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The Maternal and Neonatal Outcomes of Utilizing Nitrous Oxide for Labor Analgesia

Joy L. Sayler
Bethel University

THE MATERNAL AND NEONATAL OUTCOMES OF UTILIZING NITROUS OXIDE FOR LABOR ANALGESIA

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JOY LYN SAYLER

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JOY LYN SAYLER

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Approvals:

Project Advisor Name: Dr. Jane Wrede, PhD, APRN, CNM

Project Advisor Signature: Jane Wrede

Second Reader Name: Katrina Wu, MSN, APRN, CNM

Second Reader Signature: Katrina Wu

Director of Graduate Nursing Program Name: Dr. Jane Wrede, PhD, APRN, CNM

Director of Graduate Nursing Program Signature: Jane Wrede

ABSTRACT

Background: Inhaled nitrous oxide has been used in many developing countries for labor analgesia but fell out of practice in the United States over the past 40 years. Recently it has been reintroduced into practice in the U.S.

Purpose: The purpose of this paper is to critically examine the literature in order to determine the maternal and neonatal effects of utilizing nitrous oxide for labor analgesia.

Methods: Twenty research articles were critically reviewed in order to determine the maternal and neonatal effects of utilizing nitrous oxide for labor analgesia.

Results: Nitrous oxide appears to be safe for both mother and neonate. Nitrous oxide is effective in pain and anxiety reduction. Maternal satisfaction with pain reduction and childbirth experience with nitrous oxide is high. The duration of the first and second stages of labor were significantly shortened. About half of women that utilize nitrous oxide ultimately convert to neuraxial analgesia. There was no statistically significant reduction in epidural rates or Cesarean section rates.

Conclusion: Pharmacologic pain management options are limited and have disadvantages. Nitrous oxide appears to be a safe and effective option for labor analgesia.

Implications for Research and Practice: Nurse-midwives can educate patients prenatally and during labor regarding the use of nitrous oxide for labor analgesia. Nitrous oxide can safely be used during any stage of labor.

Keywords: Entonox, nitrous oxide, labor analgesia, labor pain, pharmacologic pain management, and inhaled analgesia

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Chapter I: Introduction

Nitrous oxide is an inhaled air-gas mixture that is commonly known in the United States for its use in dental offices for relaxation and mild pain relief during dental procedures (Becker & Rosenberg, 2008). It is also known as laughing gas. Nitrous oxide is also used in many developed countries for pain relief in labor. However it fell out of use in the U.S. over the last 40 years. This project examines the use of nitrous oxide for labor analgesia and its effect on maternal and neonatal outcomes. This is an important project in order to understand the effectiveness and safety of utilizing nitrous oxide for labor analgesia.

While pain and discomfort during labor varies among women, the physiologic cause of the pain is thought to originate in the dilation of the lower uterine segment and the cervix (Wong, 2009). Stretching, distension, and tearing of tissue can occur during this process. Later in labor as fetal descent into the birth canal occurs, there can be intense stretching and tearing of the fascia, subcutaneous tissue, and skeletal muscles in the perineum. Pain in labor can cause a woman to experience anxiety or even suffering (Wong, 2009). Although the physiologic cause of labor pain is the similar among women, pain is multidimensional and personalized (Whitburn, Jones, Davey, & Small, 2017). Some women interpret the pain as productive and are able to cope well (Whitburn et al., 2017). Pain can be addressed with non-pharmacologic and pharmacologic measures when necessary. Continuous labor support has been shown to decrease the need for pharmacologic pain medication and shorten the duration of labor (Wong, 2009).

Pharmacologic pain management options for labor is limited and has disadvantages. Two main types of pain medications utilized in labor are epidurals and

intravenous (IV) analgesics such as Fentanyl. Approximately 61% of women who had a vaginal birth in 27 states in the U.S. utilized epidural or spinal anesthesia based on a report released by the Centers for Disease Control (CDC) from data collected in 2008 (CDC, 2011). Epidurals are often chosen for their effective pain relief (Stewart & Collins, 2012). As epidurals have improved, women are often able to change positions in bed and experience consistent pain relief (Stewart & Collins, 2012). However, there are risks and disadvantages to the use of epidurals during labor. These include acute hypotension after epidural placement, prolonged second stage of labor, slowed contractions, fever, and the need for operative vaginal births (Stewart & Collins, 2012). Other considerations are the need for an IV and a urinary catheter. Furthermore, the patient will not be ambulatory (Stewart & Collins, 2012).

Intravenous analgesics also have potential disadvantages for mother include nausea, vomiting, and sedation (Ullman, Smith, Burns, & Dowswell, 2010). Changes in fetal heart rate variability and the presence of decelerations may also occur leading to additional intervention. Potential adverse effects for the infant include respiratory depression, decreased alertness, and delayed breastfeeding (Ullman et al., 2010).

Because of some of the disadvantages of epidurals and IV analgesics, many women who desire more control and involvement in their birth plan wish to avoid these if possible. Women in birth centers and those giving birth at home also have a lack of pharmacologic pain management options such as epidurals and IV analgesics. Furthermore, women that do not have IV analgesics or epidurals are able to remain upright and move more freely in labor. This allows women to utilize other non-pharmacologic approaches to pain management including hydrotherapy, ambulation, and

position changes. Women who labor in upright positions are shown to have shorter labors with less intervention (Ondeck, 2014). There is a need for alternative pain medications during labor that are safe and effective. Nitrous oxide may be an important addition to pain management for laboring patients.

Nitrous oxide is an odorless and tasteless gas that is administered via inhalation (Bishop, 2007). For labor analgesia a 50% nitrous oxide and 50% oxygen blend is used. Two separate portable cylinders are commonly utilized. Some hospitals have a regulator apparatus then pipeline the blend to the walls of labor rooms. The gas is self-administered by the patient by either a facemask or mouthpiece that only the patient holds. The patient is also instructed to exhale into the breathing device so that the gas is scavenged and not released into the room for others to breathe. Most often the gas is breathed intermittently not continuously. The woman is instructed to begin taking deep breaths 30 seconds prior to the beginning of a contraction (Bishop, 2007).

Statement of Purpose

The purpose of this literature review is to examine the available literature regarding nitrous oxide and its use for laboring women. The PICO question for this literature review is **"**What are the maternal and neonatal outcomes when laboring women use nitrous oxide for analgesia in the hospital setting?"

Evidence Demonstrating Need

The maternal mortality rate in the United States was 17.3 deaths per 100,000 live births in 2013 (CDC, 2018). The maternal mortality rate in the U.S. is higher than most other high-income countries and Iran, Libya, and Turkey (World Health Organization, 2015). The infant mortality rate was 6 deaths per 1,000 live births in 2013 (March of

Dimes, 2018). The U.S. again ranks poorly compared to other developed countries especially European countries (Chen, Oster, & Williams, 2016). The Cesarean section rate in the U.S. in 2015 was 32% of all births (CDC, 2017). These alarmingly high statistics highlight the need to continue investigating correlating factors as well as reducing unnecessary intervention in labor and birth.

In the U.S. obstetric care is often highly interventional (Ondeck, 2014). Supporting the natural physiologic approach of birth is less common (Ondeck, 2014). As previously noted approximately 61% of women in the U.S. utilize epidurals or spinal anesthesia during labor (CDC, 2011). Those women are subsequently restricted in their movement often lying in bed (Ondeck, 2014). Women who remain upright and mobile in labor however are found to have shorter durations of labor, receive less intervention, report increased satisfaction, and report severe pain less frequently (Ondeck, 2014).

The American College of Nurse-Midwives (ACNM) states that women should be offered a variety of pain management options in labor (ACNM, 2009). Furthermore, ACNM supports the use of inhaled nitrous oxide for coping with labor. ACNM recommends that women should be educated about the option of using nitrous oxide in labor. Certified nurse-midwives and certified midwives should be trained in the administration and monitoring of nitrous oxide use in labor (ACNM, 2009). The Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN) released a statement recently stating that nitrous oxide is a vital component in providing quality maternity care (Collins, 2018). Furthermore, AWHONN recommends that the bedside nurse initiate the use of nitrous oxide (Collins, 2018). The American College of

Obstetricians and Gynecologists (ACOG) currently does not have an official position statement regarding the use of nitrous oxide for labor analgesia.

Findings from a recent Cochrane Review by Klomp et al. (2012) support the recommendations of ACNM. The authors' findings indicate that nitrous oxide is effective in reducing pain intensity in labor compared with placebo or no treatment (Klomp et al., 2012). However, nitrous oxide was also found to be associated with more side effects including dizziness, nausea, vomiting, and drowsiness compared with no treatment or placebo. Authors of the Cochrane Review authors state in their implications for practice that inhaled nitrous oxide can be beneficial to women in labor especially those that desire a non-invasive method of pharmacological pain relief. The authors also recommended future research focus on maternal satisfaction and sense of control in labor (Klomp et al., 2012).

The literature review by Klomp et al. (2012) is now 5 years old and many more midwives and obstetric providers are offering nitrous oxide to their patients. Recent studies have also been completed focusing on maternal satisfaction and provider satisfaction with inhaled nitrous oxide in labor. Studies have also been performed to determine the effects of nitrous oxide use in labor on epidural rates. Due to recent research and the resurgence of inhaled nitrous oxide for labor analgesia in local hospitals and birth centers, a literature review is necessary.

Significance to Nurse-Midwifery

Certified Nurse-Midwives (CNMs) are Advanced Practice Registered Nurses (APRNs) with a master's or doctoral degree in Nurse-Midwifery (ACNM, 2016). In 2017 there were 11,826 CNMs in the U.S. They attended 8.3% of the totals births in 2014

and 12.1% of all vaginal births. CNMs practice in hospitals, clinics, birth centers, public health settings, and in homebirth environments. CNMs have prescribing privileges. They provide a wide range of primary health services for women from adolescence to beyond menopause. This includes primary care, gynecological services, family planning services, prenatal care, care during labor and childbirth, postpartum care, well newborn care in the first 28 days of life, and treatment of sexually transmitted infections for male partners (ACNM, 2016).

CNMs have a philosophy of care that is unique and separate from that of medicine and Obstetrics. First and foremost the focus is on the woman and her designated family members (ACNM, 2018). Care is individualized for each woman and provided in a compassionate manner through the use of therapeutic presence and skillful communication. The woman is a partner in her own care. Every effort is made to provide complete and accurate information so that the woman can be an informed decision-maker. Methods of care are based on the best evidence available. The normalcy of a woman's life processes is honored. In the presence of normalcy, watchful waiting and non-intervention are utilized. The use of technology and interventions are used when appropriate to improve patient outcomes and satisfaction. CNMs can collaborate with, consult with, or refer patients to other members of the healthcare team when needed for optimal care (ACNM, 2018).

Midwifery is based on the philosophy that labor and birth are physiologic or normal processes powered by the innate capacity of women and fetuses (ACNM, 2018). Normal physiologic processes are supported in order to preserve the best possible outcomes for mother and baby. Unnecessary interventions are avoided as they can disrupt

the physiologic process. The normal physiologic process includes spontaneous labor, biological and psychological conditions helpful in promotion of effective labor, vaginal birth, and support of the newborn transition including skin-to-skin contact between mother and infant as well as early breastfeeding initiation. Benefits include improved birth experience, improved maternal-infant bonding, reduced maternal morbidity related to surgical complications, reduced iatrogenic harm for infants related to induction or augmentation of labor, instrumental vaginal birth, neonatal respiratory distress, or neonatal laceration (ACNM, 2018).

Theoretical Framework

Katharine Kolcaba, PhD is a nursing theorist who developed the Kolcaba Theory of Comfort (Kolcaba, 2018). She completed her bachelor of science in nursing at Case Western Reserve University in 1987. She received her doctor of philosophy in nursing from Case Western Reserve University in 1997. She has worked in and studied the areas of gerontology and end of life. She is currently an associate professor at the University of Akron (Kolcaba, 2018).

Kolcaba's Theory of Comfort is a middle range nursing theory (Kolcaba, 2018). This means that the theory can be applied to a wide variety of nursing settings. Some of the most common areas of nursing that the theory has been applied to in the past include pediatrics, end of life, psychiatric, immobilization, general comfort, and childbirth (Kolcaba, 2018).

Kolcaba's Theory of Comfort addresses three levels of comfort (Kolcaba, 1994). The first being relief, the next is ease or contentment, and the last is transcendence. In the final level of transcendence the patient is able to rise above the present pain and

challenges. The comforting interventions in the theory address the need for comfort in the physical, psychosocial, sociocultural, and environmental domains (Kolcaba, Tilton, & Drouin, 2006). Intervening variables are factors that influence a patient's ability to experience comfort. These include past experiences, emotional state, support system, age, and attitude (Kolcaba et al., 2006). Kolcaba's theory also outlines ways to assess, measure, and evaluate patient comfort (Kolcaba, 1994). There is a strong focus on holistic care in this theory (Kolcaba et al., 2006).

Kolcaba's Theory of Comfort is one that can be applied in the context of labor. Kolcaba emphasizes the difference between a theory of comfort and theories of pain relief and anxiety as being a more holistic and complex approach (Kolcaba, 1994). The comfort theory also has a positive aspect of transcendence that pain theories do not. Comfort is also an easily understood term. Patients can understand comfort just as nurses and other providers do (Kolcaba, 1994).

Chapter II: Methods

The purpose of this chapter is to review the processes used in the critical appraisal of the literature. The studies reviewed were related to the practice question of the maternal and neonatal effects of utilizing nitrous oxide for labor analgesia. Strategies used in the search of the literature related to the practice question will be reviewed. Inclusion and exclusion criteria will also be explained. The numbers and types of studies found in the initial search will be reviewed. Finally, the process used for evaluation of the studies will also be explained.

Search Strategies

The intent of the critical appraisal of the literature was to determine the maternal and neonatal effects of utilizing inhaled nitrous oxide for labor analgesia. An initial search was conducted using the Cumulative Index of Nursing and Allied Health Literature (CINAHL) database with the search terms, “nitrous oxide” or “Entonox” and “labor”. This search resulted in 2,935 items, 944 published between 2008 and 2018. An additional search was conducted using the PubMed database using the same search terms “nitrous oxide” or “Entonox” and “labor”. This search resulted in 841 items, 310 published between 2008 and 2018. The initial search limited studies to those published in the past 10 years in order to include the most up to date and relevant literature. Data mining was performed to examine patterns and relationships in the data. Literature references also yielded additional studies. After duplicate studies were removed, the inclusion and exclusion criteria were applied.

Inclusion and Exclusion Criteria

Inclusion criteria for this literature review were:

1. Women in labor in the women's health setting using nitrous oxide
2. The general population across multiple specialties examining the effectiveness and/or side effects of inhaled nitrous oxide
3. Experimental studies and descriptive studies
4. Studies describing the maternal pain relief, anxiety relief, maternal side effects, and maternal satisfaction with the use of nitrous oxide in labor
5. Studies describing neonatal effects were also included

Exclusion criteria were:

1. Specific specialties outside of Women's Health using nitrous oxide
2. Poor design study

Many studies from the initial search were excluded due to their lack of application to the practice question.

Number and Types of Studies Selected for the Review

Table 1 shows the 20 studies selected for the final matrix. The studies selected for the final review include 9 qualitative and 11 experimental. The studies included 11 randomized controlled trials, 1 observational study, 2 descriptive studies, 3 retrospective studies, 1 prospective study, 1 prospective case control study, and 1 prospective comparative study. The matrix provided organization of the studies prior to the critical

review of the literature. The headings in the matrix include: Citation/level & quality, purpose of the study, sample/setting, design methodology and instruments, results, and authors' recommendations.

Evaluation of Research Studies

The research studies were evaluated utilizing *The Johns Hopkins Nursing Evidence-Based Practice: Model and Guidelines* (Dearholt & Dang, 2012). The studies were rated according to the level and quality of research evidence. Level I studies are experimental studies that are randomized controlled trials and systematic reviews of randomized controlled trials. Level II studies are quasi-experimental studies or systematic reviews of quasi-experimental studies. Level III studies are non-experimental studies or qualitative studies. Level IV studies are non-studies such as clinical practice guidelines or consensus panels of experts. Research studies are rated from high to low in level of quality. The level is determined by the consistency of the results, sample size, design, level of control, and the definitiveness of conclusions (Dearholt & Dang, 2012).

Summary

The use of inhaled nitrous oxide for labor analgesia although used historically in the U.S. has only recently been used. 20 studies were included in the final matrix. The critical appraisal of the literature provides an adequate evaluation of the evidence. This chapter described the search strategies, evaluation of the research studies, and inclusion and exclusion criteria. It also reviews the number and type of studies selected for the review.

Chapter III: Literature Review and Analysis

This chapter will examine the PICO question **"**What are the maternal and neonatal outcomes when laboring women use nitrous oxide for analgesia in the hospital setting?". The findings of the chapter are divided into safety, pain and anxiety relief, and outcomes. Safety includes maternal side effects, neonatal side effects, and the use of continuous versus intermittent inhalation of nitrous oxide. Pain and anxiety relief examines the effectiveness of nitrous oxide as an analgesic and anxiolytic. The outcomes section examines the rates of conversion from nitrous oxide to epidurals, effects on the duration of labor, Cesarean section rates, effects on breastfeeding, and maternal satisfaction.

Synthesis of Major Findings

Safety

Maternal side effects. A randomized controlled trial by Talebi, Nourozi, Jamilian, Baharfar, and Eghtesadi-Araghi (2009) showed that among women who used nitrous oxide in labor between 38-42 weeks gestation (N=523) a small percentage reported side effects with the most common being dizziness (22.6%) and drowsiness (15.4%). Less than 10% reported nausea and vomiting, pins and needles sensation, numbness sensation, and dry mouth (Talebi et al., 2009).

A large prospective study by Onody, Gil, and Hennequin (2006) showed that among the patients that received inhaled nitrous oxide for a variety of painful procedures (N=35,828) only 27 severe adverse effects were reported (0.08%). Only nine (0.03%) were reported to have a causal relationship with the inhaled nitrous oxide. These adverse effects included bradycardia, consciousness disorder, somnolence, sweating, headache, nightmares, and vomiting (Onody et al., 2006).

Continuous versus intermittent inhalation. Nitrous oxide is most often administered intermittently during labor. However, an older descriptive study by Latto, Molloy, and Rosen (1973) showed that mean arterial concentrations of nitrous oxide in women who inhaled nitrous oxide intermittently during a contraction were 8.5-28.3%. Previous studies showed that a mean arterial concentration of 41.2% was needed for optimal pain relief. Therefore this level would be insufficient. The authors recommended taking intermittent inhalations of nitrous oxide between contractions in addition to during the contractions, utilizing a continuous low dose of nitrous oxide through a nasal cannula and self-administering a higher dose during a contraction, or using a higher concentration of nitrous oxide (Latto et al., 1973).

A recent RCT by Agah, Baghani, Tali, and Tabarraei (2014) studied mothers who inhaled nitrous oxide intermittently in labor (n=50) and those who inhaled nitrous oxide continuously (n=50). Maternal oxygen saturation was >95% in both groups and there was no significant difference between the groups ($p>0.05$) with $p<0.05$ considered statistically significant. The adverse effects were not significantly different between the groups either ($p>0.05$) with $p<0.05$ considered statistically significant. Neonatal Apgar scores at 1 and 5 minutes of age in both groups were not significantly different ($p=0.3$) with $p<0.05$ considered significant. Maternal satisfaction in the continuous group was higher (96%) compared to the intermittent group (70%) (Agah et al., 2014). These recent findings support the findings of Latto et al. (1973) that continuous inhalation of nitrous oxide provides optimal pain relief.

Neonatal side effects. A cohort study by Rosenstein et al. (2017) showed that infants of women that used nitrous oxide in labor (n=686) did not have a significant

different rate of admission to the intensive care nursery (p=0.9). There were also no significant differences in the rate of neonatal acidemia (p=0.9) or 5 minute Apgar scores<7 (p=0.9) with p<0.05 considered statistically significant (Rosenstein et al., 2017).

The RCT by Talebi et al. (2009) found similar results showing that infants of women that used nitrous oxide in labor (N=523) did not have any significant differences in Apgar scores at 1 minute (p=0.760) and 5 minutes (p=0.860) with p<0.05 considered statistically significant (Talebi et al., 2009).

Pain and Anxiety Relief

A RCT by Pasha et al. (2012) studied women in active labor using nitrous oxide (n=49) and a control group that did not use nitrous oxide (n=49). Severity of pain in nitrous oxide group was moderate compared to severe for the control group (Pasha et al., 2012). A RCT by Talebi et al. (2009) studied women who used nitrous oxide in labor between 38-42 weeks gestation (N=523) and showed a significant reduction in pain ratings on the Visual Analog Scale (p<0.05) with p<0.05 considered statistically significant. A prospective case control study by Zanardo et al. (2017) studied women who used nitrous oxide for labor analgesia (N=62). At three months postpartum a VAS scale of both quantity and quality of pain revealed lasting positive pain relief experience in 83.5% of women that used nitrous oxide (Zanardo et al., 2017).

Many studies have been performed to determine nitrous oxide and anxiety reduction during dental procedures. A retrospective study by Hierons, Dorman, Wilson, Averley, and Girdler (2012) studied adults with moderate to severe anxiety undergoing exodontia (n=60) and adults with mild anxiety undergoing the same procedure (n=43). Both groups were given inhaled nitrous oxide along with the standard local anesthetic. A

control group (n=35) was given oxygen to inhale along with the standard local anesthetic. Among the moderate to severe anxiety group receiving inhaled nitrous oxide, the pre-operative and post-operative the modified dental anxiety scale had a significant drop of 3.68 points ($p=0.000$) with $p<0.05$ considered statistically significant. There was no significant difference between MDAS scores in the low anxiety group ($p=0.392$) with $p<0.05$ considered statistically significant (Hierons, Dorman, Wilson, Averley, & Girdler, 2012).

Outcomes

Conversion to neuraxial analgesia. Nitrous oxide can be used alone or in combination with other pain management options. Some women use nitrous oxide long enough to be in active labor or until the pain is no longer manageable. She could then convert to using an epidural that is also known as neuraxial analgesia. A retrospective study by Richardson, Lopez, Baysinger, Shotwell, and Chestnut (2017) showed that of women delivering vaginally in a hospital using nitrous oxide (N=1246) 40% ultimately converted to neuraxial analgesia. Another retrospective descriptive study by Sutton, Butwick, Riley, and Carvalho (2017) showed that of women using nitrous oxide for labor analgesia in a hospital (N=146) 63.2% converted to neuraxial analgesia. Induction of labor and augmentation of labor were independently associated with conversion to neuraxial analgesia (Sutton et al., 2017).

Duration of labor/Cesarean section rates. A RCT by Parsa, Saeedzadeh, Roshanaei, Shobeiri, and Hakemzadeh (2017) showed that primiparous women who used nitrous oxide in labor (n=60) had a significantly shorter duration of the first stage of labor on average (intervention group=64.80 minutes, control group=98.33 minutes, $p<0.001$).

In addition, the duration of the second stage of labor was also significantly shorter in the nitrous oxide group (intervention group=44.26 minutes, control group=64.25 minutes, $p<0.001$). Around 97% of women in the study had a vaginal birth and Cesarean section rates were not significantly different between the groups ($p>0.05$) with $p<0.05$ considered statistically significant. Previous study did show that less women in the nitrous oxide group had a Cesarean section compared to the control group but the difference was not significant ($p=0.52$) with $p<0.05$ considered statistically significant (Parsa et al., 2017).

Breastfeeding. The prospective case study by Zanardo et al. (2017) showed that at one month postpartum, women that used nitrous oxide in labor (n=62) were less likely to supplement with formula compared to the control ($p < 0.043$) with $p<0.05$ considered statistically significant. Even at three months postpartum women were less likely to supplement with formula compared to the control group ($p < 0.016$) with $p<0.05$ considered statistically significant (Zanardo et al., 2017). These findings support that nitrous oxide does not negatively affect mothers or neonates long-term. Women may even feel empowered by their childbirth experience, which in turn could affect breastfeeding success.

Maternal satisfaction. A retrospective study by Richardson et al. (2017) showed that although women that used nitrous in labor (n=1246) rated median pain relief lower than those who used epidurals (n=5261), they reported the same overall level of satisfaction with pain relief. The prospective case study by Zanardo et al. (2017) showed that at three months postpartum women that used nitrous oxide in labor (n=62) revealed childbirth satisfaction memory in 90% of women (Zanardo et al., 2017).

Strengths and Weaknesses of the Research Studies

Existing evidence regarding the effectiveness of inhaled nitrous oxide for pain relief in labor is strong. There is also evidence outlining the safety of using nitrous oxide for labor analgesia. Recent studies have investigated maternal satisfaction with utilizing nitrous oxide and outcomes on the labor course. Currently there are few studies related to epidural rates and Cesarean section rates. Future research focusing on out-of-hospital use of nitrous oxide is also needed.

Summary

The major findings of the critical appraisal of the literature include the safety of nitrous oxide for labor analgesia for both the mother and the neonate. Continuous inhalation versus intermittent inhalation has been reviewed. Effectiveness of pain relief was also examined. Outcomes including maternal satisfaction, conversion to neuraxial analgesia, Cesarean section rates, breastfeeding, and labor duration have also been reviewed in chapter three. Although much research has been conducted recently, further study is necessary as nitrous oxide use is becoming more prevalent in the U.S.

Chapter IV: Discussion

The critical appraisal of the literature revealed that the use of inhaled nitrous oxide in labor is safe for both mothers and neonates. It is effective in reducing labor pain although not as effective as an epidural. In addition to pain relief, it also has an anxiolytic effect, which can be very useful in labor. Throughout the literature women reported satisfaction with the use of nitrous oxide for labor analgesia.

Trends

Older research studies showed the safety of nitrous oxide for mothers and neonates as well as the level of pain relief compared to other forms of pharmacologic pain management options. Only recently have studies investigated maternal satisfaction with nitrous oxide. It is an important area of research as maternal satisfaction of labor analgesia is multifaceted.

In a study by Kabakian-Khasholian et al. (2017) maternal perception of control in childbirth was shown to be directly related to maternal satisfaction (Kabakian-Khasholian et al., 2017). The use of nitrous oxide allows for maternal control as the mother holds the mask or breathing tube and ultimately decides when to inhale the gas and when to stop. Due to the low solubility of nitrous oxide the effects are rapid (Becker & Rosenberg, 2008). It is easily reversible so if the mother would like to discontinue its use the effects will cease in 30-60 seconds (Stewart & Collins, 2012). This allows the mother to remain ambulatory and change positions easily.

Anxiety reduction in labor is also an important consideration in maternal satisfaction. Nitrous oxide is unique in the fact that it provides not only pain relief but also anxiety reduction. Higher levels of both generalized and pregnancy-related anxiety

in labor are associated with greater use of interventions (Koelewjin, Slujis, & Vrijkotte, 2017). The cycle of fear and tension is also thought to lead to increased pain (Dunn, 1994).

Gaps

While there are robust studies demonstrating the safety and effectiveness of nitrous oxide in labor there are still some gaps in the literature. This includes the use of nitrous oxide in settings other than hospitals and specific effects on epidural use including timing of epidural placement.

Most of the research completed has focused on the use of nitrous oxide in hospital settings. Nurse-midwives not only practice in the hospital setting but in out-of-hospital birth centers and in homes as well. Women in these settings have a lack of pharmacological pain management options for labor available to them in these settings. Many birth centers are utilizing nitrous oxide already. Therefore research regarding the use of nitrous oxide in these settings is needed.

There are also gaps regarding the use of nitrous oxide and its specific effects on epidural use. A few studies have focused on the rates of conversion to epidurals in women who utilize nitrous oxide studies. There is a gap in the research investigating if nitrous oxide has an effect on delaying epidural use until later in active labor. The current literature also does not specify whether epidural rates are decreased when women who desire an epidural free birth utilize nitrous oxide during labor.

Implications For Nurse-Midwifery Practice

Women should be educated about the use of nitrous oxide both prenatally and during labor. Patients can safely utilize nitrous oxide during any stage of labor for pain

and anxiety relief. Nitrous oxide can be used in conjunction with non-pharmacologic pain management options. Nitrous oxide can safely and effectively be used for other indications during labor including IV insertions, cervical exams, while waiting for epidural placement, during Cesarean section with spinal anesthesia, and during laceration repairs. Other women's health and maternity indications for nitrous oxide include external cephalic versions, pelvic exams, and IUD insertions.

Future Research

Safety and efficacy of nitrous oxide has been demonstrated by past research. Therefore future research should focus on the effects of nitrous oxide. This includes its effects on epidural rates and timing of epidural placement. It is especially important to study nurse-midwife patients that may desire an epidural-free birth or to at least delay the epidural until later in labor. Other areas of study could focus on utilizing nitrous oxide in conjunction with hydrotherapy and water birth and subsequent effects on epidural rates. Birth center and home birth settings should also be the focus of future studies including safety of nitrous oxide use, hospital transfer rates for pharmacologic pain management, and maternal satisfaction.

Application and Integration of Theoretical Framework

When considering labor analgesia Kolcaba's Theory of Comfort is very appropriate. Comfort during labor is very important and multifaceted. There are numerous ways nurses and midwives can assess for and provide comfort measures to women during labor to help promote relief, ease, and transcendence. When addressing comfort in the labor environment, one should address all four domains in Kolcaba's theory (Kolcaba et al., 2006). For the physical domain this could be the actual labor pain

and pain relief strategies utilized such as nitrous oxide, massage, or hydrotherapy. The psychosocial aspect could include providing adequate labor support and promoting confidence. The sociocultural aspect should address pertinent cultural beliefs. The environment should be addressed as well and could include a quiet and dark space.

While one may not be completely pain free in labor with nitrous oxide it can be an important piece of providing comfort and the goal of some may not even be complete pain relief. It also allows for use along with non-pharmacologic pain management options. Nitrous oxide can help to provide the physical comfort and relief from anxiety. For some women relief may be met with the use of nitrous oxide, for others they may experience ease or contentment, and others may even experience transcendence above the current pain.

Summary

This project examined the maternal and neonatal effects of utilizing nitrous oxide for labor analgesia. The critical appraisal of the literature showed that nitrous oxide is a safe and effective form of labor analgesia. Maternal satisfaction with nitrous oxide is also high. Nurse-midwives should educate patients about the use of nitrous oxide. Nitrous oxide can be used in conjunction with non-pharmacologic pain management options. Women can also utilize nitrous oxide for a variety of obstetric and women's health indications. Future research of nitrous oxide should focus on epidural rates, Cesarean-section rates, use of nitrous oxide in conjunction with hydrotherapy, and the use of nitrous oxide in the out-of-hospital setting.

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Ullman, R., Smith, L. A., Burns, E., Mori, R., & Dowswell, T. (2010). Parenteral opioids for maternal pain management in labour. *Cochrane Database Systematic Review,* (9). Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4233118/

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Table 1.

Matrix of the Literature

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Dammer, U., Weiss, C., Raabe, E., Heimrich, J., Koch, M. C., Winkler, M., … Kehl, S. (2014). Introduction of inhaled nitrous oxide and oxygen for pain management during labour – Evaluation of patients' and midwives' satisfaction. *Geburtshilfe Und Frauenheilkunde*, *74*(7), 656–660. http://doi.org/10.1055/s-0034-1368606 Level: 3 Quality: B	To determine the level of acceptance of the use of inhaled nitrous oxide by midwives and pregnant women during labor.	Sample: Pregnant women with singleton pregnancies who used nitrous oxide during labor between April-September 2013 (n= 66) Exclusion criteria: Breech presentation, primary cesarean section, intrauterine fetal death, and structural or chromosomal anomalies Setting: The Gynecology Department at the University Hospital of Erlangen	Observational study There were no changes to clinical practice. All women who met inclusion criteria between April- September 2013 were included in the study.	Questionnaire for pregnant woman: 1) Pain intensity with numerical rating scale 1-10 before and after using nitrous oxide. 2) Level patient tolerated nitrous oxide. 3) Side effects. 4) Likelihood to use nitrous oxide again. Questionnaire for midwife: 1) Midwife satisfaction of effect of nitrous oxide. 2) Stage of labor that nitrous oxide was used. 3) Why nitrous oxide was used.	Results: 1) Significant reduction of pain after nitrous oxide was administered. 2) Nitrous oxide was overall very well tolerated. 3) The majority of women reported having no side effects. 3) Most reported it was quite to very likely that they would use nitrous oxide again. 1) Most midwives reported satisfaction of nitrous oxide if their patient considered it likely they would use it again. 2) Most women used nitrous oxide during the dilation stage, but use was reported in all stages. 3) Most women used nitrous oxide because they refused an epidural. A few used it due to the inability to receive an epidural or with ineffective pain management with the epidural. Conclusion: Nitrous oxide was accepted well by laboring women and midwives in this study. Few women reported side effects and most tolerated it well. Most who used it would be prepared to use it in future labors.	Nitrous oxide is effective for use for labor analgesia and is very accepted by women and midwives. It is an important addition to other well-known pain management methods in Obstetrics.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Agah, J., Baghani, R., Tabaraei, Y., & Rad, A. (2016). Maternal side-effects of continuous vs. intermittent method of entonox during labor: A randomized clinical trial. *Iranian Journal of Pharmaceutical Research : IJPR*, *15*(2), 641–646. Level: 1 Quality: B	To determine whether the continuous administration of inhaled nitrous oxide during labor is as safe as intermittent administration.	Sample: Women in active labor using inhaled nitrous oxide (continuously= 50, intermittently= 50) Setting: Mobini Hospital in Sabzevar, Iran	Randomized clinical trial Women admitted for vaginal labor were divided by simple randomization into two equal groups for the study. Inhalation began at 3-4 cm dilation and ended was terminated by full dilation for both groups. 1) In the continuous group the woman breathed the nitrous oxide continuously. 2) In the intermittent group the woman breathed the nitrous oxide during a contraction only.	Questionnaire/Study form: 1) Maternal O2 saturation with pulse oximetry 2) Contraction duration and fetal heart rate 3) Labor progression 4) Maternal satisfaction 5) Maternal side effects	Results: 1) SpO2 was more than 95% in both groups with no significant differences between groups. 2) No significant differences in maternal and fetal outcomes between groups. 3) No significant difference in mean length of active labor between groups. 4) Maternal satisfaction was higher in the continuous group than the intermittent group. 5) No significant difference in side effects prevalence between groups. Conclusion: 1) There are no significant differences in side effects between continuous and intermittent use of nitrous oxide. 2) Maternal satisfaction was higher with continuous use.	Continuous use of inhaled nitrous oxide could lead to a reduction of pain in labor. More studies should be completed to investigate so that women can hopefully choose to use nitrous oxide either intermittently or continuously.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Pasha, H., Basirat, Z., Hajahmadi, M., Bakhtiari, A., Faramarzi, M., & Salmalian, H. (2012). Maternal expectations and experiences of labor analgesia with nitrous oxide. *Iranian Red Crescent Medical Journal*, *14*(12), 792–797. http://doi.org/10.5812/ircmj.3470 Level: 1 Quality: A	To determine the maternal experience and expectations of using nitrous oxide for labor analgesia.	Sample: Pregnant women in active labor (Intervention group = 49, control group = 49) Setting: Maternity ward of Shahid Yahyanejiad Hospital, Babol	Randomized controlled trial Subjects were randomly assigned to a nitrous oxide group or a group without nitrous oxide use.	Questionnaire including: 1) Expectation levels 2) Severity of pain 3) Satisfaction of using nitrous oxide 4) Efficacy 5) Related complications 6) Demographics	Results: 1) Expectation levels of women were weak in 40.9% of cases, medium in 17.4%, and good in 28.5 %. 2) Severity of pain in nitrous oxide group was moderate 46.9% compared to severe for the control group 55.1%. 3) 80.9% would request nitrous oxide again in the future. 4) Only 2% of intervention group were unsatisfied with nitrous oxide. 5) 93.8% experienced some complications from the nitrous oxide with varying degrees. Conclusion: 1) Pain was significantly less in the nitrous oxide group compared to the control group. 2) Adequate analgesia in labor can be a prognostic factor for satisfaction.	1) Nitrous oxide could be used to decrease the pain level of women undergoing natural birth. 2) Consideration should be given to the complications cause by the nitrous oxide including dry mouth, headache, dizziness, nausea, and drowsiness.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Talebi, H., Nourozi, A., Jamilian, M., Baharfar, N., & Eghtesadi-Araghi. (2009). Entonox for labor pain: A randomized placebo controlled trial. *Pakistan Journal of Biological Sciences, 12*(17), 1217-1221. doi:10.3923/pjbs.2009.1217.1221 Level: 1 Quality: A	To determine the effectiveness of nitrous oxide on labor contractions and maternal oxygen saturation	Sample: Women in labor between 38-42 weeks gestation (N=523) Setting: Arak University of Medical Sciences, Iran	Randomized placebo controlled trial Participants were randomly assigned to 50% nitrous oxide and oxygen inhalation or 50% oxygen inhalation groups when requesting pain medication in labor.	1) Visual analog scale (VAS) to rate labor pain from 0-10 2) Pulse oximetry to continuously measure maternal SpO2 3) Maternal blood pressure/mean arterial pressure (MAP) 4) 1 and 5 minute Apgar scores of infants 5) Questionnaire: Side effects experienced including nausea, vomiting, drowsiness, dry mouth, dizziness, and pins/needles or numbness sensation.	Results: 1) Pain was significantly lower in the nitrous oxide group. 2) The SpO2 was significantly higher in the oxygen group in the first three measurements but not in the remainder of the measurements. 3) The MAP was significantly higher in the oxygen group in the first two measurements but not in the remainder of the measurements. 4) No significant differences in 1 and 5 minute Apgar scores between groups. 5) Symptoms reported in nitrous oxide group: 22.6% dizziness, 15.4% drowsiness, 8.4% nausea, 2.3% vomiting, 8.3% dry mouth, and pins/needles or numbness 4.1%. Conclusion: There was a significant amount of reported pain relief by the nitrous oxide group. Few mild side effects were reported.	Inhaled nitrous oxide could be quickly implemented in labor for analgesia and provide significant pain relief.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Latto, I. P., Molloy, M. J., & Rosen, M. (1973). Arterial concentrations of nitrous oxide during intermittent patient-controlled inhalation of 50% nitrous oxide in oxygen (entonox) during the first stage of labour. *British Journal of Anaesthesia, 45*(10), 1029-1034. Retrieved from http://bja.oxfordjournals.org/content/45/10/1029 Level: 3 Quality: B	Determine what blood levels of nitrous oxide occur during labor when nitrous oxide is inhaled intermittently.	Sample: Women in labor (n=15) intermittently inhaling nitrous oxide for labor analgesia Setting: University Hospital of Wales	Descriptive study Women were approached before labor and were informed of the purpose of the study. They consented to use nitrous oxide intermittently during labor for analgesia. An arterial cannula was inserted during labor. Mean arterial blood levels of nitrous oxide at the beginning of a period of inhalation, at the end of a period of inhalation, 30 seconds after inhalation ends, and 60 seconds after inhalation ends.	Gas chromatography to measure mean arterial blood levels of nitrous oxide at the beginning of a period of inhalation, at the end of a period of inhalation, 30 seconds after inhalation ends, and 60 seconds after inhalation ends.	Results: The range of mean arterial concentrations at the beginning of inhalation was 0.2 mg/100 mL-6.2 mg/100 mL, at the end of inhalation was 8.5 mg/100 mL-28.3 mg/100 mL, and 30 seconds after inhalation ended was 8.2 mg/100 mL. Conclusion: Previous studies demonstrated that a mean concentration of nitrous oxide of 41.2% was required for optimum pain relief. The women in this trial did not meet this level with intermittent inhalation. There was also rapid elimination of nitrous oxide after inhalation ended	1) Administer a higher fixed concentration of nitrous oxide. 2) Inhale nitrous oxide continuously at a lower concentration through a nasal cannula that would not result in the woman losing consciousness. During a contraction the woman can then breath the 50% nitrous oxide and 50% oxygen through a facepiece. 3) Inhale a few breaths of nitrous oxide between contractions.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Sutton, C. D., Butwick, A. J., Riley, E. T., & Carvalho, B. (2017). Nitrous oxide for labor analgesia: Utilization and predictors of conversion to neuraxial analgesia. *Journal of Clinical Anesthesia, 40*, 40-45. doi: 10.1016/j.jclinane.2017.04.005 Level: 3 Quality: B	Review characteristics of women who choose nitrous oxide for labor analgesia. Determine if certain factors predict conversion from nitrous oxide to neuraxial analgesia in labor.	Sample: Women in labor (n=146) who used nitrous oxide for labor analgesia between September 2014 and September 2015 Setting: Lucille Packard Children's Hospital	Retrospective descriptive study Electronic medical records of women that used nitrous oxide at any point in labor and delivery between September 2014 and September 2015 were reviewed. No changes were made to clinical practices.	Chart review	Results: 1) 82.1% of women were English speaking. 2) 71.9% were nulliparous. 3) 51.9% previously indicated a preference for a nonmedical birth. 4) 63.2% converted to neuraxial analgesia. 5) Induction of labor and augmentation of labor were independently associated with conversion to neuraxial analgesia. Conclusion: Women who used nitrous oxide in labor were more likely to be nulliparous, English-speaking who indicated a preference for nonmedical birth. Induction and augmentation of labor was associated with conversion to epidural anesthesia.	1) Offering nitrous oxide for labor analgesia has minimal impact on the neuraxial anesthesia rate in the United States. 2) Healthcare providers can use this information during the informed consent process so that patients are aware that conversion to epidural anesthesia is a strong likelihood especially with induction and augmentation of labor.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Parsa, P., Saeedzadeh, N., Roshanaei, G., Shobeiri, F., & Hakemzadeh, F. (2017). The effect of entonox on labour pain relief among nulliparous women: A randomized controlled trial. *Journal of Clinical & Diagnostic Research, 11*(3). doi: 10.7860/JCDR/2017/21611.9362 Level: 1 Quality: B	Determine the effects of Entonox use on pain relief and labor duration for nulliparous women.	Sample: Nulliparous women in active labor (Intervention group=60, control group=60) Setting: Atieh Hospital, Hamadan, Iran	Randomized controlled trial Women were randomly chosen to receive either Entonox or oxygen during labor. Women were not aware whether they were inhaling oxygen or Entonox. Initiation of inhalation began with pain of the contraction and cease with the end of the contraction.	1) Visual analog scale (VAS) to rate labor pain from 0-10 2) Maternal blood pressure 3) Pain duration (hours) 4) Duration of labor (hours)	Results: 1) Pain was significantly lower in the Entonox group. 2) No significant difference in maternal blood pressure between groups. 3) Pain relief was demonstrated in the first and second stage of labor in the Entonox group. 4) The duration of labor was significantly shorter in the Entonox group. 5) Cesarean section rates were not significantly different between groups. Conclusion: Entonox use in labour demonstrated pain relief and shorter duration of labor. There were no significant reported complications with Entonox use.	Inhalation of Entonox is useful to decrease labor pain.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Attar, A. S., Feizabadi, A. S., Jarahi, L., Feizabadi, L. S., & Sheybani, S. (2016). Effect of entonox on reducing the need for pethidine and the relevant fetal and maternal complications for painless labor. *Electronic Physician, 8*(12), 3325-3332. doi: 10.19082/3325 Level: 1 Quality: A	Determine the analgesic effects of Entonox use in labor in regards to reducing the need for pethidine (Meperidine) and maternal and fetal complications.	Sample: Nulliparous women aged 18-40 with term pregnancy in active labor (Intervention group=200, control group=200) Setting: Mashhad University of Medical Sciences teaching hospitals, Mashhad, Iran	Double- blind randomized controlled trial Women were randomly chosen to receive either Entonox or oxygen during labor. Women and surgeons were not aware whether the patient was inhaling oxygen or Entonox. Initiation of inhalation began with pain of the contraction and cease after the contraction ended.	1) Numeric rating scale (NRS) to rate labor pain intensity from 0-10 2) Maternal hemodynamic status (blood pressure, pulse, respiratory rate, and pulse oximetry) 3) Fetal heart rate 4) Duration of active and second stage of labor 5) 1&5 minute Apgar scores 6) Infant pulse oxygen saturation 7) Infant's cord pH 8) Need for Meperidine (NSR >4) 9) Reported maternal side effects	Results: 1) Pain was significantly less in the Entonox group. 2) No significant differences in maternal hemodynamic status or fetal heart rate between groups. 3) Significantly shorter duration of delivery in the Entonox group. 4) No significant difference in neonatal Apgar scores between groups. 5) Significantly decreased need for Meperidine use in the Entonox group. 6) No significant differences for reported maternal symptoms between groups. Conclusion: Entonox significantly reduced pain without maternal or neonatal complications.	Entonox can be used to improve labor pain without increasing maternal or neonatal complications. Entonox can be used to decrease Cesarean sections due to labor pain thus decreasing risks related to surgery and also decrease costs.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Carstoniu, J., Levytam, S., Norman, P., & Daley, D. (1994). Nitrous oxide in early labor. Safety and analgesic efficacy assessed by a double-blind, placebo-controlled study. *Anesthesiology, 80*, 30-35. Level: 1 Quality: C	Determine effects of nitrous oxide inhalation on labor pain and maternal oxygen saturation during the first stage of labor.	Sample: Women greater than age 18 (n=26) requesting analgesia in the first stage of labor Setting: Toronto Hospital	Randomized, double-blind, cross-over, placebo-controlled study Once participants requested analgesia women were randomly placed in 1 of 2 groups receiving nitrous oxide intermittently for the duration of 5contractions then oxygen intermittently for the duration of 5contractions or vice versa. Masks were identical and tank equipment was hidden from participants view. Nurses offered the appropriate masks to women.	1) Visual analog scale (VAS) to rate labor pain from 0-10 2) Pulse oximetry to measure maternal SpO2	Results: 1) There were no significant differences in pain scores between air or nitrous oxide administration during contractions. 2) 21 patients were able to correctly identify the order in which gases were administered. 3) Oxygen saturation was significantly higher after women received inhaled nitrous oxide. Conclusion: 1) Study failed to demonstrate a significant analgesic effect of nitrous oxide compared to air. 2) Nitrous oxide is safe in regards to maternal oxygenation	While nitrous oxide appears to be safe, additional research is needed to determine the analgesic effect compared to air. This study is in contrast with previous studies that demonstrated a significantly decreased pain rating when nitrous oxide is used for labor analgesia.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Rosenstein, M., Flood, P., Thiet, M., Nakagawa, S., Bishop, J. & Cheng, Y. (2014). The use of nitrous oxide analgesia during labor at a single institution in the United States. *American Journal of Obstetrics and Gynecology,* S294-S295. Retrieved from http://www.ajog.org/article/S0002-9378(13)01696-7/pdf Level: 3 Quality: B	Determine the maternal and neonatal outcomes associated with nitrous oxide use for labor analgesia in a U.S. hospital.	Sample: Laboring women (n=868) that used nitrous oxide at any point during labor between 2007-2012 Setting: University of California, San Francisco	Descriptive study	Chart review	Results: 1) 42% of women that used nitrous oxide also used an epidural compared to 76% of women who did not received an epidural but did not use nitrous oxide. 2) Women receiving nitrous oxide were more likely to be nulliparous. 3) Women receiving nitrous oxide were less likely to receive oxytocin, deliver via C-section, or develop chorioamnionitis. 4) There were no significant differences in neonatal Apgar scores or acidemia between those that used nitrous oxide and those that did not. Conclusion: Nitrous oxide use in labor is not associated with increased maternal or neonatal risks.	Nitrous oxide is a safe alternative for women who do not desire and epidural or those who have a contraindication to epidural anesthesia.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Agah, J., Baghani, R., Tali, S. H., & Tabarraei, Y. (2014). Effects of continuous use of entonox in comparison with intermittent method on obstetric outcomes: A randomized clinical trial. *Journal of Pregnancy.* doi: 10.1155/2014/245907 Level: 1 Quality: B	Determine whether there are increased maternal complications associated with continuous Entonox use versus intermittent Entonox use.	Sample: Laboring women at term (Intermittent use=50, continuous use=50) Setting: Sabzevar Mobini Hospital, Iran	Randomized control trial Women were assigned to separate groups by simple randomization. In the intermittent group women inhaled the Entonox during contractions only. In the continuous group women inhaled the gas constantly.	1) Duration of labor (hours) 2) Perineal lacerations 3) Necessity to vacuum assisted delivery 4) Neonatal Apgar scores 5) Pulse oximetry to measure maternal SpO2 6) Uterine atony	Results: 1) No significant difference in labor duration between groups. 2) Perineal lacerations were significantly higher in the intermittent group. 3) No significant difference in necessity for vacuum assistance in delivery between the groups. 4) Neonatal Apgar scores were acceptable in both groups and there was no significant difference between groups. 5) Maternal SpO2 was not significantly different between the groups. Nor were there other significant reported adverse effects that were significantly different between the groups. 6) No significant difference in uterine atony between the groups. Conclusion: Entonox use did not demonstrate any adverse effects on the labor or delivery whether it was used intermittently or continuously. Perineal lacerations occurred less frequently with continuous Entonox use compared to intermittent use. Maternal satisfaction was higher in the continuous group as well.	Entonox is safe use to use continuously in labor with acceptable obstetric outcomes. Women should be free to choose whether to use Entonox continuously or intermittently.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Onody, P., Gil, P., & Hennequin, M. (2006). Safety of inhalation of a 50% nitrous oxide/oxygen premix. *Drug Safety 2006, 29*(7), 633-640. doi: 0114-5916/06/0007-0633 Level: 3 Quality: A	To analyze the factors that affect the tolerance of inhaled nitrous oxide for a wide variety of clinical indications.	Sample: Data sheets completed for patients that received an administration of 50% nitrous oxide/oxygen premix (n=35,828) for a wide variety of painful clinical procedures over 4 years Setting: 191 French hospital pediatric and adult units	Prospective study French hospitals were required to complete a data sheet on each patient receiving administration of inhaled 50% nitrous oxide/oxygen upon receiving a temporary license for the drug.	Drug data sheet to be completed by physician: 1) Patient demographics 2) Clinical indication 3) Duration of administration 4) Drug association 5) Serious and/or unexpected adverse effects 6) Non severe and/or expected events	Results: 1) Among the 27 severe adverse effects reported (0.08%) only 9 (0.03%) were reported to have a causal relationship with the drug. Consciousness disorder (n=1), bradycardia (n=1), vomiting (n=2), headache (n=1), sweating (n=1), nightmares (n=1), and somnolence (n=1). 2) Two of the most clinically significant cases reported to not be causality related to the drug included cardiac arrest (n=1) and narcolepsy (n=1) were both reported to be linked to inappropriate administration and surveillance. Conclusion: Serious adverse effects were rare (0.08%). The study verified the pharmacological safety of 50% nitrous oxide/oxygen.	50% inhaled nitrous oxide/oxygen is safe form of pain management for a wide range of clinical indications. It is important to implement specific training especially for non-anesthesiologists.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Zanardo, V., Volpe, F., Parotto, M., Giiberti, L., Selmin, A., & Straface, G. (2017). Nitrous oxide labor analgesia and pain relief memory in breastfeeding women. *The Journal of Maternal-Fetal & Neonatal Medicine.* doi: 10.1080/14767058.2017.1368077 Level: 3 Quality: B	To investigate the level of pain relief with inhaled nitrous oxide in labor, maternal emotions towards lactation, maternal satisfaction with birth experience, and whether there is a difference in breastfeeding outcomes at 3 months postpartum between mothers who used nitrous oxide and those who did not.	Sample: Term pregnant women that used inhaled nitrous oxide for labor analgesia (intervention=62) and those without inhaled nitrous oxide (control=124) from January-April 2016 Setting: Division of Perinatal Medicine in Abano Terme, Italy	Prospective case-control study The trial began when women requested inhaled nitrous oxide in labor. The nitrous oxide was used intermittently and self-administered via facemask by the patient.	1) Retrospective visual analog scale (VAS) from 0-10 to rate both the quantity and quality of pain relief, that was completed 3 months postpartum in the nitrous oxide group. 2) Chart review for breastfeeding records of both groups. 3) Telephonic interview at 1 and 3 months postpartum for breastfeeding status in both groups.	Results: 1) At 3 months postpartum a 0-10 VAS scale of quantity and quality of pain revealed lasting positive pain relief experience in 83.5% and childbirth satisfaction memory in 90% of women that used nitrous oxide. 2) At 1 month postpartum women that used nitrous oxide in labor were less likely to supplement with formula compared to the control ($p < .043$). At 3 months postpartum the nitrous oxide was still less likely to supplement with formula compared to the control group ($p < .016$). Conclusion: Use of nitrous oxide in the study was associated with lasting positive childbirth experience and pain relief as well as increased breastfeeding success.	It could be helpful to identify factors that lead to a positive birth experience due to the correlation with breastfeeding.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Burgos, J., Cobos, P., Osuna, C., Centeno, M. M., Fernandez-Llebrez, L., Astorquiza, T. M., & Melchor, J. C. (2013). Nitrous oxide for analgesia in external cephalic version at term: Prospective comparative study. *Journal of Perinatal Medicine, 41*(6), 719-723. doi: 10.1515/jpm-2013-0046 Level: 3 Quality: A	To analyze the effect of using inhaled nitrous oxide for external cephalic versions (ECV) at term.	Sample: Women with singleton breech pregnancy at term using inhaled nitrous oxide for external cephalic version (intervention=300) and those that did not use any analgesia (control=150) Setting: Cruces University Hospital in Biscay, Spain	Prospective comparative study Nitrous oxide was administered via a facemask beginning 3 minutes before the procedure and continuously throughout the procedure (2-4 min)	1) Visual analog scale (VAS) to rate labor pain from 0-10, 1-3 (mild pain), 4-7 (moderate pain), 8-10 (severe pain). 2) Chart review	Results: 1) Only 19.3% of women with nitrous oxide reported severe pain vs. 37.8% of the control group ($p<0.01$). 2) The ECV success rate was similar between the groups (intervention=52.3%, control=52.7%, P=0.94). Conclusion: Administration of inhaled nitrous oxide is safe and effective to reduce pain during ECV.	The analgesic effect is significant enough to recommend nitrous oxide use during an ECV.

Citation/Level & Quality	Purpose of Study	Sample/Setting	Design		Results	Authors' Recommendations
			Methodology	Instruments		
Singh, R. H., Thaxton, L., Carr, S., Leeman, L., Schneider, E. & Espey, E. (2016). A randomized controlled trial of nitrous oxide for intrauterine device insertion in nulliparous women. *International Journal of Obstetrics & Gynecology, 135*, 145-148. doi: 10.1016/j.ijgo.2016.04.014 Level: 1 Quality: B	To analyze the effectiveness of using inhaled nitrous oxide for pain relief during IUD insertion in nulliparous women.	Sample: Nulliparous women aged 13-45 years who chose an IUD for contraception and used inhaled nitrous oxide for insertion analgesia (intervention=40) and those who inhaled oxygen (control=40) Setting: University of New Mexico in Albuquerque, NM	Randomized, double blinded, placebo-controlled trial	1) Visual analog scale (VAS) to rate pain from 0-100. 2) 5 point Likert scale (very satisfied, satisfied, neutral, dissatisfied, and very dissatisfied).	Results: 1) Mean insertion pain scores were similar between the groups (P=0.86). 2) Significantly more women in the intervention group were more satisfied with the pain management on the Likert scale (P=0.04). Conclusion: Women who received nitrous oxide were more satisfied with their pain relief than those who received oxygen.	Women who desire pain management for IUD placement could benefit from the use of nitrous oxide. It could also be investigated for use with other gynecologic office procedures. Levels could potentially be titrated to achieve increased pain relief.

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Richardson, M. G., Lopez, B. M., Baysinger, C. L., Shotwell, M. S., & Chestnut, D. H. (2017). Nitrous oxide during labor: Maternal satisfaction does not depend exclusively on analgesic effectiveness. *Anesthesia & Analgesia, 124*(2), 548-553. doi: 10.1213/ANE.0000000000001680 Level: 3 Quality: B	To compare the relationship between the effectiveness of pain relief as well as satisfaction with pain management between women who used nitrous oxide alone, neuraxial analgesia, and nitrous oxide with conversion to neuraxial analgesia.	Sample: Women delivering vaginal using nitrous oxide (nitrous=1246) and those who used neuraxial analgesia (neuraxial=5261) Setting: Vanderbilt University Medical Center in Nashville, TN	Retrospective study Women chose their own form of pain management. Those included in the study chose either nitrous oxide and/or neuraxial analgesia.	Standardized survey: 1) 0-10 scale rating effectiveness of pain relief 2) 0-10 scale rating overall satisfaction with analgesia care	Results: 1) 40% of women that chose nitrous oxide converted to neuraxial analgesia. 2) The median score of effectiveness of pain relief with neuraxial analgesia and nitrous oxide with conversion to neuraxial analgesia was 10 (9-10). The median score of effectiveness of pain relief with nitrous oxide alone was 8 (5-10). 3) For all 3 groups the median rating of overall satisfaction of analgesia care was 10 (10-10). Conclusion: Although the effectiveness of pain relief varied in the nitrous oxide group, overall satisfaction was still high.	Satisfaction with labor is not solely determined by the effectiveness of analgesia. Other important factors to consider are mobility, strength, and preservation of bodily sensations in labor.

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Manouchehrian, N., & Bakhshaei, M. H. (2014). Nitrous oxide effect on relieving anxiety and pain in parturients under spinal anesthesia for caesarean section. *Anesthesiology and Pain Medicine*, *4*(2). http://doi.org/10.5812/aapm.16662 Level: 1 Quality: A	To determine the level of anxiety and pain relief when using inhaled nitrous oxide in women undergoing cesarean section under spinal anesthesia.	Sample: Primigravid women undergoing elective cesarean section receiving nitrous oxide (intervention=28) and those receiving oxygen (control=28) Setting: Hamadan University of Medical Sciences, Iran	Double-blind clinical trial Either inhaled nitrous oxide or oxygen was administered 3 minutes prior to inducing spinal anesthesia and was continued until delivery.	1) Visual analog scale (VAS) to rate anxiety from 0-10. 2) Visual analog scale (VAS) to rate pain from 0-10.	Results: 1) Mean anxiety levels were significantly lower in the nitrous oxide group (P=0.003). 2) Mean pain levels were significantly lower in the nitrous oxide group (0.82 ± 1.5) compared to (1.64 ± 1.45). Conclusion: Nitrous oxide is effective in reducing anxiety and pain compared to oxygen in women underdoing cesarean sections under spinal anesthesia.	Inhaled nitrous oxide can be useful in reducing anxiety and pain in women undergoing cesarean section.

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Vallejo, M. C., Phelps, A. L., Shepherd, C. J., Kaul, B., & Ramanathan, S. (2005). Nitrous oxide anxiolysis for elective cesarean section. *Journal of Clinical Anesthesia, 17*(7), 543-548. https://doi.org/10.1016/j.jclinane.2005.01.009 Level: 1 Quality: A	To investigate whether 40% nitrous oxide is an effective anxiolytic for women undergoing elective cesarean section with spinal anesthesia.	Sample: Women undergoing elective cesarean section utilizing 40% inhaled nitrous oxide (intervention=30) and those inhaling 100% O2 (control=30) Setting: University of Pittsburgh, PA	Randomized, double-blinded study	Visual analog scale (VAS) to rate pain and anxiety from 0-100.	Results: 1) Reported anxiety was significantly lower in the intervention group during the spinal injection, skin incision, and uterine incision compared to the control ($P<0.05$). 2) Among high anxiety patients anxiety was significantly lower in the intervention group during the spinal injection, skin incision, and uterine incision compared to the control ($P=0.03$). 3) Among those with low anxiety there was no statistical difference between groups (<50 VAS). Conclusion: 40% nitrous oxide is an effective anxiolytic for high anxiety women (>50 VAS) undergoing elective cesarean section at the time of spinal injection, skin incision, and uterine incision.	40% nitrous oxide can be used safely and effectively as an anxiolytic for high anxiety women undergoing elective cesarean section as opposed to intravenous sedation.

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Hierons, R. J., Dorman, M. L., Wilson, K., Averley, P., & Girdler, N. (2012). Investigation of inhalational conscious sedation as a tool for reducing anxiety in adults undergoing exodontia. *British Dental Journal, 9*. doi: 10.1038/sj.bdj.2012.839 Level: 3 Quality: B	To determine whether inhaled nitrous oxide is an effective anxiolytic in adults receiving exodontia.	Sample: Adults undergoing exodontia between July 21, 2010-December 17, 2010 with moderate to severe anxiety and receiving inhaled nitrous oxide and local anesthetic (n=60), those with mild anxiety receiving inhaled nitrous oxide and local anesthetic (n=43), and those receiving oxygen with local anesthetic (n=35) Setting: Primary care oral surgery service in England	Retrospective study	The Modified Dental Anxiety Scale (MDAS) measuring anxiety level with treatment occurring the next day, waiting in the waiting room for treatment, having a tooth drilled, having teeth scaled and polished, and having a local anesthetic injection (from not very anxious to extremely anxious).	Results: 1) Among the moderate to severe anxiety group receiving inhaled nitrous oxide, the pre-operative and post-operative MDAS had a significant drop of 3.68 points (p=0.000). 2) There was no significant difference between MDAS scores in the low anxiety group (p=0.392). Conclusion: It is effective to utilize inhaled nitrous oxide during dental procedures.	Nitrous oxide can be helpful to reduce anxiety in some patients undergoing painful dental procedures.

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Volmanen, P., Akural, E., Raudaskoski, T., Ohtonen, P., & Alahuhta, S. (2005). Comparison of remifentanil and nitrous oxide in labour analgesia. *Acta Anesthesiologica Scandinavica, 49*, 453-458. doi: 10.1111/j.1399-6576.2005.00639 Level: 1 Quality: B	To compare the effectiveness and side effects of remifentanil with nitrous oxide for labor analgesia during the first stage.	Sample: Healthy, term women in the first stage of labor randomly assigned to group 1 (n=10) and assigned to group 2 (n=10) Setting: Oulu University Hospital, Finland	Randomized, double-blind, crossover study Groups utilized the study medicines for 20 minutes with a washout period of 20 minutes between. Group 1: 1st period: Intravenous remifentanil and inhaled placebo (oxygen) 2nd period: Intravenous placebo (saline) and inhaled nitrous oxide Group 2: 1st period: Intravenous placebo (saline) and inhaled nitrous oxide 2nd period: Intravenous remifentanil and inhaled placebo (oxygen)	1) 11-point rating scale for pain (0-10) 2) Maternal vital signs including heart rate, oxygen saturation, and blood pressure 3) Fetal heart rate tracing, Apgar scores, and umbilical artery pH of neonate	Results: 1) The reported pain relief with remifentanil was significantly higher than nitrous oxide ($P<0.001$). 2) Sedation scores were higher with remifentanil than nitrous oxide ($P=0.02$). 3) There was reduced fetal heart rate variability in 3 cases with the remifentanil administration. Conclusion: Remifentanil provided greater pain relief than nitrous oxide during the second stage of labor.	The study suggests that remifentanil is more effective than nitrous oxide for labor analgesia. Additional study is needed however, due to the small sample size and the suboptimal nitrous oxide system.