** Induced:	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	Race/ethnicity: NR **Parous, n (%):** **Total:** 496 (49.6)		**G1:** 21 (16.4) **G2:** 22 (18.3) **G3:** 16 (18.2) **G4:** 4 (16.7) **G5:** 148 (35.0) **G6:** 12 (31.6) **G7:** 12 (25.5) **G8:** 21 (40.4) **G9:** 9 (11.3)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Morgan et al., 1982 (continued)			Duration, hours, mean ± SD: **G1:** 6.7 ± 3.0 **G2:** 7.3 ± 3.2 **G3:** 7.6 ± 4.1 **G4:** 5.6 ± 4.2 **G5:** 10.5 ± 4.6 **G6:** 8.6 ± 4.7 **G7:** 13.1 ± 6.1 **G8:** 10.7 ± 4.9 **G9:** 5.2 ± 3.5 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n (%):** Vaginal:* **G1:** 120 (93.7) **G2:** 111 (92.5) **G3:** 83 (94.3) **G4:** 20 (83.3) **G5:** 206 (48.7) **G6:** 23 (60.5) **G7:** 22 (46.8) **G8:** 11 (21.2) **G9:** 79 (98.7) Assisted: **G1:** 8 (6.3) **G2:** 9 (7.5) **G3:** 5 (5.7) **G4:** 4 (16.7) **G5:** 217 (51.3) **G6:** 15 (39.5) **G7:** 25 (53.2) **G8:** 41 (78.8) **G9:** 1 (1.3)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Cesarean: **Total:** 0	

Comments:

* Calculated by reviewer.

[1] 0 (no pain) to 100 mm (as much pain as is possible to imagine).

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Murphy et al., 1984 **Country:** United Kingdom **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 1970 to 1979 **Design:** Retrospective cohort ************************* **Inclusion criteria:** • Live births from 1970-1979 • Data from Cardiff Births Survey • Residents of South Glamorgan **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O 50%/O_2 50% (Entonox) used for maternal analgesia, administration not specified **G2:** Drugs and N_2O (Entonox) used for maternal analgesia **G3:** Drugs only (mainly pethidine) used for maternal analgesia **G4:** Epidural block used for maternal analgesia **G5:** No analgesia used **Ga:** Gave birth from 1970-1974 **Gb:** Gave birth from 1975-1979 **N at enrollment:** **G1:** 8,392 **G1a:** 3,798 **G1b:** 4,594 **G2:** 21,121 **G2a:** 12,375 **G2b:** 8,746 **G3:** 3,749 **G3a:** 2,855 **G3b:** 894 **G4:** 4,435 **G4a:** 1,235 **G4b:** 3,200 **G5:** 2,440 **G5a:** 1,562 G5b: 878 **N at followup:** **G1:** 8,392	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, singletons with no congenital anomalies, n:** Vaginal (vertex): **Total:** 30,172 **Ga:** 16,619 Gb: 13,553 Assisted, forceps: **Total:** 5,737 **Ga:** 2,752 Gb: 2,985 Cesarean: **Total:** 2,482 Ga: 1,038 G1b: 1,444 Elective: **Total:** 856 Ga: 411 Gb: 445 Emergency: **Total:** 1,626 Ga: 627 Gb: 999	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status, n (%):** Lower of 1 and 5 minute Apgar scores, singletons with no congenital anomalies: 1-3: **G1a:** 66 (1.8) **G1b:** 63 (1.4) **G2a:** 330 (2.7) **G2b:** 220 (2.6) **G3a:** 121 (4.4) **G3b:** 25 (2.7) **G4a:** 38 (3.1) **G4b:** 48 (1.5) **G5a:** 26 (1.7) G5b: 13 (1.5) 4-7: **G1a:** 389 (10.5) **G1b:** 388 (8.7) **G2a:** 2270 (18.8) **G2b:** 1594 (18.6) **G3a:** 586 (21.2) **G3b:** 149 (17.0) **G4a:** 274 (22.4) **G4b:** 509 (16.5) **G5a:** 183 (121) G5b: 72 (8.5) 8-10: **G1a:** 3242 (87.7) **G1b:** 3997 (89.9) **G2a:** 9484 (78.5) **G2b:** 6772 (78.8) **G3a:** 2063 (74.4) **G3b:** 700 (80.3) **G4a:** 911 (74.5) **G4b:** 2527 (82.0)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	G2: 21,121 **G3:** 3,749 **G4:** 4,435 **G5:** 2,440 **Age:** NR **Race/ethnicity:** NR **Parous, n:**[1] Primaparae: **G1a:** 642 **G1b:** 894 **G2a:** 5,667			**G5a:** 1299 (86.1) G5b: 767 (90.0) **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Murphy et al., 1984 (continued)	**G2b:** 3,806 **G3a:** 1,211 **G3b:** 313 **G4a:** 837 **G4b:** 2,101 **G5a:** 315 G5b: 125 **Ga:** 8,672 **Gb:** 7,239 Multiparae: **G1a:** 3,120 **G1b:** 3,644 **G2a:** 6,599 **G2b:** 4,893 **G3a:** 1,616 **G3b:** 577 **G4a:** 397 **G4b:** 1,048 **G5a:** 1,185 G5b: 753 **Ga:** 12,917 Gb: 10,915		Singleton births: **G1:** 8,145 **G1a:** 3,697 **G1b:** 4,448 **G2:** 20,670 **G2a:** 12,084 **G2b:** 8,586 **G3:** 3,644 **G3a:** 2,770 **G3b:** 874 **G4:** 4,307 **G4a:** 1,223 **G4b:** 3,084 **G5:** 2,360 **G5a:** 1,508 G5b: 852	

Comments:

[1] Parity was not known for 236 of women in Ga and 158 women in Gb.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Newton et al., 1999 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** NR **Design:** Cross-sectional ************************* **Inclusion criteria:** • Midwife participating in the care of women using Entonox during labor in a specific UK hospital **Exclusion criteria:** See inclusion criteria	**Groups:** **G1:** Midwives participating in the care of women wearing samplers to measure N_2O levels over 8 hrs **N at enrollment:** 16 **N at followup:** 15 **Age, mean yrs :** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** Midwife: 16 (100) **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: NR Neonatal: NR Occupational: No midwife was exposed to levels of N_2O greater than 100ppm **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Nyberg et al., 1992 **Country:** Sweden **Participant source:** Other (see inclusion criteria) **Setting:** Other (see inclusion criteria) **Enrollment period:** 1945 to 1966 **Design:** Case control ************************* **Inclusion criteria:** • Amphetamine or opiate addict • Brought to Stockholm City Custody • Opiate addict from autopsy victims at the State Institute of Forensic Medicine in Stockholm • Opiate addict accepted for the methadone program at Ulleraker Hospital **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1a:** Amphetamine addicts **G1b:** Control siblings **G2a:** Opiate addicts **G2b:** Control siblings **N at enrollment:** **G1a:** 200 **G1b:** NR **G2a:** 200 **G2b:** NR **N at followup:** **G1a:** 73 **G1b:** 109 **G2a:** 139 **G2b:** 230 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** Maternal: NR Neonatal: NR Childhood: Amphetamine addiction in offspring, relative risk for exposure to N_2O (95% CI): ≥ 4.5 hrs: **G1:** 4.4 (1.2,15.8) ≥ 2.5 to < 4.5 hrs: **G1:** 3.1 (1.2,7.9) > 1 to < 2.5 hrs: **G1:** 2.1 (1.11, 4.0) > 0.25 to ≤ 1 hr: **G1:** 1.5 (1.06, 2.0) 0 to ≤ 0.25 hr: **G1:** 1.0 Opiate addiction in offspring, relative risk for exposure to N_2O (95% CI): **G2:** NR[1] Occupational: NR

Comments:

[1] In group G2, nitrous oxide is combined with opiate and barbiturate exposure. After controlling for socio-economic level and civil status of the mother at time of delivery, the conditional logistic regression analysis confirms that administration of opiate or barbiturate or nitrous oxide during delivery is a risk factor for adult amphetamine addiction in offspring, and that the number

of administrations of either opiates, barbiturates or nitrous oxide for >1 hour, or any combination thereof, is a risk factor for opiate addiction.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Paech, 1991 **Country:** Australia **Participant source:** NR **Setting:** Hospital **Enrollment period:** NR **Design:** Cross-sectional ************************* **Inclusion criteria:** • Vaginal birth **Exclusion criteria:** • See inclusion criteria	**Groups:*** **G1:** N_2O alone **G2:** Pethidine and N_2O **G3:** N_2O and epidural **G4:** Pethidine alone **G5:** Pethidine and epidural **G6:** Epidural alone **G7:** Several methods[1] **G8:** Nonpharmacological **Ga:** N_2O **Gb:** Pethidine **Gc:** Epidural **Gd:** No epidural **N at enrollment:** (day after vaginal birth) **G1:** 220 **G2:** 175 **G3:** 84 **G4:** 83 **G5:** 86 **G6:** 112 **G7:** 100 **G8:** 140 **Ga:** NR* **Gb:** NR* **Gc:** NR* **Gd:** NR* **N at followup:** **G1:** 220 **G2:** 175 **G3:** 84 **G4:** 83 **G5:** 86 **G6:** 112 **G7:** 100 **G8:** 140 **Ga:** NR[1]	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Antenatal preparation classes, on-demand epidural service, along with noted available treatments **G8:** Transcutaneous nerve stimulation (TENS) **Pain management:** NR	**Pain, n (%):** VAS < 25: **G1:** NR[2] **G4:** NR[2] **G6:** NR[2] **G8:** NR[2] **G6/G1:** $P < 0.0001$ **G6/G4:** $P < 0.0001$ **G6/G8:** $P < 0.0001$ **Gc/Gd:** $P < 0.0001$ VAS < 50: **G1:** NR[2] **G4:** NR[2] **G6:** NR[2] **G8:** NR[2] **G6/G1:** $P < 0.0001$ **G6/G4:** $P < 0.0001$ **G6/G8:** $P < 0.0001$ **Gc/Gd:** $P < 0.0001$ More than expected: **G1:** 93 (42) **G2:** 97 (55) **G3:** 38 (45) **G4:** 47 (57) **G5:** 40 (47) **G6:** 33 (29) **G7:** 60 (60) **G8:** 46 (33) **Labor progress:** Duration of labor, minutes, mean ± SD:	**Satisfaction with pain management:** VAS > 75: **G1:** NR[2] **G4:** NR[2] **G6:** NR[2] **G8:** NR[2] **Gc:** NR[2] **Gd:** NR[2] **G6/G1:** $P < 0.0001$ **G6/G4:** $P < 0.0001$ **G6/G8:** $P < 0.0001$ **Gc/Gd:** $P < 0.0001$ VAS = 100: **G1:** NR[2] **G4:** NR[2] **G6:** NR[2] **G8:** NR[2] **Gc:** NR[2] **Gd:** NR[2] **G6/G1:** $P < 0.0001$ **G6/G4:** $P < 0.0001$ **G6/G8:** $P < 0.0001$ **Gc/Gd:** $P < 0.0001$ **Satisfaction with birth experience, n (%):** (day after birth) Dissatisfied: **Total:** 51 (5.1) **Gc:** NR (7) **Gd:** NR (4) **Gc/Gd:** P = NS **Maternal status:** NR **Neonatal status:** NR **Adverse effects:**

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	Gb: NR[1] **Gc:** NR[1] **Gd:** NR[1] **Age:** NR **Race/ethnicity:** NR		First stage: **G1:** 291 ± 191 **G2:** 338 ± 200 **G3:** 397 ± 189 **G4:** 328 ± 195 **G5:** 501 ± 250 **G6:** 397 ± 223 **G7:** 507 ± 292 **G8:** 244 ± 155 Second stage: **G1:** 29 ± 32 **G2:** 40 ± 37 **G3:** 79 ± 60 **G4:** 36 ± 35 **G5:** 98 ± 70 **G6:** 73 ± 58 **G7:** 87 ± 67 **G8:** 24 ± 31 **Fetal status:** NR	NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Paech, 1991 (continued)	**Parous, n (%):** Primapara: **G1:** 50 (23) **G2:** 86 (49) **G3:** 40 (48) **G4:** 38 (46) **G5:** 66 (77) **G6:** 56 (50) **G7:** 82 (82) **G8:** 22 (16) Multipara: **G1:** 170 (77) **G2:** 89 (51) **G3:** 44 (52) **G4:** 45 (54) **G5:** 20 (23) **G6:** 56 (50) **G7:** 18 (18) **G8:** 118 (84)		**Timeliness:** NR **Labor co-interventions, n (%):** Induced or augmented: **G1:** 91 (41) **G2:** 99 (57) **G3:** 65 (77) **G4:** 31 (37) **G5:** 69 (80) **G6:** 90 (80) **G7:** 80 (80) **G8:** 43 (31) **Adverse effects, %:** Maternal: Inadequate pain relief: **Ga:** 21 **Gb:** 27 **Gc:** 7 **G8:** 6 **Gc/Ga:** $P < 0.0001$ **Gc/Gb:** $P < 0.0001$ **G8/Ga:** $P < 0.0001$ **G8/Gb:** $P < 0.0001$ Reduced awareness of experience: **Ga:** 18 **Gb:** 16 **Gc:** 2 **G8:** 0 Nausea and vomiting: **Ga:** 13 **Gb:** 16	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Gc: 14 **G8:** 0 Dizziness: **Ga:** 5 **Gb:** 6 **Gc:** 0 **G8:** 0 Drowsiness **Ga:** 4 **Gb:** 11 **Gc:** 0 **G8:** 0 Mask phobia: **Ga:** 5 **Gb:** 0 **Gc:** 0 **G8:** 0 Shivering: **Ga:** 0 **Gb:** 0 **Gc:** 19 **G8:** 0	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Paech, 1991 (continued)			Back pain: **Ga:** 0 **Gb:** 0 **Gc:** 14 **G8:** 0 Difficulty moving: **Ga:** 0 **Gb:** 0 **Gc:** 14 **G8:** 0 Pruritus: **Ga:** 0 **Gb:** 0 **Gc:** 8 **G8:** 0 Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 204 (93) **G2:** 152 (87) **G3:** 49 (58) **G4:** 76 (92) **G5:** 47 (55) **G6:** 58 (52) **G7:** 56 (56) **G8:** 135 (96) Assisted: **G1:** 16 (7) **G2:** 23 (13) **G3:** 35 (42) **G4:** 7 (8) **G5:** 39 (45) **G6:** 54 (48) **G7:** 44 (44) **G8:** 5 (4) Cesarean: **Total:** 0	

Comments:

[1] The author states that almost all women in G7 had pethidine and nitrous oxide, followed by epidural analgesia. If this was the case for all women in G7, then the number of women in Ga, Gb, and Gc would be 579, 444 and 382, respectively.

[2] Results only displayed graphically.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Phillips and Macdonald, 1971 **Country:** United Kingdom **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************* **Inclusion criteria:** • Fetus at extra risk of intrapartum hypoxia during labor • Primigravidae aged ≥ 35 or multigravidae aged ≥ 40 • Previous stillbirth due to intrauterine hypoxia • Pregnancy prolonged beyond 41 weeks • Maternal diabetes, preeclampsia, threatened abortion or antepartum hemorrhage during current pregnancy • Small-for-dates fetus, *or* • Low urinary estrogen excretion **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** 50% N_2O/50% O_2 (Entonox; delivery NR) and pethidine **G2:** Pethidine alone (no inhaled analgesia) **G3:** Trichloroethylene and pethidine **N at enrollment:** **G1:** 50 **G2:** 51 **G3:** 51 **N at followup:** (neonatal capillary blood collected) **G1:** 30 **G2:** 30 **G3:** 28 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	Provider preferences: NR **Provider specialty:** NR Cost of intervention: NR Other pain management methods available: NR **Pain management:** NR	Pain: NR Labor progress: NR **Fetal status:** Fetal scalp blood pH, mean ± SD: Before inhaled analgesia: **G1:** 7.253 ± 0.065 (n=49) **G2:** 7.256 ± 0.064 (n=50) **G3:** 7.256 ± 0.053 After inhaled analgesia: **G1:** 7.244 ± 0.071 (n=49) **G2:** 7.241 ± 0.066 (n=50) **G3:** 7.216 ± 0.057 Fetal scalp blood PCO_2, mean ± SD: Before inhaled analgesia: **G1:** 37.0 ± 8.1 (n=49) **G2:** 39.8 ± 6.1 **G3:** 34.9 ± 5.9 After inhaled analgesia: **G1:** 35.0 ± 7.0 (n=49) **G2:** 41.8 ± 4.8 **G3:** 41.3 ± 7.7 Fetal scalp blood base deficit, mean ± SD: Before inhaled analgesia: **G1:** -9.3 ± 3.7	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Apgar score, mean: 1 minute: **G1:** 7.42 **G2:** 6.70 **G3:** 6.17 5 minutes: **G1:** 9.20 **G2:** 8.85 **G3:** 8.43 Apgar score, 1 minute, n: 4: **G1:** 0 **G2:** 3 **G3:** 9 5: **G1:** 0 **G2:** 0 **G3:** 1 6 : **G1:** 21 **G2:** 27 **G3:** 27 7: **G1:** 0 **G2:** 0 **G3:** 0 8: **G1:** 20 **G2:** 21 **G3:** 14 9: **G1:** 5 **G2:** 0 **G3:** 0 10: **G1:** 4 **G2:** 0

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G2: -10.2 ± 2.1 **G3:** -8.6 ± 2.2 After inhaled analgesia: **G1:** -9.7 ± 2.4 **G2:** -11.6 ± 1.9 **G3:** -10.7 ± 1.6	**G3:** 0

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Phillips and Macdonald, 1971 (continued)			Fetal scalp blood PO_2, mean ± SD: Before inhaled analgesia: **G1:** 27.8 ± 4.6 **G2:** 26.1 ± 6.5 (n=50) **G3:** 30.0 ± 5.8 After inhaled analgesia: **G1:** 28.7 ± 6.2 **G2:** 22.7 ± 5.7 (n=50) **G3:** 24.6 ± 4.0 **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth:** NR	Apgar score, 5 minutes, n: 4-5: **G1:** 0 **G2:** 0 **G3:** 0 6: **G1:** 0 **G2:** 1 **G3:** 5 7: **G1:** 0 **G2:** 1 **G3:** 0 8: **G1:** 19 **G2:** 18 **G3:** 30 9: **G1:** 2 **G2:** 15 **G3:** 0 10: **G1:** 29 **G2:** 16 **G3:** 16 Fetal and neonatal capillary blood pH, mean (SE): Before treatment: **G1:** 7.249 (0.012) **G2:** 7.233 (0.011) **G3:** 7.259 (0.011) After treatment: **G1:** 7.246 (0.011) **G2:** 7.226 (0.009) **G3:** 7.235 (0.010) 45/60 minutes after birth: **G1:** 7.274 (0.009) **G2:** 7.250 (0.007) **G3:** 7.188 (0.012)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Phillips and Macdonald, 1971 (continued)				Fetal and neonatal capillary blood base excess, mean (SE): Before treatment: **G1:** -8.8 (0.06) **G2:** -11.0 (0.4) **G3:** -8.2 (0.3) After treatment: **G1:** -9.1 (0.5) **G2:** -12.2 (0.3) **G3:** -10.7 (0.3) 45/60 minutes after birth: **G1:** -9.1 (0.5) **G2:** -8.2 (0.3) **G3:** -11.4 (0.3) Fetal and neonatal capillary blood PO_2, mean (SE): Before treatment: **G1:** 27.0 (1.1) **G2:** 26.8 (1.1) **G3:** 31.7 (1.2) After treatment: **G1:** 29.3 (0.9) **G2:** 21.6 (0.8) **G3:** 25.3 (1.1) 45/60 minutes after birth: **G1:** 64.0 (2.0) **G2:** 46.4 (1.2) **G3:** 44.8 (0.9) **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Ranta et al., 1995 **Country:** Finland **Participant source:** Academic multisite Community **Setting:** Hospitals **Enrollment period:** 04/1992 to 07/1992 Design: Cross-sectional ************************* **Inclusion criteria:** • All pregnant women admitted for vaginal delivery during the study period **Exclusion criteria:** • Elective cesareans	**Groups:** **G1:** 50/50 N_2O/O_2 mix by face mask **G2:** Pethidine 50-75 mg IM administered by midwife **G3:** Paracervical block with 0.25% bupivacaine 5 ml on each side of cervix, administered by obstetrician G4: Segmental epidural analgesia administered by an anesthetist; initially bupivacaine 0.25% 5-10 ml with intermittent top-ups in 42% and continuous infusion in 52%. **G5:** No analgesia **Ga:** Primiparous **Gb:** Multiparous, 2-4 **Gc:** Multiparous, 5-17 **N at enrollment:** (admitted to delivery room at the beginning of labor) **Total:** 1,091 **G1:** NR[1] **G2:** NR[1] **G3:** NR[1] G4: NR[1] G5: 213 **Ga:** 360 **Gb:** 468 Gc: 45 **N at followup:** (pain score measurements were obtained in the delivery room) **Total:** 833 (postpartum followup) **Total:** 1,024	**Provider preferences:** NR **Provider specialty, %:** Midwife: **Total:** 100 **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, %:** N_2O/O_2 mix: **Ga:** 20 **Gb:** 23 **Gc:** 18 Pethidine: **Ga:** 2 **Gb:** 0.4 **Gc:** 0 Paracervical block: **Ga:** 24 **Gb:** 24 **Gc:** 20 Epidural: **Ga:** 39 **Gb:** 5.3 **Gc:** 1 No analgesia: **Ga:** 17 **Gb:** 48 **Gc:** 61	**Pain, %:** (11-point Box Scale 1-10) High pain score (8-10) after analgesia in first stage of labor: **G1:** 46 **G2:** 5 **G3:** 23 **G4:** 5 Low pain score (0-2) after analgesia in first stage of labor: **G1:** 35 **G2:** 4 **G3:** 27 **G4:** 57 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions, %:** Induction of labor: **Total:** 8.7 **Adverse effects, %:** Maternal: Episiotomy: **Total:** 45 Peeineal laceration: **Total:** 29 Neonatal: NR Occupational: NR **Route of birth, %:** Vaginal, normal: **Total:** 80 Assisted: **Total:** 4.2 Cesarean, nonelective: **Total:** 7	**Satisfaction with pain management, %:** First stage: Very Good: **Total:** 45 Moderate: **Total:** 37 Poor: **Total:** 18 Second stage: Satisfied: **Total:** 53 **Satisfaction with birth experience, %:** Satisfied: **Total:** 95 Dissatisfaction to some degree: **Total:** 4 Compete dissatisfaction: **Total:** 1 **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	Age: NR **Race/ethnicity:** NR			

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Ranta et al., 1995 (continued)	**Parous:** Primiparous: **Total:** 360 **G5:** 30 Multiparous, 2-4: **Total:** 360 Multiparous, 5-17: **Total:** 360			

Comments:

[1] Numbers of patients in groups G1-4 can be calculated (approximately) from the percentages for pain management by parity group.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Ranta et al., 1994 **Country:** Finland **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 1992 **Design:** Prospective cohort Patients selected pain relief methods in agreement with obstetric staff. ************************* **Inclusion criteria:** • Intended to deliver vaginally **Exclusion criteria:** • Elective cesarean	**Groups:** **G1:** 50% N_2O and O_2 administered by midwife **G2:** Water block using 0.1 ml intracutaneous injections of sterile water at four points in lower back admini-stered by midwife **G3:** IM pethidine 1 mg/kg administered by midwife **G4:** Paracervical block with bilateral injection of 0.25% bupivacaine 5 ml **G5:** Epidural catheter induced with initial doses of 5-7 ml 0.25% bupivacaine (divided doses) and continued with 5 ml/hour infusion of same solution or further 5 ml top-ups, withheld after cervix was 8-10 cm dilated. **G6:** Several forms of analgesia[1] **G7:** No analgesia **N at enrollment:** (patients who had attended antenatal	**Provider preferences:** NR **Provider specialty:** **G1:** Midwives admini-stered N_2O **G2:** Midwives admini-stered water blocks **G3:** Midwives admini-stered pethidine **G4:** Obstetricians administered paracervical blocks **G5:** Anesthetists administered epidural **G6:** NR **G7:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain, median (IQR):** (VAS from 0=no pain to 10=intolerable pain) First stage, before treatment (baseline): **G1:** 6 (5-7) **G2:** 6 (5-7) **G3:** 5 (4-7) **G4:** 7 (6-8) **G5:** 7 (6-8) **G6:** 7 (5-8) **G7:** 6 (5-7) **G4/G1-3:** $P < 0.01$ **G4/G7:** $P < 0.01$ **G5/G1-3:** $P < 0.01$ **G5/G7:** $P < 0.01$ **G6/G1-3:** $P < 0.01$ **G6/G7:** $P < 0.01$ First stage, after treatment: **G1:** 8 (6-9) **G2:** 7 (6-8) **G3:** 8 (7-8) **G4:** 6 (4-8) **G5:** 2 (1-4) **G6:** 7 (5-7) **G7:** NR **G1/BL:** $P < 0.01$ **G2/BL:** $P < 0.01$ **G3/BL:** $P < 0.01$ **G4/BL:** $P < 0.01$ **G5/BL:** $P < 0.0001$ Second stage: **G1:** 8 (6-9) **G2:** 7 (5-9) **G3:** 8 (5-9) **G4:** 8 (5-9) **G5:** 7 (4-9) **G6:** 7 (5-9) **G7:** 7 (5-9) Third stage: **G1:** 3 (1-5) **G2:** 2 (1-4) **G3:** 2 (1-4) **G4:** 2 (1-4) **G5:** 2 (1-5) **G6:** 2 (1-4)	**Satisfaction with pain management, %:** (Verbal scale 0-5) Total pain experience, reported on the third day after delivery: No or mild (0-1): **G1:** 3 **G2:** 4 **G3:** 0 **G4:** 4 **G5:** 5 **G6:** 2 **G7:** 4 Moderate to severe (2-3): **G1:** 50 **G2:** 78 **G3:** 67 **G4:** 57 **G5:** 36 **G6:** 47 **G7:** 74 Very severe to intolerable (4-5): **G1:** 49 **G2:** 28 **G3:** 34 **G4:** 39 **G5:** 60 **G6:** 51 **G7:** 22 **G5/G1-4:** $P < 0.01$ **G5/G6-7:** $P < 0.01$ Adequacy of pain relief method: Good: **G1:** 33 **G2:** 59 **G3:** 60 **G4:** 59 **G5:** 94 **G6:** 32 **G7:** Not applicable Moderate: **G1:** 39 **G2:** 26 **G3:** 23 **G4:** 26 **G5:** 6 **G6:** 43 **G7:** Not applicable

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	clinics, selected pain relief method and consented to participation) **G1:** 210 **G2:** 69 **G3:** 50 **G4:** 128 **G5:** 82 **G6:** 339 **G7:** 213 **N at followup:** (during first, second and third stage) **G1:** 200 **G2:** 68 **G3:** 44 **G4:** 119 **G5:** 80 **G6:** 151 **G7:** 171		**G7:** 2 (0-4)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Ranta et al., 1994 (continued)	**Age, mean yrs (range):** **Total:** 28.6 (16-47) **Race/ethnicity:** NR **Parous, %:** Primiparous: **G1:** 27 **G2:** 14 **G3:** 26 **G4:** 23 **G5:** 71 **G6:** 49 **G7:** 13		**Labor progress:** Duration of labor, hours, mean ± SD: **G1:** 6.0 ± 3.3 **G2:** 5.8 ± 3.2 **G3:** 7.1 ± 4.5 **G4:** 6.7 ± 3.9 **G5:** 10.8 ± 4.9 **G6:** 9.3 ± 4.9 **G7:** 6.5 ± 2.9 **Fetal status:** pH < 7.15, umbilical artery, % (N=616): **G1:** 9 **G2:** 15 **G3:** 6 **G4:** 6 **G5:** 4 **G6:** 4 **G7:** 9 **Timeliness, %:** Received analgesia within ½ hour of request: **G1-4:** 72 **G5:** 63 Had to wait more than one hour for analgesia after requesting it: **G1:** 19 **G2:** 10 **G3:** 5 **G4:** 9 **G5:** 26 **G6:** NR **Labor co-interventions, %:** Induced labor: **G1:** 10 **G2:** 3 **G3:** 9 **G4:** 13 **G5:** 15 **G6:** 11 **G7:** 5 **Adverse effects:** NR	Poor: **G1:** 28 **G2:** 15 **G3:** 17 **G4:** 15 **G5:** 0 **G6:** 15 **G7:** Not applicable **G5/G1-4:** *P* < 0.01 **G5/G6-7:** *P* < 0.01 **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status, %:** Apgar score ≤ 7: 1 minute: **G1:** 7 **G2:** 10 **G3:** 9 **G4:** 3 **G5:** 6 **G6:** 6 **G7:** 11 5 minutes: **G1:** 1 **G2:** 3 **G3:** 0 **G4:** 3 **G5:** 4 **G6:** 3 **G7:** 1 **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Ranta et al., 1994 (continued)			**Route of birth, %:** Vaginal:* **G1:** 95 **G2:** 90 **G3:** 91 **G4:** 93 **G5:** 80 **G6:** 86 **G7:** 94 Assisted, vacuum extraction: **G1:** 2 **G2:** 3 **G3:** 2 **G4:** 4 **G5:** 11 **G6:** 7 **G7:** 1 Cesarean: **G1:** 3 **G2:** 7 **G3:** 7 **G4:** 3 **G5:** 9 **G6:** 7 **G7:** 5	

Comments:

* Calculated by reviewer.

[1] Authors state that almost all patients in G6 first received water blocks and/or pethidine and/or N_2O followed by a paracervical (n=123, 36%) or epidural (n=84, 25%) block.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Reed et al., 1989 **Country:** United Kingdom **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Case series ************************* **Inclusion criteria:** • Caucasian • Normal medical and obstetric histories • Did not intend to request extradural analgesia **Exclusion criteria:** • Those who subsequently received extradural analgesia • Those who delivered within one hour	**Groups:**[1] **G1a:** N_2O (Entonox, 50% N_2O in O_2) only in the first stage of labor **G1b:** Pethidine plus N_2O (Entonox) in the first stage of labor **G2:** Pethidine only in first stage of labor **G3:** No analgesia **N at enrollment:** **Total:** 41 **N at followup:** **G1a:** 6 **G1b:** 20 **G2:** 7 **G3:** 0 **Age:** NR **Race/ethnicity, %:** Caucasian: **Total:** 100 **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** See groups.	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: Hypoxic episodes: **G1a:** 5/6 **G1b:** 9/20 **G2:** 2/7 Duration of monitoring, minutes:* **G1a:** 520 **G1b:** 1,819 **G2:** 1,677 **G3:** 2,452 Hypoxic episodes per hour of monitoring:* **G1a:** 0.57 **G1b:** 1.4 **G2:** 0.43 **G3:** 0.049 Neonatal: NR Occupational: NR **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Comments:

[1] Participants assigned to groups *a posteriori*. Indicated results refer to total minutes in which analgesia was nitrous oxide, pethidine, nitrous oxide plus pethidine, or no analgesia.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Rosen et al., 1972 **Country:** United Kingdom **Participant source:** Academic multisite **Setting:** Hospital **Enrollment period:** NR **Design:** RCT ************************* **Inclusion criteria:** • NR for either study within this paper **Exclusion criteria:** • NR for either study in the paper	**Groups:** **G1:** Study 1 **G2:** Study 2 **Ga:** N_2O mix and delivery 50% N_2O and 50% O_2 (Entonox) **Gb:** Methoxyflurane 0.35% **N at enrollment:** (day prior to labor) **G1a:** 25 **G1b:** 25 (day of discharge from labor ward) **G2a:** 100 **G2b:** 100 **N at followup:** (entire 6 days) **G1a:** 19 **G1b:** 20 **G2a:** 100 **G2b:** 100 **Age, mean yrs ± SD:** **G1a:** 23.6 ± 5.4 **G1b:** 26.9 ± 7.1 **G2a:** 25.5 ± 5.9 **G2b:** 24.5 ± 5.3 **Race/ethnicity:** NR **Parous, n:** Primagravidas: **G1a:** 18 **G1b:** 15 **G2a:** 36 **G2b:** 47	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, mean ± SD:** Maternal: Blood urea, mg/100 ml, before delivery: **G1a:** 16.0 ± 4.5 **G1b:** 16.3 ± 7.3 **G1a/G1b:** *P* = NS Urinary/blood urea ratio, before delivery: **G1a:** 71.0 ± 22.3 **G1b:** 80.8 ± 43.2 **G1a/G1b:** *P* = NS Serum osmolality, before delivery, mOsm/kg: **G1a:** 289.7 ± 7.7 **G1b:** 290.7 ± 7.5 **G1a/G1b:** *P* = NS Urinary/serum osmolality ratio, before delivery: **G1a:** 1.88 ± 0.68 **G1b:** 1.92 ± 0.93 **G1a/G1b:** *P* = NS Packed cell volume, before delivery, mean % ± SD: **G1a:** 38.6 ± 2.5 **G1b:** 37.5 ± 3.1 **G1a/G1b:** *P* = NS Neonatal: NR Occupational: NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status, n (%):** Blood urea, mg/100 ml, mean ± SD: 1st day after delivery: **G1a:** 20.0 ± 6.9 **G1b:** 16.6 ± 5.2 **G1a/G1b:** *P* = NS 2nd-3rd day after delivery: **G1a:** 21.4 ± 5.7 **G1b:** 21.3 ± 6.3 **G1a/G1b:** *P* = NS 4th-6th day after delivery: **G1a:** 21.0 ± 5.2 **G1b:** 20.8 ± 4.4 **G1a/G1b:** *P* = NS Day of discharge: **G2a:** NR* **G2b:** NR* **G2a/G2b:** *P* = NS Urinary/blood urea ratio, mean ± SD: 1st day after delivery: **G1a:** 57.3 ± 27.1 **G1b:** 55.2 ± 31.8 **G1a/G1b:** *P* = NS 2nd-3rd day after delivery: **G1a:** 73.4 ± 27.3 **G1b:** 70.5 ± 28.6 **G1a/G1b:** *P* = NS 4th-6th day after delivery: **G1a:** 81.4 ± 24.9 **G1b:** 67.2 ± 29.1 **G1a/G1b:** *P* = NS Day of discharge: **G2a:** NR[1] **G2b:** NR[1] **G2a/G2b:** *P* = NS Serum osmolality, mOsm/kg, mean ± SD: 1st day after delivery: **G1a:** 288.5 ± 7.1

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Route of birth: NR	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Rosen et al., 1972 (continued)				**G1b:** 291.8 ± 5.7 **G1a/G1b:** *P* = NS 2nd-3rd day after delivery: **G1a:** 294.5 ± 4.4 **G1b:** 294.6 ± 5.9 **G1a/G1b:** *P* = NS 4th-6th day after delivery: **G1a:** 294.7 ± 3.8 **G1b:** 295.4 ± 5.0 **G1a/G1b:** *P* = NS Urinary/serum osmolality ratio, mean ± SD: 1st day after delivery: **G1a:** 1.69 ± 0.85 **G1b:** 1.49 ± 0.62 **G1a/G1b:** *P* = NS 2nd-3rd day after delivery: **G1a:** 2.17 ± 0.75 **G1b:** 2.09 ± 0.66 **G1a/G1b:** *P* = NS 4th-6th day after delivery: **G1a:** 2.22 ± 0.59 **G1b:** 2.04 ± 0.61 **G1a/G1b:** *P* = NS Packed cell volume, mean % ± SD: 1st day after delivery: **G1a:** 38.5 ± 4.8 **G1b:** 37.8 ± 3.8 **G1a/G1b:** *P* = NS 2nd-3rd day after delivery: **G1a:** 35.5 ± 4.4 **G1b:** 34.6 ± 5.2 **G1a/G1b:** *P* = NS 4th-6th day after delivery: **G1a:** 37.2 ± 3.1 **G1b:** 35.2 ± 5.7 **G1a/G1b:** *P* = NS Mean hospital stay, days: **G2a:** 5.5 **G2b:** 5.3 **Neonatal status:** NR **Adverse effects:** NR

Comments:
[1] Results only displayed graphically.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Rosen et al., 1969 **Country:** United Kingdom **Participant source:** Community **Setting:** Maternity units **Enrollment period:** NR **Design:** Nonrandomized trial Choice of drug for the day was randomized on a calendar present in labor room, with Sundays labeled as open choice of midwife. ************************* **Inclusion criteria:** • Mothers **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O 50% /O_2 50% given by Entonox apparatus **G2:** Trichloroethylene (0.5% and 0.35% in air) **G3:** Methoxyflurane (0.35% in air) **N at enrollment:** **G1:** 265 **G2:** 394 **G3:** 598 **N at followup:** **G1:** 265 **G2:** 394 **G3:** 598 **Age:** NR **Race/ethnicity:** NR **Parous, n (%):** Multiparae: **G1:** 130 (49) **G2:** 226 (57.5) **G3:** 347 (58)	**Provider preferences:** Choice of agent on Sundays, n (%): **G1:** 47/180 (26) **G2:** 32/180 (18) **G3:** 101/180 (56) Midwives response to questionnaire (n=77): In favour of use, before trial began, %: **G1:** 85 **G2:** 50 **G3:** NR Methoxyflurane is improvement over chosen agent, after experience of trial, %: **G1:** 53 **G2:** 78 **G3:** NA **Provider specialty, %:** Midwife: **Total:** 100 **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management, n (%):** No additional drugs: **G1:** 87 (33) **G2:** 151 (38) **G3:** 238 (40) Pethidine: **G1:** 166 (63) **G2:** 228 (58) **G3:** 333 (56) Others: **G1:** 12 (4) **G2:** 15 (4) **G3:** 27 (4)	**Pain relief, n (%):** (scale NR) Maternal report, immediately after delivery: Complete: **G1:** 29 (11) **G2:** 47 (12) **G3:** 69 (11.5) Considerable: **G1:** 161 (61) **G2:** 235 (60) **G3:** 352 (59) Slight: **G1:** 66 (25) **G2:** 98 (25) **G3:** 154 (26) None: **G1:** 9 (3) **G2:** 14 (3) **G3:** 23 (3.5) Midwife report: Excellent:[1] **G1:** 19 (7) **G2:** 43 (11) **G3:** 81 (14) **G1/G3:** $P < 0.01$ Good:[1] **G1:** 92 (35) **G2:** 148 (38) **G3:** 235 (39) Adequate: **G1:** 129 (49) **G2:** 161 (41) **G3:** 225 (38) Inadequate: **G1:** 25 (9) **G2:** 42 (10) **G3:** 57 (9) **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:**	**Satisfaction with pain management:** NR **Satisfaction with birth (labor) experience, n (%):** Maternal report, multiparous: Better: **G1:** 45 (35) **G2:** 94 (42) **G3:** 189 (55) **G1/G3:** $P < 0.001$ **G2/G3:** $P < 0.01$ Same: **G1:** 33 (25) **G2:** 66 (29) **G3:** 62 (18) Worse: **G1:** 18 (14) **G2:** 29 (22) **G3:** 32 (9) Don't know: **G1:** 9 (3) **G2:** 44 (19) **G3:** 34 (26) **Maternal status:** NR **Neonatal status:** Apgar score, 1 minute, pethidine within 4 hours of inhalation: **G1:** NR[2] **G2:** NR[2] **G3:** NR[2] **Adverse effects:** Maternal: Nausea/felt sick, %: **G1:** 19 **G2:** 22 **G3:** 23 Vomited, %: **G1:** 7.5 **G2:** 6 **G3:** 7.5 Restlessness, midwife report, n (%): Never: **G1:** 95 (36)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
		Duration of inhalation, minutes, mean: **G1:** 103.14 **G2:** 97.15 **G3:** 91.19	NR **Route of birth, n (%):** Vaginal:	**G2:** 153 (39) **G3:** 242 (41) Short periods:

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Rosen et al., 1969 (continued)		**G1/G3:** *P* < 0.02 Midwives opinion on concentration of agents, n (%): Satisfied: **G1:** 213 (79) **G2:** 299 (76) **G3:** 412 (69) **G1/G3:** *P* < 0.001 **G2/G3:** *P* < 0.05 Requested stronger: **G1:** 36 (14) **G2:** 42 (11) **G3:** 72 (12) Requested weaker: **G1:** 5 (3) **G2:** 35 (9) **G3:** 64 (11) Don't know: **G1:** 11 (4) **G2:** 18 (4) **G3:** 50 (8) Reasons and incidence of inhalation abandoned, n (%): Ineffective: **G1:** 6 (2) **G2:** 6 (1.5) **G3:** 18 (9) Too powerful: **G1:** 1 (0.6) **G2:** 9 (2.2) **G3:** 12 (2) Obstetric reason: **G1:** 2 (0.8) **G2:** 6 (1.5) **G3:** 9 (1.5) Other: **G1:** 5 (1.8) **G2:** 33 (8) **G3:** 45 (7.5) Reasons and incidence of inhalation abandoned, also took pethidine, n (%): Ineffective: **G1:** 6/12 (50) **G2:** 4/37 (10.8) **G3:** 14/49 (28.5) Too powerful: **G1:** 1/12 (8.3) **G2:** 9/37 (24.3) **G3:** 5/49 (10.2) Obstetric reason:	**G1:** 235 (88.7) **G2:** 345 (87.6) **G3:** 525 (87.8) Assisted: **G1:** 30 (11.3) **G2:** 46 (11.7) **G3:** 68 (11.4) Cesarean: **G1:** 0 **G2:** 3 (0.8) **G3:** 5 (0.8)	**G1:** 157 (59) **G2:** 206 (52) **G3:** 310 (52) Long periods: **G1:** 13 (5) **G2:** 35 (9) **G3:** 46 (7) Cooperation, midwife report, n (%): Satisfactory: **G1:** 213 (81) **G2:** 298 (76) **G3:** 413 (69) **G1/G3:** *P* < 0.001 **G2/G3:** *P* < 0.05 Drowsy: **G1:** 38 (14) **G2:** 68 (17) **G3:** 135 (23) Too drowsy: **G1:** 6 (2) **G2:** 14 (4) **G3:** 29 (5) Asleep: **G1:** 1 (1) **G2:** 5 (1) **G3:** 13 (2) Uncooperative: **G1:** 7 (2) **G2:** 9 (2) **G3:** 8 (1) Neonatal, n (%): Apnoea, treatment: Artificial ventilation alone: **G1:** 8 (3.5) **G2:** 15 (3.5) **G3:** 13 (2.5) Artificial ventilation and tracheal intubation: **G1:** 6 (2) **G2:** 7 (2) **G3:** 19 (3) Apnoea, mortality:

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
		G1: 1/12 (8.3) **G2:** 3/37 (8.1)		**G1:** 2 (0.5) **G2:** 3 (0.5) **G3:** 3 (0.5) Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Rosen et al., 1969 (continued)		G3: 5/49 (10.2) Other: **G1:** 4/12 (33.3) **G2:** 34/37 (64.8) **G3:** 25/49 (51.0)		

Comments:

[1] **G3/G2:** $P < 0.01$ (excellent *or* good)

[2] Data only represented graphically. There were a significantly higher percentage of babies with a low Apgar score in G1 than in G2 (*P* < 0.01) or G3 (*P* < 0.05).

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Ross et al., 1999 **Country:** Scotland **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Uncontrolled trial ************************* **Inclusion criteria:** • Mother in labor • Selection of mothers for isoflurane with nitrous left to discretion of midwives **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** 50% N_2O / 50% O_2 (Entonox) mixed with isoflurane (IN_2O), given through a gas scavenging system **Ga:** Apgar score < 8 at 1 minute **Gb:** Agpar score 8-10 at 1 minute **Gc:** No resuscitation required **Gd:** Resuscitation required **N at enrollment:** (consented early in labor prior to need for a stronger agent than Entonox) **G1:** 221 **N at followup:** **G1:** 221 **Ga:** 74 **Gb:** 147 **Gc:** 162 **Gd:** 59 **Age, median yrs (range):** **G1:** 29 (16-43) **Race/ethnicity:** NR **Parous, n (%):** Primiparous: **G1:** 126 (57) Multiparous: **G1:** 93 (43) **Gestation, median weeks (range):** **G1:** 40 (34-42)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Opioids (either diamorphine 10 mg or morphine 15 mg given by intramuscular injection), pethidine **Pain management, n (%):** Epidural: **G1:** 32 (14.8) Opioids: **G1:** 173 (78.3) Pethidine: **G1:** 4 (1.8)	**Pain:** NR **Labor progress:** Duration of first stage, hours, median (IQR): **G1:** 9.13 (5.62-13.13) Duration of second stage, hours, median (IQR): **G1:** 0.70 (0.25-1.86) **Fetal status:** NR **Timeliness:** NR Labor co-interventions: NR **Adverse effects, n (%):** Maternal: Smelled: **G1:** 5 (2.3) Disliked: **G1:** 1 (0.4) Nausea: **G1:** 2 (0.9) Dizziness: **G1:** 2 (0.9) Drowsiness: **G1:** 2 (0.9) Neonatal: NR Occupational: NR **Route of birth, n:** Vaginal: **G1:** 151 Assisted (forceps or ventouse): Primiparous: **G1:** 49 Multiparous: **G1:** 9 Cesarean: Primiparous: **G1:** 12 Multiparous: **G1:** 0	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Apgar score < 8, 1 minute: **G1:** 74 Apgar score < 8, 5 minutes: **G1:** 6 Duration of IN_2O use, hours, median (IQR): **G1a:** 2.41 (1.15-4.12) **G1b:** 2.22 (0.90-4.23) **G1c:** 2.38 (0.92-4.38) **G1d:** 2.0 (1.15-4.0) IN_2O stopped less than 1 hour before delivery, n (%): **G1a:** 57 (33) **G1b:** 117 (67) **G1c:** 127 (73) **G1d:** 47 (27) IN_2O stopped more than 1 hour before delivery, n (%): **G1a:** 17 (36) **G1b:** 30 (67) **G1c:** 35 (75) **G1d:** 12 (25) Opioid use by mother, n (%): No opioid: **G1a:** 8 (17.6) **G1b:** 40 (83) **G1c:** 45 (94) **G1d:** 3 (6) Opioid less than 5 hrs before delivery, n (%): **G1a:** 40 (46) **G1b:** 48 (55) **G1c:** 48 (55) **G1d:** 40 (45)

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
				Opioid more than 5 hrs before delivery, n

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Ross et al., 1999 (continued)				(%): **G1a:** 26 (31) **G1b:** 59 (69) **G1c:** 69 (81) **G1d:** 16 (19) **Adverse effects:** Maternal: Blood loss, ml, median (IQR): **G1:** 200 (100-300) Blood loss, mean ml: **G1:** 241 Blood loss, n (%): 500-999 ml: **G1:** 26 (11.1) > 1000 ml: **G1:** 3 (1.3) Neonatal: Admission to special care baby unit, n: **G1**: 2 Tracheal tube, n: **G1:** 1 Mild respirator depression: **G1:** 1 Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Smith et al., 1968 **Country:** U.S. **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 08/1966 to 08/1967 **Design:** Nonrandomized trial ************************* **Inclusion criteria:** • Multiparous (except for comparison group) **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** N_2O (individualized, usual amount 2-4 L of 25-40% concentration) **G2:** Methoxyflurane (usual amount 12-30 ml, 0.2-0.5% setting on a Pentec vaporizer) **G3:** Cyclopropane (usual amount 60-300 ml, 1-5% concentra-tion) **G4:** Pudendal **G5:** Spinal **N at enrollment:** (during labor if analgesia needed in addition to local or pudendal nerve block) **G1:** 553 **G2:** 525 **G3:** 279 **G4:** 259 **G5:** 450 **N at followup:** NR[1] **Age, mean yrs:** NR **Race/ethnicity:** NR **Parous, n (%):** Primiparous: **G1:** 0 **G2:** 0 **G3:** 0 **G4:** 0 **G5:** 450 (100) Multiparous: **G1:** 553 (100) **G2:** 525 (100) **G3:** 279 (100) **G4:** 259 (100) **G5:** 0	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain, %:** (5 point scale 0-4)[2] Patient report: Score 0: **G1:** 4 **G2:** 4 **G3:** 4 Score 1: **G1:** 8 **G2:** 7 **G3:** 8 Score 2: **G1:** 10 **G2:** 16 **G3:** 14 Score 3: **G1:** 27 **G2:** 35 **G3:** 33 Score 4: **G1:** 50 **G2:** 38 **G3:** 40 Patient report, < 5 minutes administra-tion: Score 0: **G1:** 9 **G2:** 8 **G3:** 10 Score 1: **G1:** 13 **G2:** 12 **G3:** 10 Score 2: **G1:** 17 **G2:** 17 **G3:** 25 Score 3: **G1:** 20	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status, mean:** Apgar score, 1 and 5 minutes:[3] NR pO_2: **G1:** 19 (n=23) **G2:** 20 (n=30) **G3:** 23 (n=7) **G4:** 20 (n=17) pH: **G1:** 7.23 (n=23) **G2:** 7.25 (n=30) **G3:** 7.25 (n=7) **G4:** 7.29 (n=17) pCO_2: **G1:** 62 (n=23) **G2:** 55 (n=30) **G3:** 49 (n=7) **G4:** 46 (n=17) Buffer base: **G1:** 39 (n=23) **G2:** 38 (n=30) **G3:** 39 (n=7) **G4:** 40 (n=17) Standard bicarbonate: **G1:** 17 (n=23) **G2:** 17 (n=30) **G3:** 18 (n=7) **G4:** 18 (n=17) **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G2: 32 **G3:** 30 Score 4: **G1:** 41 **G2:** 31 **G3:** 25 Patient report, ≥ 5 minutes administra-tion: Score 0: **G1:** 1 **G2:** 1 **G3:** 3 Score 1: **G1:** 4	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Smith et al., 1968 (continued)			**G2:** 5 **G3:** 7 Score 2: **G1:** 6 **G2:** 16 **G3:** 11 Score 3: **G1:** 32 **G2:** 36 **G3:** 34 Score 4: **G1:** 57 **G2:** 42 **G3:** 44 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, %:** Maternal: Amnesia: **G1:** 11 **G2:** 8 **G3:** 11 Amnesia, < 5 minutes administration: **G1:** 16 **G2:** 4 **G3:** 5 Amnesia, ≥ 5 minutes administration: **G1:** 7 **G2:** 10 **G3:** 13	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Nausea and vomiting: **G1:** 3 **G2:** 13 **G3:** 0.5 **G1/G2:** *P* < 0.05 **G2/G3:** *P* < 0.001 Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 505 (91.3) **G2:** 441 (84.0)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Smith et al., 1968 (continued)			G3: 185 (66.3) **G4:** 241 (93.1) **G5:** 0 Assisted, low forceps: **G1:** 36 (6.5) **G2:** 76 (14.5) **G3:** 73 (26.2) **G4:** 12 (4.6) **G5:** 448 (99.6) Assisted, breech: **G1:** 12 (2.2) **G2:** 8 (1.5) **G3:** 21 (7.5) **G4:** 6 (2.3) **G5:** 2 (0.4) Cesarean: **Total:** 0	

Comments:

[1] Results for analgesia and amnesia scores note they include "all vaginal vertex deliveries in multiparous patients" so presumably these results exclude breech births.

[2] Patient analgesia score scale: 0=didn't help or made it worse, 1=only helped a little, 2=the anesthetic helped, 3=only a little pain, 4=no pain at all.

[3] Apgar scores at 1 and 5 minutes only displayed graphically.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Soyannwo, 1985 **Country:** Nigeria **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************* **Inclusion criteria:** • Participants in established labor **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Entonox administered via portable demand apparatus **G2:** 100 mg injection of pethidine or pethilorphan in early labor followed by Entonox inhalation **N at enrollment:** (during established labor) **G1:** 114 **G2:** 36 **N at followup:** (after labor) **G1:** 114 **G2:** 36 **Age, mean yrs:** **Total:** 27.2 **Race/ethnicity:** NR **Parous, n (%):** **Total:** 114 (76.0)	**Provider preferences:** NR **Provider specialty, n (%):** Resident anesthetist or midwife: **Total:** 150 (100) **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain, n (%):** Excellent relief: **G1:** 24 (21.1) **G2:** 12 (33.3) Good relief: **G1:** 74 (64.9) **G2:** 24 (66.7) Fair relief: **G1:** 14 (12.3) **G2:** 0 Poor relief: **G1:** 2 (1.7) **G2:** 0 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n (%):** Maternal: Drowsiness: Mild: **G1:** 76 (66.7) **G2:** 20 (55.6) Moderate: **G1:** 36 (31.6) **G2:** 16 (44.4) Severe: **G1:** 2 (1.7) **G2:** 0 Time for inhalation of Entonox, minutes, mean (range): Mild drowsiness: **Total:** 210 (45-320) Moderate drowsiness: **Total:** 340 (60-480) Vomiting:[1]	**Satisfaction with pain management, n (%):** (after delivery) Willing to use Entonox in subsequent deliveries: **Total:** 135 (90.0) **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status, n (%):** Apgar score 8-10, vaginal deliveries: **Total:** 136 (97.1) **Adverse effects:** Maternal: NR Neonatal: Apgar score < 5, vaginal deliveries: **Total:** 4 (2.9)[2] Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Total: 4 (2.7) Unconsciousness:[1] **Total:** 1 (0.7) Neonatal: NR Occupational: NR	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Soyannwo, 1985 (continued)			**Route of birth, n (%):** Vaginal: **Total:** 130 (86.7) Assisted, forceps or breech delivery: **Total:** 10 (6.7) Cesarean: **Total:** 10 (6.7)	

Comments:

[1] Groups unspecified but adverse effects due to Entonox inhalation.

[2] All breech deliveries and all resuscitated.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Stirk et al., 2002 **Country:** United Kingdom **Participant source:** Community **Setting:** Hospital **Enrollment period:** 02/1998 to 10/1998 **Design:** Prospective cohort ************************* **Inclusion criteria:** • Primigravida • ≥ 36 weeks' gestation **Exclusion criteria:** • Caesarean sections	**Groups:** **G1:** Entonox (mix and delivery method NR) **G2:** Diamorphine only **N at enrollment:** (chart review) **G1:** 45 **G2:** 70 **N at followup:** **G1:** 45 **G2:** 70 **Age:** NR **Race/ethnicity:** NR **Parous, n (%):** Primigravida: **G1:** 45 (100) **G2:** 70 (100)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** None **Pain management:** NR	**Pain:** NR **Labor progress:** Duration of labor, hours:minutes, mean (range):[1] **G1:** 5:00 (0:45-12:15) **G2:** 8:40 (1:45-20:15) **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** NR **Route of birth, n:** Vaginal: NR Assisted: NR Cesarean: **Total:** 0	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** Apgar score, mean: 1 minute: **G1:** 8.2 **G2:** 8.3 5 minutes: **G1:** 9.6 **G2:** 9.4 Length of hospital stay, days, mean: **G1:** 3 **G2:** 2 **Adverse effects, n (%):** Maternal: NR Neonatal: Neonatal unit admission: **G1:** 7 (18.4)[2] **G2:** 2 (2.8) **G1/G2:** $P < 0.027$ Given Narcan: **G1:** 5 (7) **G2:** 0 Given facial oxygen and intermittent positive pressure ventilation: **G1:** 3 (4.2) **G2:** 0 Childhood: NR Occupational: NR

Comments:

[1] The text reports the mean duration of labor for G2 as 8:20, but Figure 3 reports the value as 8:40.

[2] Text notes 7 out of 38 in G1 (18.4%) group were admitted, but the Figure 1 indicates that 38 were *not* admitted, so the correct value could be 7 out of 45 (15.6%).

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Talebi et al., 2009 **Country:** Iran **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 09/2004 to 09/2006 **Design:** RCT ************************* **Inclusion criteria:** • ASA I and II • 16 to 35 yrs old • Primigravid or second gravid, term (38 to 42 wks GA) parturients in active phase of labor (dilation > 4 cm) **Exclusion criteria:** • Evidence of fetal distress or abnormal heart rate pattern • GA < 37 wks or > 42 wks • Maternal cardiorespitory disease or any condition affecting the accuracy of pulse oximetry • History of taking opioids, administration of sedatives or regional analgesia • Unable to tolerate Entonox • Cesarean or forceps delivery	**Groups:** **G1:** 50% N_2O and O_2, self administered via facemask **G2:** 50% O_2, self administered via facemask **N at enrollment:**[1] (first request for analgesia) **Total:** 523 **N at followup:**[1] **G1:** 260 **G2:** 249 **Age, mean yrs ± SD:** **G1:** 24.2 ± 4.0 **G2:** 24.9 ± 4.7 **Race/ethnicity:** NR **Parous, n (%):** **G1:** 97 (37.3) **G2:** 123 (49.4)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** (VAS, at onset of active labor and hourly at 1-5 hours afterward) NR[2] **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, %:** Maternal: Nausea: **G1:** 8.4 **G2:** 0 **G1/G2:** $P = 0.001$ Vomiting: **G1:** 2.3 **G2:** 0 G1/G2: $P = .030$ Dizziness: **G1:** 22.6 **G2:** 0 G1/G2: $P = 0.001$ Dry mouth: **G1:** 8.3 **G2:** 0 G1/G2: $P = 0.001$ Pins and needles/numbness: **G1:** 4.1 **G2:** 0 G1/G2: $P = .001$ Drowsiness: **G1:** 15.4 **G2:** 0 **G1/G2:** $P = 0.001$ Neonatal: NR Occupational: NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** (SaO_2 levels measured at onset of active labor and hourly at 1-5 hours afterward) NR[2] **Neonatal status:** Apgar scores, mean ± SD: 1^{st} min: **G1:** 8.5 ± 0.9 **G2:** 8.5 ± 0.8 5^{th} min: **G1:** 9.5 ± 0.8 **G2:** 9.5 ± 0.7 **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Route of birth, n (%): Vaginal: **G1:** 260 (100) **G2:** 249 (100) Assisted: **Total:** 0	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Talebi et al., 2009 (continued)			Cesarean: **Total:** 0	

Comments:

[1]Authors state that four patients were lost from the study, followup N from parity reported in Table 1.

[2]Results only displayed graphically. For pain, G1 values were significantly lower than G2 at all time points; for SaO2 levels, G2 levels were significantly higher than G1 at the first three time points.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Waldenstrom et al., 2006 **Country:** Sweden **Participant source:** Antenatal clinics **Setting:** Other **Enrollment period:** 05/1999 to 01/2000 **Design:** Trend ************************** **Inclusion criteria:** • Pregnant woman • Fluent in Swedish **Exclusion criteria:** • Miscarriage • Elective cesarean • Emergency cesarean not preceded by labor	**Groups:** **G1:** All women **G1a:** N_2O used during labor **N at enrollment:** (completed first questionnaire in early pregnancy) **G1:** 3,061 **N at followup:** **G1:** 2,482 **G1a:** 1,997 **Age, mean yrs, %:** < 25: **G1:** 15 25-35: **G1:** 75 > 35: **G1:** 10 **Race/ethnicity, %:** Native-born Swedes: **G1:** 91 **Parous, n (%):** Primipara: **G1:** 1,096 (44) **G1a:** 926 (46) Multipara: **G1:** 1,386 (55) **G1a:** 1,071 (54)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Epidural block, pethidine, paracervical block, pudental block, bath or shower, acupuncture, psycho-prophylaxis, TENS, sterile water papules **Pain management, %:** Epidural block: **G1:** 31.1 N_2O: **G1:** 80.5 Pethidine: **G1:** 9.1 Paracervical block: **G1:** 3.3 Pudental block: **G1:** 4.4 No pharmacological pain management: **G1:** 14 Bath or shower: **G1:** 32.9 Acupuncture: **G1:** 21.5 Psychoprophylaxis: **G1:** 13.9 TENS: **G1:** 11.8 Sterile water papules: **G1:** 3.4 No pain management: **G1:** 9	**Pain, n:** (7 point scale ranging from 1 = no pain at all to 7 = worst imaginable pain, reported at two Pain reported at two months post partum) 1-3: **G1:** 173 **G1a:** 88[1] 4: **G1:** 243 **G1a:** 174[1] 5: **G1:** 596 **G1a:** 471[1] 6: **G1:** 749 **G1a:** 637[1] 7: **G1:** 721 **G1a:** 627[1] **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** Oxytocin: **G1:** NR **Adverse effects:** NR **Route of birth:** NR	**Satisfaction with pain management, %:** (scale created by author/researchers, reported two months after birth) Primaparas: Very effective: **G1:** 37.6 Some effect: **G1:** 45.6 No effect: **G1:** 16.8 Multiparas: Very effective: **G1:** 49.0 Some effect: **G1:** 42.0 No effect: **G1:** 9.0 **Satisfaction with birth experience:** Recollection of labor pain at 1 year: **G1a:** NR[2] **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Comments:

[1] Computed from overall numbers for G1 and percentages in Table III.

[2] Results only displayed graphically. The authors state that high rates of nitrous oxide were associated with remembering less pain.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Waldenstrom, 1999 **Country:** Sweden **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** 10/1989 to 01/1992 **Design:** Cross-sectional • Groups were randomized to either birth center or hospital birth initially, but treated as 1 group for this study ************************* **Inclusion criteria:** • Women giving birth between 10/1989 and 01/1992 • Low medical risk • Recruited from greater Stockholm area in early pregnancy **Exclusion criteria:** • Miscarriage, fetal or neonatal loss • Elective cesarean	**Groups:** **G1:** Entire group consisted of women randomly assigned to either standard care or in-hospital birth center birth, but treated as one group for this study **G1a:** Positive group (6 or 7 on a 7-point overall birth experience scale 1 = very negative, 7 = very positive) **G1b:** Less positive group (1-5 on a 7-point overall birth experience scale) **N at enrollment:** (early pregnancy before randomization) **G1:** 1,230 **N at followup:** (returned followup questionnaire) **G1:** 1,148 (two months after birth, after exclusions) **G1:** 1,111 **G1a:** 790 **G1b:** 321 **Age, mean yrs ± SD:** **G1a:** 30.2 ± 4.4 **G1b:** 30.5 ± 4.3 **Race/ethnicity:** NR **Parous, n (%):** Primiparity:	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Epidural, pethidine **Pain management, %:** Nitrous: **G1a:** 25.9 **G1b:** 49.2 **Ga/Gb:** $P < 0.001$ Epidural: **G1a:** 5.6 **G1b:** 26.6 **Ga/Gb:** $P < 0.001$ Pethidine: **G1a:** 5.9 **G1b:** 14.9 **Ga/Gb:** $P < 0.001$	**Pain:** Pain intensity, mean ± SD (1 = none at all, 7 = worst imaginable): **G1a:** 4.8 ± 1.5 **G1b:** 5.6 ±1 .5 **Labor progress, duration of labor, mean ± SD:**[1] **G1a:** 12.5 ± 9.2 **G1b:** 18.0 ± 12.7 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions, %:** Induction of labor: **G1a:** 2.0 **G1b:** 7.2 **Augmentation of labor, %:** **G1a:** 12.5 **G1b:** 37.8 **Adverse effects, mean ± SD:** Maternal: Anxiety (where 1 = not at all anxious, and 7 = very anxious): **G1a:** 2.1 ± 1.5 **G1b:** 3.6 ± 1.9 Neonatal: Transfer, %: **G1a:** 7.2 **G1b:** 16.8 Occupational: NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status, %:** Apgar score < 7, 5 minutes: G1a: 0.4 G1b: 2.5 **Adverse effects:** Maternal: NR Neonatal: See neonatal transfer in labor and intermediate outcomes column. Childhood: NR Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	G1a: 47.1 **G1b:** 71.3 **G1a/G1b:** *P* < 0.001		**Route of birth, %:** Vaginal: **G1a:** NR G1a: NR Vacuum extraction: **G1a:** 1.3 **G1b:** 9.7 Emergency cesarean: **G1a:** 1.4 **G1b:** 14.3	

Comments:

[1] Assumed to be hours, unit not provided.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Waldenstrom et al., 1996 **Country:** Sweden **Participant source:** Academic multisite Community **Setting:** Hospital **Enrollment period:** 11/1994 to 12/1994 **Design:** Cross-sectional ************************* **Inclusion criteria:** • All women who gave birth at any of three hospitals providing maternity care in the Gothenburg region in enrollment period **Exclusion criteria:** • Had a stillborn or severely ill baby • Suffered from postpartum psychosis • Did not have mastery of Swedish language • Did not agree to participate or were not contacted due to very early discharge • Underwent elective cesarean	**Groups:**[1] **G1:** Entonox (50/50 N_2O and O_2 mix) **G2:** Epidural **G3:** Local infiltration **G4:** Acupuncture **G5:** Bath **G6:** Breathing technique (psycho-prophylaxis) **Ga:** Less severe pain (score=1-6) **Gb:** Severe pain (score=7) **N at enrollment:** (all births from 11/21 to 12/6/1994) **Total:** 385 **N at followup:** (completed question-naires 4 hours to 7 days after birth, mean 45 hours) **Total:** 278 **G1:** 219 **G2:** 95 **G3:** 69 **G4:** 51 **G5:** 107 G6: 85 Ga: 165 Gb: 113 **Age, mean yrs ± SD:** **Ga:** 29.5 ± 5.1 **Gb:** 28.9 ± 4.2 **Ga/Gb:** *P* = NS **Race/ethnicity:** NR **Parous, n (%):** Primiparas: **Total:** 134 (48) **Ga:** NR (45.5)	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Pethidine, morphine, paracervical block, pudendal block, shower, massage, sterile water s.c., TENS, movement, music **Pain management, %:** Entonox: **Total:** 78.8 **Ga:** 70.9 **Gb:** 85.8 Epidural block: **Total:** 34.2 **Ga:** 29.1 **Gb:** 38.9 Pethidine, morphine: **Total:** 3.4 Paracervical block: **Total:** 5.0 Pudental block: **Total:** 7.2 Local infiltration: **Total:** 24.8 **Ga:** 21.8 **Gb:** 27.4 No pharmacological analgesia: **Total:** 9.3 Nonpharmacological methods: Tub bath: **Total:** 40.5	**Pain, n (%):** (7 point scale 1-7)[2] Pain score, n (%): 7: **Total:** 113 (41) 1-6: **Total:** 165 (59) Pain score, mean: Primaparas: **Total:** 6.1 Multiparas: **Total:** 5.9 **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions, %:** Induction: **Ga:** 15.9 **Gb:** 19.8 Augmentation: **Ga:** 36.4 **Gb:** 53.8 **Adverse effects:** Maternal: Anxiety score, mean ± SD:[3] **Ga:** 3.3 ± 1.8 **Gb:** 4.4 ± 2.1 **Ga/Gb:** *P* < 0.001 Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **Total:** 236 (84.9) **Ga:** NR (88.5) **Gb:** NR (79.6) Assisted: **Total:** 22 (7.5) **Ga:** NR (4.8) **Gb:** NR (12.4)	**Satisfaction with pain management, n (%):** Would use pain relief method in future labor: **G1:** 188 (69.9) **G2:** 122 (45.3) **G3:** 93 (34.6) **G4:** 55 (20.4) **G5:** 180 (66.9) **G6:** 110 (40.9) **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
	Gb: NR (52.2)	**Ga:** 33.3 **Gb:** 46.0 Shower: **Total:** 14.8 Massage:	Emergency cesarean: **Total:** 20 (6.8) **Ga:** NR (6.7) **Gb:** NR (8.0)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Waldenstrom et al., 1996 (continued)		**Total:** 28.4 Special breathing technique: **Total:** 32.2 **Ga:** 33.9 **Gb:** 25.7 Acupuncture: **Total:** 19.3 **Ga:** 14.5 **Gb:** 23.9 Sterile water s.c.: **Total:** 7.6 TENS: **Total:** 6.4 Movement (walking around): **Total:** 39.8 Music: **Total:** 16.3		

Comments:

1 Groups are not exclusive.

[2] 1=no pain at all; 7=worst imaginable pain

[3] 1=not at all anxious, 7=very anxious

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Westberg et al., 2008 **Country:** Sweden **Participant source:** NR **Setting:** Hospital **Enrollment period:** 03/2003 to 05/2004 **Design:** Prospective cohort ************************ **Inclusion criteria:** • All subjects available during the selected shifts were included. **Exclusion criteria:** NR	**Groups:** **G1:** Midwives **G2:** Assistant midwives **N at enrollment:** **G1:** 25 **G2:** 11 **Total:** 36 **N at followup:** NR **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: NR Neonatal: NR Occupational: Air concentrations (mg/m^3) of 8 h time-weighted averages nitrous oxide levels in delivery suite, geometric mean ± geometric standard deviation (range): **G1:** 17 ± 4.4 (2.5-260) **G2:** 42 ± 4.7 (< 3.5-220) **Total:** 22 ± 4.7 (2.5-260) **Route of birth:** NR	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Westling et al., 1992 **Country:** Sweden **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Crossover RCT ************************* **Inclusion criteria:** • Healthy • Normal singleton pregnancy • Vertex presentation **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1a:** Intermittent N_2O/O_2 (40/60) **G1b:** Intermittent N_2O/O_2 (70/30) **G1c:** Continuous N_2O/O_2 (40/60) **G1d:** Intermittent O_2 Intervention delivered via face mask **N at enrollment:** (labor) **G1:** 24 **N at followup:** **G1:** 24 **Age, mean yrs ± SD:** **G1:** 26.8 ± 0.9 **Race/ethnicity:** NR **Parous, n (%):** **G1:** 12 (50)	**Provider preferences:** NR **Provider specialty, n (%):** Midwife: **G1:** 24 (100) **Cost of intervention:** NR **Other pain management methods available:** None **Pain management:** NR	**Pain:** VAS, participant report, mean: **G1:** NR[1] VAS, midwife report, mean: **G1:** NR[1] **Labor progress,** Cervical dilation, mean ± SD: Before measurements: **G1:** 5.8 ± 0.4 After measurements: **G1:** 7.9 ± 0.4 **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n (%):** Maternal: Nausea **G1a:** 0 **G1b:** 0 **G1c:** 1 (4) **G1d:** 0 Vomiting: **G1:** 0 Loss of consciousness: **G1:** 0 Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal: **G1:** 23 (96)	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** Heart rate, mean: **G1:** NR[1] Stroke volume, mean: **G1:** NR[1] Cardiac output, mean: **G1:** NR[1] Systolic arterial pressure, mean: **G1:** NR[1] Diastolic arterial pressure, mean: **G1:** NR[1] Mean arterial pressure: **G1:** NR[1] Total peripheral vascular resistance, mean: **G1:** NR[1] **Neonatal status:** Weight, g, mean ± SD: **G1:** 3,652 ± 121 Apgar score, mean ± SD: 1 minute: **G1:** 9.2 ± 0.6 5 minutes: **G1:** 10.0 ± 0.2 10 minutes: **G1:** 10.0 ± 0 Umbilical cord pH, mean ± SD: **G1:** 7.29 ± 0.05 **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Assisted: **G1:** 0 Cesarean: **G1:** 1 (4)	

Comments:

[1] Data only displayed graphically.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Yeo et al., 2007 **Country:** United Kingdom **Participant source:** NR **Setting:** NR **Enrollment period:** NR **Design:** Crossover RCT ************************* **Inclusion criteria:** • Active labor • GA > 36 weeks **Exclusion criteria:** • Major uterine abnormalities • Multiple gestation • CV or respiratory instability • Acute/chronic OB pathology/disease • Received any prior form of analgesia	**Groups:** **G1:** ESE[1] (double cross-over) **G2:** SES[1] (double cross-over) **Ga:** Entonox (E) **Gb:** Sevoflurane (S) **N at enrollment:** **G1:** 16 **G2:** 16 **N at followup:** **G1:** 8 **G2:** 14 **Age, mean yrs:** **Total:** 32 **Race/ethnicity:** NR **Parous, %:** Nulliparous: **Total:** 91	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** Epidural **Pain management, n (%):** Epidural: **G1a:** 4[2] **G1b:** 0 **G2a:** 2 **G2b:** 0	**Pain:** (100 mm VAS) VAS score, mean difference (95% CI): Pain intensity, 1st cross-over period: **Gb/Ga:** 5 (0.2,11) **Gb/Ga:** *P* = 0.0395 Pain relief, 2nd cross-over period: **Gb/Ga:** 2 (-2,6) **Gb/Ga:** *P* = 0.0006 Pain relief, 1st cross-over period: **Gb/Ga:** 12 (3,21) **Gb/Ga:** *P* = 0.0115 Pain relief, 2nd cross-over period: **Gb/Ga:** 18 (8,28) **Gb/Ga:** *P* = NS Pain relief, VAS score, median (IQR): **Ga:** 51 (32-65) **Gb:** 67 (55-74) **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects, n:**	**Satisfaction with pain management, % (95% CI):** Preferred sevoflurane to Entonox: **Total:** 97 (84,99) **Ga/Gb:** *P* < 0.0001 **Satisfaction with birth experience:** NR **Maternal status:** (100 mm VAS) VAS score, mean difference (95% CI): Mood, 1st cross-over period: **Gb/Ga:** 3 (-3,8) **Gb/Ga:** *P* = NS Mood, 2nd cross-over period: **Gb/Ga:** 10 (3,19) **Gb/Ga:** *P* = 0.0088 Coping, 1st cross-over period: **Gb/Ga:** 0.2 (-6,6) **Gb/Ga:** *P* = NS Coping, 2nd cross-over period: **Gb/Ga:** 3 (-4,10) **Gb/Ga:** *P* = NS **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			Maternal: Vomiting: **Ga:** 4 **Gb:** 0 Nausea: **Ga:** 8 **Gb:** 1 **Ga/Gb:** $P = 0.004$ Neonatal: NR Occupational: NR **Route of birth, n (%):** Vaginal spontaneous: Total: 21 (68) Assisted vaginal: **Total:** 6 (19)	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Yeo et al., 2007 (continued)			Cesarean: **Total:** 4 (13)	

Comments:

[1] E: nitrous mix (Entonox by piped gas supply and demand valve); S: sevoflurane with O_2 via draw-over vaporizer.

[2] All were in the last phase.

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Zack et al., 1991 **Country:** Sweden **Participant source:** Other (registry data) **Setting:** Not applicable (registry data) **Enrollment period:** 1973 to 1984 **Design:** Case control ************************* **Inclusion criteria:** • Born between 1973 and 1984 • Registered at birth in the Swedish Medical Birth Register • Diagnosed with leukemia • Enrolled in Swedish National Cancer Registry **Exclusion criteria:** • See inclusion criteria	**Groups:** **G1:** Has leukemia **G2:** Control matched for sex, birth year, and birth month **N at enrollment:** **G1:** 411 **G2:** 2,055 **N at followup:** **G1:** 411 **G2:** 2,055 **Age:** NR **Race/ethnicity:** NR **Parous:** Not applicable	**Provider preferences:** Not applicable **Provider specialty:** Not applicable **Cost of intervention:** Not applicable **Other pain management methods available:** Not applicable **Pain management, nitrous oxide, n (%):** **G1:** 245 (60) **G2:** 1,118 (54)	**Pain:** Not applicable **Labor progress:** Not applicable **Fetal status:** Not applicable **Timeliness:** Not applicable **Labor co-interventions:** Not applicable **Adverse effects:** Not applicable **Route of birth, n:** Vaginal: NR Assisted: **G1:** 22 **G2:** 116 Cesarean: **G1:** 39 **G2:** 201	**Satisfaction with pain management:** Not applicable **Satisfaction with birth experience:** Not applicable **Maternal status:** Not applicable **Neonatal status:** Not applicable **Adverse effects:** Maternal: Not applicable Neonatal: Not applicable Childhood leukemia, odds ratio for N_2O analgesia, (95% CI): **G1/G2:** 1.3 (1.0,1.6) Occupational: NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Author: Zelcer et al., 1989 **Country:** Australia **Participant source:** Academic single site **Setting:** Hospital **Enrollment period:** NR **Design:** Prospective cohort ************************ **Inclusion criteria:** • First stage of labor **Exclusion criteria:** • Analgesic group changed during recording • Distressed and did not want to continue study	**Groups:** **G1:** N_2O for every contraction, no pethidine **G2:** N_2O during every contraction and received intramuscular pethidine within the previous 150 minutes **G3:** No analgesia (control) **G4:** Good analgesia from epidural block, no opioid in preceding 150 minutes **G5:** Intramuscular pethidine within the previous 150 minutes, no N_2O **N at enrollment:** (first stage of labor) **Total:** 75 **N at followup:** **G1:** 10 **G2:** 10 **G3:** 10 **G4:** 10 **G5:** 10 **Age:** NR **Race/ethnicity:** NR **Parous:** NR	**Provider preferences:** NR **Provider specialty:** NR **Cost of intervention:** NR **Other pain management methods available:** NR **Pain management:** NR	**Pain:** NR **Labor progress:** NR **Fetal status:** NR **Timeliness:** NR **Labor co-interventions:** NR **Adverse effects:** Maternal: Inspired oxygen, F_IO_2, mean: **G1:** 0.69 **G2:** 0.65 **G3:** 0.21 **G4:** 0.21 **G5:** 0.21 Oxygen saturation, 5 contractions, mean %: Maximum: **G1:** 100 **G2:** 100 **G3:** 99 **G4:** 99 **G5:** 99 Minimum: **G1:** 94 **G2:** 91 **G3:** 94 **G4:** 94 **G5:** 92 **G2/G3:** $P < 0.05$ Average maximum: **G1:** 100	**Satisfaction with pain management:** NR **Satisfaction with birth experience:** NR **Maternal status:** NR **Neonatal status:** NR **Adverse effects:** NR

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
			G2: 99 **G3:** 99 **G4:** 99 **G5:** 98 Average Minimum: **G1:** 96 **G2:** 94 **G3:** 96 **G4:** 96 **G5:** 96 **G2/G3:** $P < 0.05$ Difference between maximum and minimum (Max-Min): **G1:** 6	

Evidence Table 1: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and Intermediate Outcomes	Birth and Long-Term Outcomes
Zelcer et al., 1989 (continued)			**G2:** 9 **G3:** 5 **G4:** 5 **G5:** 7 **G2/G3:** $P < 0.05$ Neonatal: NR Occupational: NR **Route of birth:** NR	

Appendix D. Applicability and Quality Tables

Table 1. Key Question 1—Applicability

Domain	**Description of Applicability of Evidence Compared With Question**
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. In addition, mechanical equipment for delivery of N2O in labor and delivery has very limited availability in the U.S.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	The most frequent outcome was an assessment of pain, generally during labor. Some studies retrospectively assessed pain in the immediate postpartum period and/or weeks to months after birth. The methods of pain assessment were heterogeneous. Those assessing outcomes included participants, obstetricians, midwives, and anesthesia providers.
Setting	Only five of 21 studies were conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S. All of the studies were conducted in hospitals, thus the effectiveness of the intervention in birth centers and the home setting has not been reported.

Table 2. Key Question 2—Applicability

Domain	**Description of Applicability of Evidence Compared With Question**
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. In addition, mechanical equipment for delivery of N2O in labor and delivery has very limited availability in the U.S.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	Satisfaction with pain management and the birth experience were the outcome measures, as reported by the women.
Setting	Only three of nine studies were conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S. All of the studies were conducted in hospitals, thus the satisfaction with the intervention in birth centers and the home setting has not been reported.

Table 3. Key Question 3—Applicability

Domain	**Description of Applicability of Evidence Compared With Question**
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. In addition, mechanical equipment for delivery of N2O in labor and delivery has very limited availability in the U.S.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	The outcomes were vaginal birth, assisted vaginal birth, and cesarean. None of the studies had a cesarean birth rate greater than 10%, which is much lower than the most recently reported U.S. rate of 32%.[1]
Setting	Only one of six studies was conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S. All of the studies were conducted in hospitals, thus the route of birth in birth centers and the home setting has not been reported.

Table 4. Key Question 4—Applicability

Domain	**Description of Applicability of Evidence Compared With Question**
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. The intervention varied significantly in terms of dose, frequency, and duration. In many studies participants received unspecified amounts of narcotics and/or sedating agents. Studies prior to 1980 are not applicable to current guidelines for clinical use.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and nonpharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	The most frequent outcomes were assessments of nausea, vomiting, dizziness, drowsiness, hypoxia, oxygen saturation, Apgar scores, and cord blood gases. Apoptosis was not addressed because there are no human studies.
Setting	Only six of 48 studies were conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S.

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials

RANDOM SEQUENCE GENERATION **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.**	
Criteria for a judgment of 'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
Criteria for the judgment of 'High risk' of bias.	The investigators describe a nonrandom component in the sequence generation process. Usually, the description would involve some systematic, nonrandom approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other nonrandom approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of nonrandom categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
Criteria for the judgment of 'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials (continued)

<table>
<tr><td colspan="2">ALLOCATION CONCEALMENT
Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.</td></tr>
<tr><td>Criteria for a judgment of ‘Low risk’ of bias.</td><td>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:
• Central allocation (including telephone, web-based and pharmacy-controlled randomization);
• Sequentially numbered drug containers of identical appearance;
• Sequentially numbered, opaque, sealed envelopes.</td></tr>
<tr><td>Criteria for the judgment of ‘High risk’ of bias.</td><td>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:
• Using an open random allocation schedule (e.g. a list of random numbers);
• Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);
• Alternation or rotation;
• Date of birth;
• Case record number;
• Any other explicitly unconcealed procedure.</td></tr>
<tr><td>Criteria for the judgment of ‘Unclear risk’ of bias.</td><td>Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.</td></tr>
<tr><td colspan="2">SELECTIVE REPORTING
Reporting bias due to selective outcome reporting.</td></tr>
<tr><td>Criteria for a judgment of ‘Low risk’ of bias.</td><td>Any of the following:
• The study protocol is available and all of the study’s prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way;
• The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).</td></tr>
<tr><td>Criteria for the judgment of ‘High risk’ of bias.</td><td>Any one of the following:
• Not all of the study’s prespecified primary outcomes have been reported;
• One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified;
• One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
• One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
• The study report fails to include results for a key outcome that would be expected to have been reported for such a study.</td></tr>
<tr><td>Criteria for the judgment of ‘Unclear risk’ of bias.</td><td>Insufficient information to permit judgement of ‘Low risk’ or ‘High risk’. It is likely that the majority of studies will fall into this category.</td></tr>
</table>

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials (continued)

OTHER BIAS **Bias due to problems not covered elsewhere in the table.**	
Criteria for a judgment of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgment of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
Criteria for the judgment of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.
BLINDING OF PARTICIPANTS AND PERSONNEL **Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.**	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials (continued)

BLINDING OF OUTCOME ASSESSMENT **Detection bias due to knowledge of the allocated interventions by outcome assessors.**	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.
INCOMPLETE OUTCOME DATA **Attrition bias due to amount, nature or handling of incomplete outcome data.**	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.

Thresholds for converting the Cochrane Risk of Bias tool to AHRQ standards (good, fair, and poor):

Good quality: All criteria met (i.e. low for each domain)

Using the Cochrane ROB tool, it is possible for a criterion to be met even when the element was technically not part of the method. For instance, a judgment that knowledge of the allocated interventions was adequately prevented can be made even if the study was not blinded, if EPC team members judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.

Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was **unlikely** to have biased the outcome, and there is no known important limitation that could invalidate the results

Poor quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was **likely** to have biased the outcome, and there are important limitations that could invalidate the results

Poor quality: Two or more criteria listed as high or unclear risk of bias

Table 6. Quality ratings for randomized control trials

Citation	Quality Rating	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Sources of Bias	Blinding (Participants and Personnel)	Blinding (Outcome Assessment)	Incomplete Outcome Data
Abboud et al.,[2] 1995	Poor	L	L	L	L	H	H	L
Abboud et al.,[3] 1989	Poor	U	U	L	L	H	H	L
Abboud et al.,[4] 1981	Poor	U	U	L	U	H	H	L
Arora et al.,[5] 1992	Fair	L	L	L	U	L	L	L
Bergsjo and Lindbaek,[6] 1971	Poor	L	L	L	U	U	U	L
Carstoniu et al.,[7] 1994	Poor	L	H	L	L	H	H	L
Chia et al.,[8] 1990	Poor	H	H	L	H	H	H	L
Constantine et al.,[9] 1989	Poor	U	H	L	U	H	H	L
Einarsson et al.,[10] 1996	Poor	U	U	L	U	U	U	L
Jones et al.,[11] 1969	Poor	U	U	L	U	L	U	L
Jones et al.,[12] 1969	Poor	U	U	L	U	U	U	L
McGuinness and Rosen,[13] 1984	Poor	U	U	L	U	U	L	L
McLeod et al.,[14] 1985	Poor	U	U	L	U	L	U	L
NA,[15] 1970	Fair	U	L	L	L	L	L	L

Table 6. Quality ratings for randomized control trials (continued)

Citation	Quality Rating	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other Sources of Bias	Blinding (Participants and Personnel)	Blinding (Outcome Assessment)	Incomplete Outcome Data
Phillips and Macdonald,[16] 1971	Poor	U	U	L	H	U	U	H
Rosen et al.,[17] 1972	Poor	H	U	L	L	H	U	L
Talebi et al.,[18] 2009	Poor	L	U	L	U	U	U	U
Westling et al.,[19] 1992	Poor	H	H	L	U	H	H	L
Yeo et al.,[20] 2007	Poor	U	H	H	U	H	H	L

H = high; L = low; U = unclear

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

1) Representativeness of the exposed cohort
   a) Truly representative ***(one star)***
   b) Somewhat representative ***(one star)***
   c) Selected group
   d) No description of the derivation of the cohort
2) Selection of the nonexposed cohort
   a) Drawn from the same community as the exposed cohort ***(one star)***
   b) Drawn from a different source
   c) No description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) Secure record (e.g., surgical record) ***(one star)***
   b) Structured interview ***(one star)***
   c) Written self report
   d) No description
   e) Other
4) Demonstration that outcome of interest was not present at start of study
   a) Yes ***(one star)***
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
   - □ The study controls for age, sex and marital status ***(one star)***
   - □ Study controls for other factors (list) __________________________________ ***(one star)***
   - □ Cohorts are not comparable on the basis of the design or analysis controlled for confounders
   - □ No comparison group*
   - □ N/A*

Outcome

1) Assessment of outcome
   a) Independent blind assessment ***(one star)***
   b) Record linkage ***(one star)***
   c) Self report
   d) No description
   e) Other
2) Was followup long enough for outcomes to occur
   - □ Yes ***(one star)***
   - □ No

Indicate the median duration of followup and a brief rationale for the assessment above:____________________

3) Adequacy of followup of cohorts

a) Complete follow up- all subject accounted for ***(one star)***
b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. ***(one star)***
c) Follow up rate greater than 80% and no description of those lost
d) No statement

*A*dded by Vanderbilt EPC*

Newcastle-Ottawa Quality Assessment Form for Case-control Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) Yes, with independent validation ***(one star)***
   b) Yes, e.g., record linkage or based on self report
   c) No description
2) Representativeness of the cases
   a) Consecutive or obviously representative series of cases ***(one star)***
   b) Potential for selection biases or not stated
3) Selection of controls
   a) Community controls ***(one star)***
   b) Hospital controls
   c) No description
4) Definition of controls
   a) No history of disease (endpoint) ***(one star)***
   b) No description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis controlled for confounders
   - ☐ The study controls for age, sex and marital status ***(one star)***
   - ☐ Study controls for other factors (list) ______________________________ ***(one star)***
   - ☐ Cohorts are not comparable on the basis of the design or analysis controlled for confounders
   - ☐ No comparison group*
   - ☐ N/A*

Exposure

1) Ascertainment of exposure
   a) Secure record (e.g., surgical record) ***(one star)***
   b) Structured interview where blind to case/control status ***(one star)***
   c) Interview not blinded to case/control status
   d) Written self report or medical record only
   e) No description
2) Same method of ascertainment for cases and controls
   - ☐ Yes ***(one star)***
   - ☐ No
3) Nonresponse rate
   a) Same rate for both groups ***(one star)***
   b) Nonrespondents described
   c) Rate different between cases and controls with no description

**Added by Vanderbilt EPC*

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

The Vanderbilt EPC included two additional options in the comparability domain not generally included in the Newcastle-Ottawa scales: "no comparison group" and "not applicable". This was necessary because the review included single-arm studies for both the effectiveness and harms assessments.

Studies of the effectiveness of nitrous oxide for the management of labor pain that included only one study arm were marked as "no comparison group", which equates to receiving no stars and an automatic rating of poor quality.

Cross sectional studies used to identify potential harms and measures of environmental exposure could appropriately have no comparison group, and were marked for comparability as "not applicable." The quality scores for these studies were downgraded to account for their noncomparative study designs. For example, a study with three or four stars in the selection domain and two or three stars in the outcome/exposure domain, which would normally equate to a "good" quality rating, would be deemed "fair" quality if the comparability domain response was "not applicable".

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials)

		Selection (0-4 Stars)				Comparability (n/a, 0-2 Stars)	Outcome (0-3 Stars)		
Citation	**Quality Rating**	**Represen-tativeness of Exposed Cohort**	**Selection of Nonexposed**	**Ascertain-ment of Exposure**	**Outcome Not Present at Start of Study**	**Comparability of Cohorts**	**Assess-ment**	**Long Enough Followup**	**Adequacy of Followup**
Ahlborg et al.,[21] 1996	Fair	c)selected group	a)drawn from same community	c)written self report	a) yes	N/A	c)self report	a) yes	b)unlikely to introduce bias
Arfeen et al.,[22] 1994	Poor	a)truly representative	a)drawn from same community	a)secure record	a) yes	no	b)record linkage	a) yes	b)unlikely to introduce bias
Arthurs et al.,[23] 1979	Poor	d)no description	a)drawn from same community cohort	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up for
Axelsson et al.,[24] 1996	Poor	c)selected group	a)drawn from same community	c)written self report	a) yes	N/A	c)self report	a) yes	b)unlikely to introduce bias
Beppu[25] 1968	Poor	d) no description	c) no description	a)secure record	a) yes	NC	b) record linkage	a) yes	a)complete follow up
Bodin et al.,[26] 1999	Poor	c)selected group	a)drawn from same community	c)written self report	a) yes	no	b)record linkage	a) yes	b)unlikely to introduce bias lost
Clark et al.,[27] 1967	Fair	d) no description	c) no description	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Deckardt et al.,[28] 1987	Poor	d)no description	a)drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

		Selection (0-4 Stars)				Comparability (n/a, 0-2 Stars)	Outcome (0-3 Stars)		
Citation	**Quality Rating**	**Represen-tativeness of Exposed Cohort**	**Selection of Nonexposed**	**Ascertain-ment of Exposure**	**Outcome Not Present at Start of Study**	**Comparability of Cohorts**	**Assess-ment**	**Long Enough Followup**	**Adequacy of Followup**
Harrison et al.,[29] 1987	Poor	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up
Harrison and Cullen[30] 1986	Poor	b)somewhat representative	a) drawn from same community	a) secure record	a) yes	no	a)independent assessment	a) yes	a)complete follow up
Henderson et al.,[31] 2003	Fair	a)truly representative	a)drawn from same community	a)secure record	b) no	N/A	a)independent assessment	a) yes	a)complete follow up
Henry and Nand,[32] 2004	Poor	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias
Holdcroft and Morgan,[33] 1974	Poor	b)somewhat representative	a) drawn from same community	c)written self report	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias
Landon et al.,[34] 1992	Poor	a)truly representative	a)drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Leong et al.,[35] 2000	Good	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	both	c) self report	a) yes	b)unlikely to introduce bias

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

		Selection (0-4 Stars)				Comparability (n/a, 0-2 Stars)	Outcome (0-3 Stars)		
Citation	**Quality Rating**	**Represen-tativeness of Exposed Cohort**	**Selection of Nonexposed**	**Ascertain-ment of Exposure**	**Outcome Not Present at Start of Study**	**Comparability of Cohorts**	**Assess-ment**	**Long Enough Followup**	**Adequacy of Followup**
Marx et al.,[36] 1970	Poor	c)selected group	a) drawn from same community	a)secure record	a) yes	NC	b) record linkage	a) yes	d) no statement
McAneny and Doughty,[37] 1963	Poor	d) no description	a) drawn from same community	a)secure record	a) yes	no	a)indepen dent blind assessmen t	a) yes	b)unlikely to introduce bias
Mills et al.,[38] 1996	Fair	c)selected group	a) drawn from same community	a)secure record	a) yes	N/A	b) record linkage	a) yes	a)complete follow up
Morgan et al.,[39] 1982	Poor	a)truly representative	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up
Murphy et al.,[40] 1984	Poor	a) truly representative	a) drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Newton et al.,[41] 1999	Fair	c)selected group	a) drawn from same community	a)secure record	a) yes	N/A	b) record linkage	a) yes	b)unlikely to introduce bias
Peach,[42] 1999	Fair	a)truly representative	a)drawn from same community	a)secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias lost

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

		Selection (0-4 Stars)				Comparability (n/a, 0-2 Stars)	Outcome (0-3 Stars)		
Citation	**Quality Rating**	**Represen-tativeness of Exposed Cohort**	**Selection of Nonexposed**	**Ascertain-ment of Exposure**	**Outcome Not Present at Start of Study**	**Comparability of Cohorts**	**Assess-ment**	**Long Enough Followup**	**Adequacy of Followup**
Ranta et al.,[43] 1995	Fair	a) truly representative	a) drawn from same community	a)secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias
Ranta et al.,[44] 1994	Poor	b)somewhat representative	a) drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias
Reed et al.,[45] 1988	Poor	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Rosen et al.,[46] 1969	Poor	a)truly representative	a) drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias -
Ross et al.,[47] 1999	Poor	c)selected group	c)no description	a)secure record	a) yes	NC	b) record linkage	a) yes	b)unlikely to introduce bias
Smith et al.,[48] 1968	Poor	a) truly representative	a) drawn from same community	a)secure record	a) yes	no	a)indepen dent assessmen t	a) yes	b)unlikely to introduce bias
Soyannwo,[49] 1985	Poor	d)no description	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

		Selection (0-4 Stars)				Comparability (n/a, 0-2 Stars)	Outcome (0-3 Stars)		
Citation	**Quality Rating**	**Representativeness of Exposed Cohort**	**Selection of Nonexposed**	**Ascertainment of Exposure**	**Outcome Not Present at Start of Study**	**Comparability of Cohorts**	**Assessment**	**Long Enough Followup**	**Adequacy of Followup**
Stirk et al.,[50] 2002	Poor	b)somewhat representative	a) drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a) complete follow up
Waldenstrom and Irestedt,[51] 2006	Fair	a)truly representative	a)drawn from same community	c) written self report	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias -
Waldenstrom,[52] 1999	Fair	b)somewhat representative	a)drawn from same community	a) secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias -
Waldenstrom et al.,[54] 1996	Fair	a) truly representative	a) drawn from same community	a)secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias
Westberg et al.,[53] 2008	Fair	c)selected group	a) drawn from same community	a)secure record	a) yes	N/A	b) record linkage	a) yes	a)complete follow up
Zelcer et al.,[55] 1989	Poor	d)no description	c)no description	a)secure record	a) yes	no	b) record linkage	a) yes	b)unlikely to introduce bias

Table 8. Quality ratings for case-control studies

		Selection (0-4 Stars)				Comparability (n/a, 0-2 Stars)	Outcome (0-3 Stars)		
Citation	**Quality Rating**	**Adequate Case Definition**	**Represen-tativeness of Cases**	**Selection of Controls**	**Definition of Controls**	**Comparability of Cases and controls**	**Ascertain-ment of Exposure**	**Same Method of Ascertainment**	**Nonresponse rate**
Jacobson et al.,[56] 1990	Poor	b) yes, e.g., record linkage or based on self report	b) potential for selection biases or not stated	a)community	a) no history of disease (endpoint)	no	a) secure record	a) yes	a) same
Jacobson et al.,[57] 1988	Poor	b) yes, e.g., record linkage or based on self report	b) potential for selection biases or not stated	a)community	a) no history of disease (endpoint)	no	a) secure record (	a) yes	a) same
Nyberg et al.,[58] 1992	Poor	b) yes, e.g., record linkage or based on self report	a) consecutive or obviously representative series of cases	a)community	a) no history of disease (endpoint)	no	a) secure record	a) yes	a) same
Zack et al.,[59] 1991	Good	b) yes, e.g., record linkage or based on self report	a) consecutive or obviously representative series of cases	a)community	a) no history of disease (endpoint)	other	a) secure record	a) yes	a) same

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Appendix E. Excluded Studies

Exclusion codes:

X-1: Not original research (reviews, editorials, commentaries, letters to editor, etc)

X-2: Ineligible study size

X-3: Not related to the use of nitrous oxide for the management of labor pain

X-4: Not published in English

X-5: Did not address study questions

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Appendix F. Regulatory Considerations of Nitrous Oxide

Nitrous oxide is used in the U.S. for both medical and nonmedical purposes. The following section will focus on the regulation of nitrous oxide used as analgesia for labor pain. Nitrous oxide as a labor analgesia is governed by a limited patchwork of laws, regulations, and standards.

Regulation by federal entities

Like all medical gases, nitrous oxide is regulated by the U.S. Food and Drug Administration (FDA) as a prescription drug.[1] Title 21 of the Code of Federal Regulations describes the required manufacturing (Good Manufacturing Practices) and distribution practices for prescription drugs, performance standards for medical gas delivery devices, and safety requirements for medical gas containers. There are only a few FDA regulations that specifically or solely apply to nitrous oxide. These regulations describe labeling requirments, manufacturing requirements, and performance standards for delivery systems.[2]

Nitrous oxide also falls under the purview of the United States Pharmacopeia (USP). The USP is a scientific nonprofit organization that sets standards for the quality, purity, identity, and strength of medicines and food ingredients distributed and consumed worldwide. USP standards are enforced by the FDA.

Two federal agencies have weighed in on the use of nitrous oxide in the workplace. The National Institute for Occupational Health and Safety (NIOSH), the federal agency responsible for conducting research and making recommendations to prevent injury and illness in the workplace, has established a recommended exposure limit (REL) for nitrous oxide of 25 parts per million as a eight hour time weighted average. In 1994, NIOSH published an alert (DHHS (NIOSH) Publication No. 94-100) that provided guidance on how to control workplace exposures to nitrous oxide during anesthetic administration.[3]

The Occupational Safety and Health Administration (OSHA) is the federal agency that sets and enforces workplace health and safety standards. OSHA has not set a threshold standard for nitrous oxide exposures in the workplace,[3] but is developing requirements for monitoring workplace exposures to nitrous oxide.[4] OSHA has addressed public safety by requiring all piped systems that transfer and distribute nitrous oxide to comply with safety standards set by the Compressed Gas Association.[5]

Companies that sell nitrous oxide and facilities that store nitrous oxide are subject to certain environmental regulations. The U.S. Environmental Protection Agency (EPA) maintains and publishes every two years a list of chemicals sold in the U.S. This list, the Toxic Substances Control Act (TSCA) inventory, includes nitrous oxide. Facilities that use and store nitrous oxide must submit material safety data sheets and report nitrous oxide inventories to the local emergency planning commission, the organization responsible for local emergency preparedness and response.

Regulation by state legislatures and agencies

In addition to the federal regulations that govern the manufacture, distribution, and storage of nitrous oxide, there are state laws that are meant to promote the safe use, storage, and delivery of nitrous oxide. An increasing number of states have enacted legislation that attempt to limit youth access to nitrous oxide in order to reduce the prevalence of nitrous oxide abuse by young people. Some state legislatures and licensing boards have enacted legislation or rules that define who may administer or assist in administering nitrous oxide in a medical setting. Some states have enacted community and worker right to know laws. These laws mandate reporting of environmental exposures (accidental releases and on-site storage exposures) to a local agency and mandate notice of exposures to employees and community residents. Finally, it is not uncommon for state and local governments to regulate and enforce building codes that address the installation, testing, and maintenance of pipelines used to deliver nitrous oxide to medical facilities.

Regulation by national organizations

Professional organizations are an integral part of the regulator environment for nitrous oxide. The American Conference of Governmental Industrial Hygienists (ACGIH) is a professional association of industrial hygiene personnel within government agencies. ACGIH establishes the Threshold Limit Values (TLVs) for chemical substances and physical agents and Biological Exposure Indices (BEIs) as guidelines for use in the industrial hygiene field. This group has set a threshold limit value (TLV) for nitrous oxide of 50 ppm of air as an eight hour time weighted average.[6]

The Compressed Gas Association (CGA) writes regulations and standards for compressed gases. Title 41 of the Code of Federal Regulations applies to federal contracts and requires that "the pipe systems for the in-plant transfer and distribution of nitrous oxide shall be designed, installed, maintained and operated in accordance with Compressed Gas Association Pamphlet G8.11964."[7] OSHA has also adopted the CGA code for piped systems that deliver and transfer nitrous oxide.[5]

The National Fire Protection Association (NFPA) develops and writes consensus standards for medical gas delivery systems (pipelines) in healthcare facilities. NFPA 99 sets standards for monitoring and testing of nitrous oxide delivery systems. The Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) requires healthcare facilities to comply with NFPA 99 (Annex C). The American Welding Society, the Manufacturers' Standardization Society of the Valve and Fittings Industry, the American Society of Mechanical Engineers, and the American National Standard Institute (ANSI) all have set standards for the installation, design and testing of medical gas pipelines.

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