2016

The Use of Nitrous Oxide in the Management of Labor Pain: Safet and Effiacy

Jennifer Ruth Christensen
Bethel University

THE USE OF NITROUS OXIDE IN MANAGEMENT OF LABOR PAIN: SAFETY AND EFFICACY

A MASTER'S PROJECT

SUBMITTED TO THE GRADUATE FACULTY

OF THE GRADUATE SCHOOL

BETHEL UNIVERSITY

BY

JENNIFER R. CHRISTENSEN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

MASTER OF SCIENCE IN NURSE-MIDWIFERY

MAY 2016

BETHEL UNIVERSITY

The Safety and Efficacy of Nitrous Oxide in Labor and Delivery: A Critical Review of the Literature

Jennifer Ruth Christensen

May, 2016

Approvals

Project Advisor Name: __Katrina Wu_APRN, CNM_____

Project Advisor Signature: _____

Second Reader Name: __Dr. Julie Ann Vingers APRN, CNM_____

Second Reader Signature: _____

Director of Graduate Nursing Program Name: __Dr. Jane Wrede APRN, CNM_____

Director of Graduate Nursing Program Signature: _____

Acknowledgements

I would like to start my acknowledgements by thanking my Mom and my Dad. It is with extreme sadness that I say neither of them will be here to read this in person, though I believe they are reading it from heaven. My mother succumbed to Lymphoma just days after turning 62, as she should have been retiring to enjoy life and what she worked so hard earn. Mom was the most beautiful person most people ever met. Everyone who ever met her loved her, and she was an amazing mother. I still remember the pride she had when she found out I would be going to University to Wisconsin – River Falls for my undergrad … and the disappointment when I first told her I was "taking some time off" and coming home, when I was not far from actually graduating. Those reactions are forever in my head and in my heart, as I have worked so hard to make her proud both in life and in death. I can't believe my mom won't be there in person to see me walk across the stage. It is one of my greatest regrets in life that I did not finish my Bachelor's degree while she was still alive. I love you and miss you Mom and I did this for you!

To my Dad who died of a lost and broken heart, just 18 months after Mom died, from whom I received my character for better or for worse. At a time in my life when I was angry at the sudden loss of both my parents, and floundering around not sure what to do, or where to go next, I remember overhearing my Dad (who had never shown one iota of interest in my academic endeavors) proudly telling his hospice nurse that I was going to school for my Master's degree. I was not at the time. I was slowly, aimlessly working my way towards finishing my Bachelor's degree, but by gosh I'll be darned if I was going to tell anyone that wasn't the truth. Hearing him say that gave me something to live up to, and it gave me new aim.

To my husband John, who has been my best friend and my rock as we have endured the loss of all of our parents in a very short time frame together, and hardship these past two years as

we have traveled this road together, I love you. Without your sacrifices and help, none of this would have been possible. I know we have fought and I have gotten upset with undone chores and messes at times, but you have done an amazing job of keeping everything running while I have been away for days at a time. My city slicker has become quite the little farm boy these last several years, and I would be lost without you. I promise that when this is done, I will never sit behind a computer screen ignoring you for hours on end again.

I owe gratitude to my beautiful pets - my family members who have stood by faithfully while I have locked myself away writing this paper. My beloved Izzy and Ginger have grown to be old and gray in the last two years. The happy-go-lucky pup is no longer a pup and has now suffered a debilitating injury, while I pushed her away through her years of youth, health and playfulness. Dear Frannie, the cat, has had a stroke and can no longer jump on the bed for cuddles.

I would like to thank my advisor Katrina Wu, who had insight into the use of nitrous oxide and was an encouragement throughout the process. Whenever I got stuck throughout both this review as well as during the program in general, I could always count on Katrina to explain perfectly so that I understood, but without outright giving me the answer. Katrina's influence to think of women's health in a more natural way, with her tales of home births and diaphragms and menstrual cups, has been invaluable to me and I will carry with me wherever I go.

It is important to me to thank Jane Wrede as well for believing in me, for being my friend and taking me in and encouraging me when I needed it most.

To my preceptors: Penny Menke, Chillon McKibbon, Renee McNeil, Jane Wrede, and Paige Hardy – There is more to say than what I am able to put on this paper. Each and every one of you has become an integral part of who I am and how I practice. I hope that I can always give

safe, innovative, holistic and downright amazing care to women and live up to everything you have hoped for me.

I would like to thank the staff and patients of Methodist Hospital in St. Louis Park MN for letting me be a part of the inaugural implementation of nitrous oxide in Minnesota, which served to add personal insight, richness and depth to my writing as I worked on this literature review.

I cannot conclude a list of acknowledgements without thanking my past employer, who gave me the motivation that I needed to move on to something bigger and better. This one is for you! On a more serious note, it really was at this job that I first met nurses who were pursuing Master's degrees, including some very good friends whose footsteps I was able to follow in through grad school. Without this exposure, the thought may never have entered my mind.

Three pages later and I realize I have a lot to be thankful for. But my acknowledgments sections would be missing something if I did not take the time to thank my 3000-plus Facebook friends who have had to bear with me, as I have status updated my way through the last two unbelievable years. You have been some of my best supporters and encouragers, even when I way over-posted about my woes!

Very last, but not least in any way – my classmates, my ♥♥♥ -- XOXO always.

Table of Contents

Abstract

Background: All women will experience pain while going through childbirth. The pain is caused by pressure and stretching on the uterus and visceral organs, lack of oxygen during uterine contractions, and musculoskeletal and perineal stretching. Difficulty coping with pain leads to an increase in catecholamines, which further complicates the labor process and can contribute to long term psychological consequences. Up to 75% of women in other countries use nitrous oxide, a colorless odorless gas, to manage their labor pain. In the United States, the options for managing labor pain have consisted of non-pharmacological methods such as massage, breathing and relaxation techniques, hydrotherapy, etc; neuraxial methods ie: epidurals or spinals; and parenteral narcotic administration. Up until about 2015, only five hospitals in the United States offered nitrous oxide and women in the United States have fewer options available for pain management than other countries. Multiple other hospitals and birth centers have begun to offer this option. The American College of Nurse Midwives has indicated that women should have as many safe options for pain management as possible and has encouraged the use of nitrous oxide, as well as continuing research.

Purpose: To evaluate the safety and efficacy of nitrous oxide in labor and delivery.

Results: Twenty-four articles were identified for review and appraised using the Johns Hopkins Research Evidence Appraisal Tool. The major findings of the reviewed literature include that nitrous oxide is safe to use for both mothers and babies. Nitrous oxide is safe to use in special circumstances, such as when epidural or parenteral opioids are contraindicated, for postpartum perineal repair or cephalic version, and has some anxiolytic properties that appear valuable as well. The efficacy of nitrous oxide is less clearly defined due to difficulty in measuring pain and the highly individualized nature of labor and delivery. Efficacy appears highly dependent on

patient expectation, though in populations where nitrous oxide has been used, its use is heavily favored and recommended.

Conclusions: Nitrous oxide is very safe for both mothers and infants. It is cheap, easy to use, and does not require the presence of anesthesia staff to administer. It is easily portable and fast to set up and administer. Discussing pain management goals and expectations will help improve satisfaction, as well as ensuring proper use to achieve maximum effectiveness. Consistent with King's Theory of Goal Attainment, nitrous oxide offers a patient-controlled analgesia option that maximizes a woman's access to, and control of, safe, effective options for managing their pain while in labor.

Implications for Research and Practice: There is considerable room for further, good quality, randomized controlled trials. Areas of study needed include the use of nitrous oxide in specific situations, and especially its use as an anxiolytic. There is enough evidence currently to support the promotion and use of nitrous oxide for pain management in labor and delivery. The use of nitrous oxide fits the practice philosophy of nurse-midwives well, and nurse-midwives are well-suited to champion the use of nitrous oxide in practices of all types, including birth centers and rural settings.

Key Words: Nitrous oxide, Entenox, Nitronex, Patient-controlled analgesia, pain management, anxiolytic, nurse-midwives, labor pain, childbirth, pain management alternatives, safety, efficacy

Chapter 1: Introduction

Background

Since life began, women have been giving birth to future generations and since that time pain has been a part of this process. Labor pain is one of the most acute pains women will experience in their lives (Pasha et al., 2012). Labor pain has been attributed to stretching and pressure on the uterus and visceral organs, lack of oxygen during uterine contractions, and musculoskeletal and perineal stretching (King, Brucker, & Fahey, 2013; Posner, Dy, Black, & Jones, 2013). Every individual will experience pain in a different way, both in terms of what she is feeling, as well as in terms of how she is able to cope. When women have difficulty coping with pain, it leads to an increase in catecholamines, which can reduce the effectiveness of contractions and contribute to fatigue, dystocia, and fetal distress (Adams, Eberhard-Gran, & Eskild, 2012). One concept that is almost universally accepted is that labor and birth are a pain unlike any other experienced in life. Some women may suffer psychological consequences secondary to ineffective coping and disempowerment, long after the actual birth that can be so severe as to contribute to the development of post-traumatic stress disorder (Andersen, Melvaer, Videbech, Lamont, & Joergensen, 2012; Nilsson, Bondas, & Lundgren, 2010; Rooks, 2012).

In the United States, the options for managing labor pain have consisted of non-pharmacological methods such as massage, breathing and relaxation techniques, hydrotherapy, etc; neuraxial methods ie: epidurals or spinals; and parenteral narcotic administration. In other countries, the majority of women use a fourth option – nitrous oxide. About 50-75% of women in the UK and 60% of women in Finland use it. Its use is also common in Australia, New Zealand, and even in Canada (Likis et al., 2014; Rooks 2007).

Nitrous Oxide

Nitrous oxide is a colorless, odorless, tasteless gas composed of two nitrogen atoms and one oxygen atom that can be inhaled in various concentrations with oxygen. The most commonly used concentration during labor today is 50% of each (Stewart & Collins, 2012). It is thought to stimulate endogenous endorphins as well as the release of corticotropins and dopamines, which creates a euphoric effect. Women experience less pain and/or care less about the pain they do experience, along with having decreased anxiety. The effects are experienced usually within 30-60 seconds from initiation. Women remain awake and alert, with full sensory and motor functioning. They may use nitrous continuously, intermittently with their contractions, or they may use it in blocks of time alternating between use and non-use (Stewart & Collins, 2012). It leaves the maternal system as quickly as it enters, via exhalation (Akerman & Dresner, 2009). IV access or continuous fetal monitoring are not required as a result of nitrous oxide use (Stewart & Collins, 2012).

Statement of Purpose

The purpose of this project is to critically appraise scholarly literature to answer the following question: "Is nitrous oxide a safe and effective alternative to current pain management practices for laboring women?" In addition to general safety and effectiveness, the areas of discussion will include whether nitrous oxide is an acceptable alternative to options such as narcotic pain medications and neuraxial pain medications. The project will also seek to consider whether it is an acceptable alternative for when current practices are not feasible, such as when epidurals are contraindicated, or in low resource settings. King's Theory of Goal Attainment will be the underlying theory in this paper, as it seeks to evaluate how the use of nitrous oxide can help women meet their goals and select means with which to meet their goals.

Evidence Demonstrating Need for Critical Review

More than 131 million babies are born worldwide annually, yet many of their mothers will lack the means to effectively cope with their pain. Inexpensive, safe, and simple methods are essential (Rooks, 2012). As stated by the American College of Nurse-Midwives (ACNM), women here in the United States have fewer options for pain control in labor than women in many other countries. The ACNM has also asserted that women have a right to access all safe options for pain relief in labor and birth. Included in the ACNM statement is a provision that where nitrous oxide is being used, there should be accompanying research and ongoing evaluation to add to the existing body of knowledge (American College of Nurse-Midwives, 2010). Nitrous oxide is used successfully and extensively in many countries outside of the United States, and in some areas it is the primary means of pain control. Nitrous oxide has been used in Europe for more than 100 years, with rates of use around 70% (Collins, 2015). It was in England in 1934 that a device for self-administration was developed and it became commonplace throughout Europe. As of 2014, there were only five known centers here in the United States that provided nitrous oxide as an option for laboring women (Likis, et al., 2014). Due to its gain in popularity and the fact that it is on the verge of a boom here in the United States, the Agency for Healthcare Research and Quality (AHRQ) identified a significant lack of quality research on the subject (AHRQ, 2011). The potential benefits and usefulness of nitrous oxide here in the United States, along with its impending widespread use, necessitates a critical review of the literature. Specific needs for nitrous oxide are discussed in the following sections.

Patient-controlled Analgesia. Nitrous oxide is a patient controlled method of analgesia giving patients more of a sense of control. Patient-controlled analgesia (PCA) is a conceptual framework that is not restricted to a single class of analgesics, or a single mode of delivery, but

rather any analgesic that is administered on immediate patient demand in sufficient quantities (Grass, 2005). In searching the literature regarding PCA in labor, the vast majority of the information available is focused on PCA epidurals. This is because currently, PCA is the only choice available for patient-controlled analgesia for most laboring mothers in the United States, and even those are limited in the amount of control the patient has. Most are administered with a continuous infusion, and even if they are a bolus only delivery program, the effects are relatively slow acting and the patient is not really at liberty to be free of the epidural catheter, monitoring, and other restrictions at will. Generally speaking, once an epidural is in place, there is little option to reverse it. The other major option to women is an intermittent parenteral narcotic administration such as fentanyl, nalbuphine, or butorphanol. While these provide periods of strong pain control, there are strict administration guidelines and patients are reliant on healthcare providers to administer these. The degree of empowerment associated with the self-administration of nitrous oxide is one factor that may be important in promoting and enhancing women's satisfaction (Collins, 2015).

Anxiolytic. Nitrous oxide is an anxiolytic. The presence of stress, anxiety, catecholomines, and epinephrine has been shown to have a definitive effect on labor (Adams et al., 2012). Catecholamines decrease the effectiveness of contractions and lead to dystocia and maternal exhaustion. Additionally, the fight or flight response caused by these stress hormones diverts oxygen-rich blood from the uterus and causes non-reassuring fetal heart tones (Levinson & Schnider, 1979). It also enhances the perception of post-traumatic stress disorder post-partum (Lederman, Lederman, & McCann, 1985). Adding a labor-coping option that helps to reduce anxiety, that could be used alone or even in conjunction with current options, could be profound.

Contraindications to Neuraxial Analgesia. Often, an epidural analgesia is not an option, such as when spina bifida or Harrington Rods are present. Patients may also have such extreme anxiety about the procedure that they are not able to tolerate it. Although epidural analgesia for labor is generally reported to be safe in most cases where there is a history of spinal surgery, studies have shown increased difficulty with placement and an increased rate of failed or inadequate anesthesia in laboring women, as compared to the general population of women who do not have a history of spinal surgery (Ko & Leffert, 2009). As medicine improves at managing neural tube defects, increasingly more women born with these defects are reaching childbearing age and achieving pregnancy. Neuraxial pain management in these women is challenging at best, due to underlying skeletal, musculoskeletal, and nervous system deformities and may not be an option (Kuckowski, 2007). Although cesarean section and general anesthesia is necessitated in many of these women, many others are still able to deliver vaginally and they are in need of pain management options. Additionally, there are several other contraindications to a labor epidural, which include low platelet levels, septicemia, progressive neurological diseases such as multiple sclerosis, elevated intracranial pressure and hypovolemia. It also includes the presence of conditions that affect the cardiac output, such as aortic stenosis (Silva & Halpern, 2010). Lastly, another major contraindication to epidural placement is refusal or inability of the patient to cooperate with the procedure and maintain proper positioning, which may be caused by labor pains, or patient anxiety about the procedure. Either way, it leaves the patient with one less option for pain relief if this situation occurs (Poole, 2003).

Contraindications to Parenteral Opioids. Parenteral opioids are one of the other major options for labor pain management after neuraxial analgesia. Parenteral opioids may also be contraindicated for many women, which leaves them with few remaining options. Allergy or

sensitivity to narcotic analgesia is an absolute contraindication. Many women have also found themselves coping well with labor up until the last few centimeters of dilation, when they could really use something for pain. At this stage of dilation, they are unable to use parenteral opioids because of the risk for respiratory depression in their newborns, should the narcotics be administered too close to delivery (Rooks, 2012). Additionally, if water birth is desired, women may be faced with having to abandon their hopes of water birth entirely if they choose to receive parenteral opioids.

Adverse effects of current methods of analgesia. Both parenteral opioid labor analgesia, as well as epidural labor analgesia, are associated with numerous adverse effects which women may prefer to avoid. These are well studied in the literature and far too numerous to go into detail in this discussion. However, among the reported side effects are lower one-minute Apgar scores and increased need for naloxone; prolonged second stage, more frequent need for oxytocin augmentation, hypotension, and maternal fever (Anderson, 2011; Leighton & Halpern, 2002). Also, women may have concerns about the effects that analgesia could have on breastfeeding. There is data that confirms both parenteral opioids, as well as epidurals, may be detrimental to early breastfeeding (Sinusas & Gagliardi, 2001).

Significance to Midwifery

Nitrous oxide has the potential to have a very profound benefit to the practice of nurse-midwifery. Conversely nurse-midwifery is perfectly positioned to promote the use of nitrous oxide. As a matter of course, patients who seek care outside of traditional obstetrical care and choose midwives may also be likely to seek out alternative methods of pain management. Rooks (2007, p. 187) stated, “nitrous oxide complements and is synergistic with the midwifery model of care.” Currently the ACNM is the only professional organization that has addressed the use of

nitrous oxide in the United States (Collins, 2015). In their position statement, the ACNM has stated that midwives should play a role in the administration of nitrous oxide, as well as contribute to research and evaluation. (ACNM, 2010). Nitrous oxide can be administered without the oversight of an anesthesiologist. It also has the benefit of being easily portable. Therefore, it is especially useful to midwives who deliver in birth centers, or at home. Nitrous oxide can be particularly beneficial in these settings, as laboring women would not have access to all the pharmacological options for pain available in hospital settings. In fact, many rural hospitals right here in the United States do not staff Certified Registered Nurse Anesthetists, or Anesthesiologists twenty-four hours a day, or they may serve a cluster of hospitals and thus are not always readily available to administer epidural anesthesia. Thus nitrous oxide is perfectly suited to the smaller practices of many midwives today, who also strive to provide their patients with as many options in pain relief as possible.

Theoretical Framework

King's Theory of Goal Attainment states that human beings are rational and sentient. It states that human beings have the ability to perceive, think, feel, choose, set goals, and select means to achieve those goals and make decisions. The theory asserts that humans have three fundamental needs which are the need for health information when it can be used, the need for care that seeks to prevent illness, and the need for care when he or she is unable to care for oneself (Nursing Theory, 2015).

King's Theory can be applied to labor and birth in that women inherently understand that labor and birth will involve some kind of pain. The perception of pain is different for all women, but women all consider how they will cope during the labor process, and what resources they will utilize. They will likely have an ideal for how they would like their labor to progress and

what they want to experience, or not experience. They use whatever information is available to them to make decisions on how best to manage their pain for their unique preferences and experiences. They set goals. Women need to have options available to them that are safe and that do not cause greater harm to them and their newborns. Lastly, they need to know that if and when they are not able to think clearly while in the midst of labor, their caretaker, the midwife, will provide for them in a matter consistent with their original plans and current needs. Thus King's Theory of Goal Attainment is very applicable to the use of nitrous oxide because it gives women another option. Not only an option that is shown to be safe, effective, and less invasive with less side effects to them and their baby, nitrous oxide also provides an element of self-control, even from one contraction to the next, that is unparalleled in other methods.

Summary

Nitrous oxide is widely used in other countries and is rapidly spreading here in the United States, as is the practice of midwifery. Yet there is a lack of comprehensive resources regarding its use, especially by nurse-midwives in the non-traditional settings they often practice in. This chapter considered pain in labor and introduced nitrous oxide. Nitrous oxide is a gas, which is mixed with oxygen and administered during labor and/or other painful procedures such as postpartum perineal repair. It is used as an alternative to the current methods of pain management, such as parenteral opioids or epidural, which may be contraindicated or have unacceptable side effects. The ACNM has expressed their support of nitrous oxide in congruence with the midwifery model of care. The need for a critical review of the literature was discussed. Lastly, King’s Theory of Goal Attainment as it is applied to labor and delivery, pain management, and nitrous oxide was discussed.

Chapter 2 describes the methods used for this critical appraisal of the literature, and includes search strategies, inclusion and exclusion criteria, a summary of the number and types of research selected for the review, and criteria for evaluating research studies. Chapter 3 provides a review and analysis of the evidence and includes a synthesis of major findings, as well as strengths and weaknesses of the studies. Chapter 4 concludes with a synthesis of the literature answering the research question, current trends and gaps in the literature, implications for pain midwifery and recommendations for further research.

Chapter Two: Methods

This chapter will review the process used in the critical appraisal of the literature pertaining to the practice question of, "is nitrous oxide a safe and effective alternative to current pain management practices for laboring women?" Key words and phrases were chosen and a search of multiple databases was conducted. Through an inclusion and exclusion process twenty-four of the most salient articles were chosen for critique.

Search Strategies Used to Identify Research Studies

This review of the literature covers the years from 1969-2015. Seventeen out of twenty-four of the articles were from the time from of 2000-2015, but some of the earlier studies were evaluated due to their significance, and because much of the research in relation to nitrous oxide was conducted at the latter part of the last century. The following databases were used: Academic Search Premier, Scopus, CINAHL, Google Scholar, PubMed/MEDLINE, Cochrane Database of Systematic Reviews, and Science Direct. Key words and phrases used in the search process included: Nitrous Oxide, Entonox, Nitronex, patient-controlled analgesia, safety of nitrous oxide, Efficacy of nitrous oxide, anxiety in labor, and use of nitrous oxide in rural settings. In addition, references within the research articles were analyzed yielding additional literature for review.

Inclusion and Exclusion Criteria

The initial inclusion criteria required studies to have been completed in the last 10 years and to be available in English. Earlier published studies were added after the initial inclusion/exclusion process, according to their pertinence to the topic. These additional studies have publication dates of 1969 to 1999. Included were articles that compared nitrous oxide to other modalities of pain management not commonly used her in the United States, as long as a

control was also present. These include the use of enflurane, sevoflurane, pethidine, meperidine, and remifentanil. Articles were initially evaluated on title and abstract to determine if inclusion criteria were met.

Along with the inclusion criteria, multiple exclusion factors were utilized in the identification of appropriate scholarly articles. Excluded were articles that were not original research, such as professional opinions, guidelines, literature reviews, meta-analysis and statements of policy, although their references were searched for additional research articles. Also excluded were articles whose focus did not fit the purpose of the review, such as those that focused exclusively on safety for care providers. Multiple articles were also excluded pertaining to the use of nitrous oxide in the field of dentistry, as well as pediatric pain management, except in some cases where their results were generalizable to the obstetric population. Articles, which compared different percentages of nitrous oxide, were not included either, unless they included a control against no treatment and the 50% concentration, which is the concentration now used in labor settings in the United States. Articles were further reviewed to verify applicability to labor and birth, infant outcomes, breastfeeding, painful procedures such as IV starts, versions, and perineal repair, and to the practice of midwifery.

Summary of Number and Type of Studies

The abstracts of the original forty-five articles were evaluated for pertinence to the topic of interest and narrowed down to twenty-four articles. The matrix includes nine randomized controlled studies, one survey, one prospective comparative study, one retrospective review, one case study, one observational study, one non-experimental descriptive comparative study, three cross-sectional studies, three prospective longitudinal studies, two cohort studies, and one random quasi-experimental crossover study. The review includes research from the United States

as well as Iran, France, Australia, Ireland, Sweden, Ecuador, Canada, and the United Kingdom. The articles were categorized using the criteria from Johns Hopkins (Dearholt & Dang, 2012):

- Level I, experimental studies: (n=8)
- Level II, quasi-experimental studies: (n=5)
- Level III, non-experimental studies: (n=9)
- Level IV, clinical practice guidelines: (n=0)
- Level V, non-research literature reviews and case studies: (n=2)

Criteria for Evaluating Research Studies

The final twenty-four articles were evaluated using the Johns Hopkins Research Evidence Appraisal Tool, in order to critique the strengths and quality of the evidence presented in each article (Dearholt & Dang, 2012). Evidence levels were determined using an I-IV scale. Level I studies included experimental, randomized controlled trials (RCTs) and systematic reviews of RCTS. Level II studies include quasi-experimental studies and systematic reviews that include RCTs with the quasi-experimental or quasi-experimental studies only. Level III studies include non-experimental studies or systematic reviews that question a combination of RCTs, quasi-experimental studies and non-experimental, or qualitative studies. Level IV evidence includes the opinion of respected authorities and/or nationally recognized expert committees/consensus panes based on scientific evidence (Dearholt & Dang, 2012).

According to the John Hopkins Model, the quality of the reviewed article was then determined to be of high quality, good quality, or low quality based on the criteria associated with each level. Research studies are considered good quality if there are reasonably consistent results, have a sufficient sample size, design, some control, and a fairly definitive conclusion.

They are considered low quality if there is little evidence, with inconsistent results, insufficient sample size for the study, and if conclusions cannot be drawn (Dearholt & Dang, 2012).

The articles were analyzed based on their purpose, sample size, design, measurement, results/conclusions, and recommendations. They were also analyzed to determine if they adequately addressed the research question. In order to determine the quality of the evidence, the articles were required to have consistent results, a sufficient sample size, adequate control, and definitive conclusions. In addition, consistent recommendations reflective of the literature review were included (Dearholt & Dang, 2012).

Summary

A database search was conducted using the Bethel University library services to provide a large sample of scholarly articles to undergo an inclusion and exclusion process. The final twenty-four articles, from multiple study designs, were chosen for appraisal and inclusion in the matrix. The Johns Hopkins Research Evidence Appraisal Tools were used during the analysis to evaluate the quality and strength of the chosen studies. This chapter described the search strategies and evaluation methods used for this critical appraisal of the literature.

Chapter Three: Literature Review and Analysis

Chapter three synthesizes the major findings of the literature as it pertains to the use of nitrous oxide in the labor and delivery setting. Weaknesses and strengths of several of the top articles in each subcategory will be discussed. The major findings of the reviewed literature include that nitrous oxide was safe to use for mothers and their infants. It is also safe in certain special circumstances pertaining to the labor and delivery sitting. Efficacy is highly dependent on what the patient's goal for pain management is, though it does appear to help women cope with labor pain. Lastly, women usually appear to be satisfied with the pain management nitrous oxide provides and would use it again.

The Matrix

The matrix includes nine randomized controlled studies, one survey, one prospective comparative study, one retrospective review, one case study, one observational study, one non-experimental descriptive comparative study, three cross-sectional studies, three prospective longitudinal studies, two cohort studies, and one random quasi-experimental crossover study. Each scholarly article was appraised using the Johns Hopkins Research Evidence Appraisal Tool (Dearholt & Dang, 2012). The quality and evidence of each individual article was identified through the appraisal process, and listed within the matrix. The study design, methods, sample size, strengths, limitations, findings, and nursing implications also are addressed in the matrix for each article.

Safety

Mothers. Nitrous oxide has proven to be safe to use for both mothers and infants. In one very large study of 35,828 administrations there were 1,581 adverse events, which accounts for 4.4% of the total uses. Of these 86% were limited to neuropsychiatric, such as agitation and

euphoria, and gastrointestinal disorders, such as nausea and vomiting (Onody, Gil, & Hennequin, 2006). There were 18 serious adverse events, which could not be accounted for by problems with the mixture of the gas. These included four O2 desaturations, one laryngospasm, one cardiac arrest, and two cases of convulsions. The cardiac arrest and one of the desaturations were linked to inappropriate use and insufficient surveillance.

The above referenced study by Onody, Gil, and Hannequin was appraised to be of a grade A and is considered a level III, in terms of the strength of the evidence. This study is the largest pharmacological trial yet reported on safety and conditions and use of this premix gas, when considered as a drug. As part of the licensing agreement with the French government, all administrations of the 50% N2O/O2 premix product known as Kalinox over a period of 3.5 years, from June 1998 to January 2002, were followed by obligation through the completion of a data sheet. Thus, the strength of this study lies in its large sample size and compulsory participation. The study was limited by the lack of an experimental design.

In looking for a randomized controlled trial regarding the safety of nitrous oxide for mothers, Carstoniu et al. (1994) must be considered. Carstoniu et al. conducted a level I study whose aim was to evaluate the effects of nitrous oxide on the oxygen concentration of women who used it in the first stage of labor. Even though the oxygen concentration of room air is 21%, while the commonly administered concentration of nitrous oxide is 50% with 50% oxygen, it remains an ongoing concern that use of nitrous oxide may somehow negatively affect maternal oxygen concentrations. Carstoniu et al. were able to prove that nitrous oxide use did not have this effect and that it was safe for use. This study was limited by the small sample size of twenty-nine and therefore appraised as a grade B.

Agah, Baghani, Tali, and Tabarraei, (2014) is a good sample to discuss in this section as well, because in addition to general safety, they also look at the propensity of nitrous oxide to have some kind of an effect on the labor pattern. The study was a randomized controlled trial in which study subjects were divided into groups and received specific training on the use of the nitrous oxide. The major limitation of the study is they did not compare the use of nitrous oxide to a control. They compared the intermittent method of nitrous oxide use, with the continuous method. The study is valuable nonetheless, because they were able to demonstrate there was no overall safety risk with increasing use, nor was there any increased risk to the events of labor and delivery. This included duration of the second stage of labor, severity of perineal laceration, rate of assisted vaginal birth, or uterine atony. The study appraised as a level I. It was a grade B for its smaller sample size.

Similar findings were repeated in several articles in the matrix (Annequin, Carbajal, Chauvin, Gall, Tourniaire, & Murat, 2000; Khadem, Zirak, Soltani, Sahebdelfar, Sepehri Shamloo, & Ebrahimzadeh, 2013; Mcguinnes & Rosen, 1984; Talebi, Nourozi, Jamilian, Baharfar, & Eghtesadi-Araghi, 2009; Pita et al., 2012; Rosenstein, Flood, Thiet, Nakagawa, Bishop, & Cheng, 2014; Pasha, Basirat, Hajahmadi, Bakhtiari, Faramarzi, & Salmalian, 2012). The findings of multiple good quality articles provide strength to the concept that use of nitrous oxide is safe for women.

Infants. Regarding the safety of nitrous oxide for the neonate, there appears to be even less risk involved. Stefani et al. (1982) conducted a randomized controlled trial of sixty-one healthy full term infants and found no difference in five-minute apgars, acid-base status, or any neurological status at two and twenty-four hours between infants in the nitrous oxide group, and infants in the control group. Infants were tested at various time intervals using the Early

Neonatal Behavioral Scale and the Neurologic and Adaptive Capacity score, as well as the traditional Apgar scoring. This study was appraised to be of a Grade B and is considered a level I in terms of the strength of the evidence, primarily due to the small sample size of sixty-one. Although an older study that was completed in 1982, the study is well designed and the data well analyzed, therefore the results remain valid today. The strength of the study is that it compared the use of nitrous oxide to a control group that received no intervention. The study is also valuable because it is one of the few studies whose primary purpose was to evaluate safety in newborns. Repeating the study today with a larger sample size would strengthen the findings.

Multiple other studies included in the matrix (Agah et al., 2014; Harrison, Shore, Woods, Mathews, Gardiner, & Unwin, 1987; Talebi et al., 2009) concluded with the same results – that nitrous oxide appears to have little to no effect on infants. These studies range in sample size from 100 to 534 participants. They included two randomized controlled trials and a non-experimental descriptive comparative study and appraised as a grade A or B. They all found that the use of nitrous oxide did not have any effect on one or five minute Apgar scores of newborn infants.

In looking for a more current study, Rosenstein et al. (2014) provided useful data with a study whose primary focus was effect on newborns. The primary outcome was admission to the NICU, although secondary outcomes such as Apgar scores and acidemia were also collected and evaluated. The study confirmed there were no significant differences in the odds of admission to the NICU, acidemia, or five minute Apgar score less than seven, and that its use was safe for newborns. The study did appraise at a Level III, as it was a cohort study and did not include an experimental design. The strength is that with 6,192 participants, it was a large study.

Nonetheless, it appraised as a grade B, primarily because of the lack of a control and the fact the study included participants whose mothers had also received epidurals, for example.

Special Circumstances. One of the intriguing aspects of nitrous oxide is that it can be used in special circumstances. Through repeated studies the safety has continued to be demonstrated in all cases. Agah et al. (2014) reported nitrous oxide is filtered completely by the lungs, meaning it is particularly useful in instances of hepatic and renal impairment. Chi, Lee, England, Hingorani, Paintsil, and Kadir, (2009) demonstrated its safety in women with inherited bleeding disorders, which would otherwise prevent women from using an epidural for pain management. Pita et al. (2012) reported no increased risk in low-income settings, which was also verified by Agah et al. who reported nitrous oxide was safe and appropriate in all social classes. Collins (2015) reported on the anxiolytic benefits of nitrous oxide. Burgos et al. (2013) reported no additional complications when nitrous oxide was used in external cephalic version.

Of these special circumstances Berlit, Tuschy, Brade, Mayer, Kehl, and Sütterlin, (2013) reported on what is likely to be one of the most common and practical uses of nitrous oxide for alternative purposes, which is for postpartum perineal repair. Berlit et al. compared the effectiveness of nitrous oxide with the traditional method of infiltration with anesthesia. Pain during repair was determined using a questionnaire and they were able to demonstrate that there was no statistical difference between the two methods. Additionally, the nitrous oxide was well tolerated with no severe side effects, and only 8% of the participants had to abandon use of the nitrous oxide completely, which was due to non-tolerance of the mask. In these situations the patients were then able to revert to traditional infiltrative techniques. The benefits to the use of nitrous oxide is that it is self-administered, it avoids the edema of the tissue and wound edges that may be caused by infiltration of lidocaine, and it avoids the procedural pain of infiltration

that is associated with lidocaine. The study was a level I randomized controlled trial, though appraised at grade B for its relatively small sample size of 100 women. Further studies would help to strengthen the claim regarding the usefulness of nitrous oxide for perineal repair, though there certainly does not appear to be any increased safety concerns inherent to its specific use.

Another attractive quality of nitrous oxide is its safety profile for use when epidural is contraindicated because of inherited bleeding disorders, which predisposes women to epidural or spinal hematoma and permanent neurological deficit (Chi et al., 2009). Chi et al. studied the use of analgesics in a sample of sixty-seven women who had conditions such as factor XI deficiency, von Willebrand disease, platelet function disorders, and a handful of other clotting disorders. Forty-one of the women used Entonox at some point in their labor. No complications were recorded and the authors found it useful, as administration is noninvasive. This study was a retrospective review of case notes after the fact, which earned it a designation as a level V study. It appraised to be a grade B. The topic was difficult to study because of the rare prevalence of the disorders. Including women with platelet disorders as a result of preeclampsia or HELLP syndrome would be especially useful to the field of obstetrics in future studies.

Efficacy

Results regarding the efficacy of nitrous oxide for laboring women are less consistent and highly dependent on the nature of the study, although findings are overall favorable. The study by Talebi et al. (2009) is a randomized controlled trial that compared the use of nitrous oxide in labor with oxygen as the control. Using a Visual Analogue Scale, Talebi et al. found that pain scores were significantly lower when 50% nitrous oxide was used. This study was appraised to be a grade A study and is considered a level I study. The strength of this study lies in the fact that it is a randomized controlled trial that compares the use of nitrous oxide against a control.

Limitations in the study were related to difficulty in timing the administration of nitrous oxide, which resulted in widely varying bloodstream levels at any given time, as well as the subjectiveness of pain perception. The study could have been improved by continuing to reassess pain measurements at periods of time after delivery.

Pita et al. (2012) presented a study that is a great contribution, not only for the information it provides on efficacy, but also because it discusses the information from the context of a low-income hospital setting a midwife may by likely to work in. The study was performed in a low-income hospital in Ecuador. Patients rated pain on a ten-point Visual Analog Scale at baseline, one hour after initiation and during episiotomy repair. Pain decreased from a score of 8.9 out of 10 at baseline, to a score of 4.9 after one hour. Pain score during episiotomy repair was 3.1 on the Visual Analog Scale. The study is limited by the fact it was a Level II study, in which it was designed as an observational study and there was no control. The sample size of 126 was not overly large either. Hence it appraised at a grade B in quality. That said, the authors concluded that nitrous oxide was, "devoid of complications, does not require high technology or qualified personnel (although appropriate training is needed and rapidly obtained), is affordable, does not increase obstetrical surgical complications, and enables women to make decisions and control pain."

One of the larger studies concerning the efficacy of nitrous oxide was by Morgan, Bulpitt, Clifton, & Lewis (1982). The study was conducted in 1982 and thus is considered outdated, although the study was well designed and its data is still applicable today. The study consisted of 1,000 women who gave birth in London. They were asked to rate their pain from zero to 100 on a 10 cm linear analogue scale, within 48 hours after birth. The average pain scores

for women who used nitrous oxide was 61, as compared to 70 for women who did not use any form of analgesia. This study appraised as a level III and grade B.

Similar results were found in several articles in the matrix, which provides strength to the argument that nitrous does provide pain relief when compared to a control or no intervention (Dammer et al, 2014; McGuiness & Rosen, 1984; & Pasha et al., 2012).

One study with findings that were in direct contradiction of the above findings was by Carstoniu et al. (1994) that found there was no statistically significant difference in pain when nitrous oxide was used versus compressed air. The limitations of this study were that it was a much smaller study of only 26 patients, making it a Grade B in quality, though it was still a level I in terms of strength of evidence. It is also a much older study, having occurred in 1994. The design of the study was a randomized, double-blind, cross-over, placebo controlled study. The trial began when each subject requested analagesia. There were two groups, and subjects in each group inhaled either nitrous oxide or compressed air for a series of five contractions, and then switched for the next series of contractions. The second group did them in the opposite order. They collected data at various points, including pain rating, and found no significant differences in pain scores between the nitrous oxide and the compressed. In considering more current knowledge, one possible explanation for the results of this study is that five contractions was not enough time for the study subjects to adequately adjust their intermittent administration timing, or to make an overall evaluation of the effectiveness.

One of the recurring themes in the literature is the comparison of nitrous oxide to other modes of pain relief such as epidurals and IV narcotics. An example is the 2013 randomized controlled trial by Khadem et al. (2013) which found pain scores were lower in all stages of labor when an epidural was used, than when nitrous oxide was used. That said, they argued that it

depends on the patient's goals for the labor. Therefore, if a patient desires a painless labor, an epidural is the best choice. But if neuraxial pain management is not desired, nitrous oxide is a good option. This study by Khadem et al. was a randomized controlled trial with a sample size of 84 women. Half of the women inhaled nitrous oxide at the beginning of each contraction and half of them received an epidural. They rated their pain using a 0-10 scale at multiple points before and during the intervention. The study was appraised to be a grade B and was a level I in terms of strength and evidence. The limitations of the study were that it was performed in Iran and it is difficult to tell for sure that everything was adequately controlled. Other studies in the matrix compared nitrous oxide to other interventions, as well with similar findings and recommendations (Morgan et al 1982; Harrison et al., 1987; Duarte, McNeill, Drummond, & Tiplady, 2008; Waldenstrom & Irestedt, 2006; Agah et al. 2014; Mcguinnes & Rosen, 1984).

Maternal Satisfaction. Several of the studies in the matrix evaluated maternal satisfaction or preferences as a variation of efficacy. The study by Dammer et al (2014) was one such study. The study was an observational study. Patient satisfaction was documented based on the patient's subjective statements on tolerance, side effects, and whether she would choose this method of analgesia again. The primary outcome measured was the likelihood that the patient would use the inhaled analgesia again. A total of 68% of the women indicated they were "quite to very" likely to use nitrous oxide again. The findings of the study indicated that women were more likely to choose nitrous oxide again if they tolerated it well, used it in second stage, or were bearing down. The study appraised as a Level III and Grade B. One limitation to the design of the study was that by default, it was primarily limited to patients who had either opted out of epidural analgesia, or were ineligible. Many were critical of epidural anesthesia and/or had fear of complications as their primary reason for refusing it. Therefore the study sample likely

included a fair amount of preexisting bias. This presents an opportunity for improvement in future studies where researchers could better select their sample from the general population.

In the discussion regarding maternal satisfaction, it is prudent to include the study by Henry and Nand (2004), which was conducted on a sample of 496 women who delivered at the Royal Hospital for Women in Sydney Australia. The study was a cross-sectional design in which women were handed a survey to be completed in the first week postpartum. This study did demonstrate similar findings to the one by Dammer et al (2014). Henry and Nand (2004) found that 65% of the women would "definitely" or "probably" use nitrous oxide again. This was compared to 82% for an epidural and 79% for natural methods. A strength of the study was that although there were numerous variants that were not controlled, such as place of delivery (delivery suite versus birth center), demographic factors, differences in providers, etc., they were at least well accounted for, with date broken down for each subsection. This study was a level III study that was appraised to be a grade B. A limitation of this study is that it was not specific to nitrous oxide. They were evaluating intrapartum pain management in general. The study could be improved by further limiting variables, while at the same time expanding the scope of the study to include a larger sample.

Waldenstrom (1999) should be discussed in this section as well, particularly because of the study findings that nitrous oxide was associated with a less positive birth experience. Waldonstrom also performed a cross-sectional study in which women completed a questionnaire in early pregnancy, as well as two months postpartum. The principle outcome "overall experience of labor and birth" was measured, as well as pain, anxiety, freedom of expression, involvement, midwife, and partner support. In this study, the use of nitrous oxide was associated with dissatisfaction with the birth experience, which illustrates the complexity of not only

childbirth, but of the study process and how the study aim and approach to the study can influence the results. Waldonstrom hypothesizes there is some other factor that predisposes women to the use of nitrous oxide, as well as affects their satisfaction with birth. This could be related to a personality feature for example. Or, it could also be related to the methodological problems associated with the measurement of pain. The study also demonstrated that the presence of pain, at all, was associated with a less positive birth experience. Similar to the other studies that evaluated this measure, it also appraised at a level III grade B, which highlights the lack of good, randomized controlled trials and the difficulty in quantifying this aspect of the labor and delivery experience. A relative strength of this study is that with a sample size of 1,111 participants, it one of the larger studies available.

Along the same lines, Lindholm & Hildingsson (2015) found that nitrous oxide was the most preferred or recommended method of pain control. The caveat in the study by Lindholm & Hildingsson is that it was conducted in Sweden, which is a country that has been using nitrous oxide for much longer and it is much more prevalent then here in the United States. So it assumed there was a cultural bias present. That said, it is an interesting study and worth mentioning because it gives insight into what women prefer and recommend to each other, even when they have all of the options available to them that women in the United States do, including access to epidurals. This was a prospective longitudinal study of 536 women who completed three questionnaires about their demographic background, preferences for labor and delivery, and what they actually received and what their experiences were. Nitrous oxide was the most preferred at 79% of the sample, as well as the most received, which was also 79%. A total of 62% of the women reported their experience as being positive with use of an epidural, having the strongest correlation with the least positive birth experience. The study appraised as a level III

for its non-experimental design and is a grade B. One of the recommendations from the study is that providers need to discuss preferences with women, because they had better overall birth experiences when they got what they had planned on and when it included nitrous oxide.

Strengths and Weaknesses

The articles in the matrix were predominantly of good quality. Four articles appraised as high quality and one article appraised as low quality using the Johns Hopkins Research Evidence Appraisal Tool. A low quality rating was given predominantly due to small sample size. Significant variations in the articles were present, in terms of study design. There were eight level I articles, five level II articles, eight level III articles and two level V articles. The study involved professionals from several disciplines including obstetrics, midwifery, and anesthesia. One study was from 1969, but was included because it demonstrated the safety of nitrous oxide and was otherwise of appropriate design and size.

Selection of articles was limited due to the lack of studies that answered the research question "is nitrous oxide a safe and effective alternative to current pain management practices for laboring women?" Often articles that studied nitrous oxide did not compare it to a control and/or compared it to other gases or substances not commonly used in obstetrics today. There was also a wide variety of subtopics studied such as safety for women, safety for newborns, women's preferences, efficacy, etc., as well as a large variety of including and excluding conditions such as parity, age, obstetrical history, stage of labor initiated, and prior pain medication use.

The critical appraisal of the evidence was strengthened by the inclusion of original research from obstetrics, midwifery, and anesthesia. Several of the studies were strengthened by large sample sizes. Seven studies had over 100 participants and seven studies had 1,000 or more.

Despite struggling to find applicable current research, about half of the articles (14) are recent, having been published in the last 10 years. Perhaps the greatest strength of the articles was in the similarity of findings regarding the safety of nitrous oxide. Without fail, study after study found that nitrous oxide was safe, with very mild side effects noted.

Lastly several articles were not from the United States. These could be viewed as strengths or weaknesses and including cultural factors and viewpoints is important. However, it could also be considered a limitation, as researchers and their values differ from one culture to another.

Summary

In this chapter, the major findings of the appraised articles were presented in a way that demonstrated answers to the question: "Is nitrous oxide a safe and effective alternative to current pain management practices for laboring women?" A total of 24 research articles were evaluated and cross-referenced. Overwhelmingly, the evidence indicates that nitrous oxide is a safe choice for laboring women, their infants, and may also be used safely for alternative applications in the labor and delivery setting, including when other methods of analgesia may be contraindicated. Efficacy is more difficult to measure, due to the highly subjective nature of pain and childbirth. In essence, efficacy in the studies was dependent on what women's expectations were going into childbirth, as well as what controls or other variables the nitrous oxide was being compared to. The majority of the data did find nitrous oxide to provide some amount of pain relief. Strengths and weaknesses of the research were then discussed. Primarily the weakness of the data was a wide variety of study designs and aims, which often did not directly answer the study question. Current data was also difficult to come by, although several of the older studies were of good design and control, and contained data that contributed to the current knowledge. Lastly, a matrix

of the articles was included, which summarized the studies and organized them in a manner for easy comparison and analysis.

Chapter IV: Discussion, Implications, and Conclusions

The original question of interest was "is nitrous oxide a safe and effective alternative to current pain management practices for laboring women"? The Johns Hopkins Research Evidence Appraisal Tool was used to appraise 24 scholarly articles related to these topics. The findings were then synthesized to evaluate trends and gaps in the literature, and identify implications for changes to nursing practice and future research needs. King's Theory of Goal Attainment was applied to the use of nitrous oxide in the labor and delivery setting, as it allows for mothers to have safe, effective choices for the management of their pain, with nitrous oxide also having the added element of self-administration.

Safety

The use of nitrous oxide in the labor and delivery setting has proven to be safe. This includes not only uncomplicated labor and deliveries, but also in specific scenarios such as postpartum perineal repair, external cephalic versions, or when contraindications to neuraxial methods are present, such as in the case of inherited bleeding disorders.

Onody et al. (2006) conducted a large study in which they collected information from all of the women in France who used nitrous oxide in the specified time period. The sample size was over 35,000. In this study there were only eighteen serious adverse effects. Carstoniu et al. (1994) conducted a study evaluating the effects of nitrous oxide on the oxygen saturations of laboring women and was unable to find any correlation or detrimental effects to the use of nitrous oxide, which could be related to the fact that nitrous oxide is administered with 50% oxygen - a concentration that is higher than room air. Agah et al.’s (2014) contribution to the research included proving there was no overall safety risk with increasing use, and no untoward effects on the length of labor and delivery, severity of perineal laceration, rate of unassisted

vaginal birth or uterine atony. The safety of nitrous oxide was reiterated repeatedly by almost all of the studies in the matrix, regardless of whether safety was their primary outcome or was just an incidental finding in the study (Annequin et al., 2000; Berlit et al., 2013; Burgos et al., 2013; Chi et al., 2009; Dammer et al., 2104; Harrison et al., 1987; Mcguinness & Rosen, 1984; Pasha et al., 2012; Pita et al., 2012; Rosenstein et al., 2014).

Nitrous oxide has also been shown to have little to no effect on newborns (Harrison et al., 1987; Khadem at al,, 2013; Rosenstein et al., 2014; Stefani et al., 1982) These findings were consistent in multiple studies that appraised to be of good quality in the John's Hopkins Research Evidence Appraisal Tool. There were two studies that specifically looked at the effects of nitrous oxide on infants. The first study that was considered was the one by Stefani et al. (1982). The study was one of the oldest in the matrix, but did have good design. It was a randomized controlled trial with 61 healthy full-term infants. They demonstrated there was no difference in five minute apgars, acid-base balance, and there were no differences in neurological status at two and 24 hours of age, between the control group and the nitrous oxide group. Rosenstein et al. (2014) was the other more current study that was evaluated. This was a large study with 6,192 infants. They found no effect on the risk of admission to the NICU, academia, or lower apgar scores when nitrous oxide was used.

It should be recognized that in the majority of the studies, safety was not the primary study focus, but rather it was noted incidentally. This was true of safety matters concerning newborns as well. Fortunately, one of the largest studies in the matrix, the one by Onody et al. (2006) with a sample size of 35, 828 did specifically focus on safety and concurred with the rest of the studies that found nitrous oxide to be safe in a wide variety of clinical scenarios, though this still was not a randomized controlled study.

The safety of nitrous oxide when used in various special circumstances is of particular interest. Examples include situations in which either epidural or parenteral narcotics are contraindicated, or when nitrous oxide is of use because of a property it has. For example, nitrous oxide is well-suited to post-partum perineal repair because it is rapid-acting, eliminates the pain of infiltration of local analgesic, and does not result in further tissue edema and damage (Berlit et al., 2013). Nitrous oxide also has anxiolytic properties that are promising (Collins, 2015). In all these cases thus far, nitrous oxide has proven to be safe. Nitrous oxide has also been studied in some cases that epidural cannot be used, such as inherited bleeding disorders (Chi et al., 2009). A third category of special circumstances is the use of nitrous oxide in alternative settings and several authors corroborated its safety. Pita et al. (2012) reported there was no increased risk in low-income settings. Agah et al. (2014) found it was safe to use in all social classes.

Efficacy

The effectiveness of nitrous oxide is a more loosely defined term, subject to a greater variety of interpretations that varied from study to study. For example, in Talebi et al. (2009) efficacy was evaluated in terms of how nitrous oxide affected pain, while Waldenstrom & Irestedt (2006) evaluated how women remembered pain after the fact. As such there was also less consistency regarding whether nitrous oxide helped with pain. Pain, being a highly individualized and subjective measurement, is difficult to quantify, especially in small increments. There was a level I, grade A randomized controlled trial among the studies regarding efficacy. This was the study by Talebi et al. (2009). In a relatively large sample of 534 participants, they used a Visual Analogue Scale and demonstrated a statistically significant reduction in pain, as compared to the control. Pita et al. (2012) was another study that sought to

evaluate the efficacy of nitrous oxide. Although this study was smaller, it is a very nice contribution to the literature, as they had good conclusive findings that showed a reduction in pain that was demonstrated using Visual Analogue Scales. Morgan et al. (1982) was included in the literature despite being one of the older studies. Again, these studies were included when they had relatively good design and findings that contributed to the body of knowledge. This study was a non-experimental design, though it consisted of 1,000 women. A linear analogue scale was used in this case to demonstrate a significantly lower average pain score when nitrous oxide was used, then when it was not.

Carstoniu et al. (1994) contradicted the findings of other studies. In a randomized, controlled trial they found no statistical difference between nitrous oxide and compressed air. The results of this study may be explained by the relatively short duration of time the controls and experimental gases were administered.

Overall the findings suggest that nitrous oxide may be effective in relieving labor pain, though efficacy can best be described as dependent on each individual's desires and expectations for pain management (Morgan et al., 1982).

Perhaps one of the most intriguing concepts in nitrous oxide is its anxiolytic properties and ability to affect pain from there. As previously mentioned at the beginning of the review, anxiety and inability to cope with pain lead to an increase in catecholamines, which feeds into a cycle of fatigue, dystocia, fetal distress and then back to increased pain (Rooks, 2012). Collins (2015) addressed the psychosocial features of labor and found nitrous oxide to influence this. It should be recognized that the study by Collins, though a grade A in quality, was a level V single-case study and no other studies addressed this quality of nitrous oxide. This presents an excellent area for further research.

Implications for Midwifery Practice

Though the use and study of nitrous oxide here in the United States appears to just be entering a new phase of renewed interest, there is sufficient evidence available to influence current practice. There are no indications that nitrous oxide should be withheld as an option because of safety concerns. Nurse-midwives are in a key position to assess and evaluate current policies and practices that promote offering nitrous oxide as an additional option in management of pain associated with labor and delivery. Consistent with the ACNM's Hallmarks of Midwifery (ACNM, 2012), midwives are perfectly positioned to promote the use of nitrous oxide. The Hallmarks that the use of nitrous oxide embodies are advocacy of non-intervention in normal processes in the absence of complications; incorporation of scientific evidence into clinical practice; promotion of family- and women-centered care; empowerment of women as partners in health care; advocacy for informed choice, shared decision making, and the right to self-determination; and skilled communication, guidance, and counseling. Nitrous oxide is by far the least invasive of the medicinal options available to women, making it well suited to the midwifery model of care. Nitrous oxide does not require the presence of anesthesia, can be quickly administered, and is far cheaper than some other options. Evidence exists that nitrous oxide may be useful in scenarios that neuraxial options or IV options may not be appropriate as well such as postpartum perineal repair, or cephalic versions (Berlit et al., 2013 & Burgos et al., 2013). With their position as emerging and popular leaders in their field, nurse-midwives are well situated to promote the implementation and use of nitrous oxide in their place of practice and to help develop policy for its use.

Recommendations for Research

There is opportunity for further research in the areas of safety and efficacy of nitrous oxide in laboring women. Current literature has a significant variety in study design. Randomized controlled trials comparing nitrous oxide to a placebo are needed. Studies specific to safety would help to bolster the literature, including studies evaluating both the immediate, as well as long term effects on neonates specifically. Some additional scenarios warranting further study include the use of nitrous oxide in conjunction with other therapies such as water birth, or aromatherapy. It may be prudent to evaluate the safety of nitrous oxide in the presence of Category II or III fetal heart tones, hypertension, or preeclampsia for example, as well as to look at the safety of having nitrous oxide in the system when emergent general anesthesia becomes warranted due to sudden cord prolapse, or uterine rupture. Current studies tend to be broad, looking at multiple variables and a more defined focus is needed. There is plenty of evidence comparing the efficacy of nitrous oxide to epidurals and IV narcotic administration. It is evident that they are not comparable and further study is not likely to be beneficial. That said, comparison of nitrous oxide to alternative therapies such as massage, TENS, or aromatherapy could be useful.

Integration of King's Theory of Goal Attainment

King's Theory of Goal Attainment coincides directly with the model of care called for in nurse-midwifery. Both call for providing as many safe and effective options for women to choose from as possible in managing their pain. King's Theory says women set goals for themselves, including goals to safely and effectively manage their pain in labor. Nurse-midwives can help fulfill this goal by teaching their patients about nitrous oxide as an option and then later while in labor, how best use it for maximum safety and efficacy. Nitrous oxide is a PCA or self-

administered medication, which gives women the maximum amount of self-control in managing their pain and achieving their goal.

Conclusion

The major findings from this critical review emphasize the safety and efficacy of nitrous oxide for use in labor and delivery. The literature overwhelmingly supports the safety of nitrous oxide for both mothers and their newborns including in scenarios where traditional methods would otherwise be contraindicated. Offering nitrous oxide, which is safe, effective, and self-administered, is empowering to women in accordance with King's Theory of Goal Attainment. Nitrous oxide is cost effective and easy to use. Nurse-midwives are well positioned to promote the implementation of nitrous oxide, particularly in rural or other low-volume settings where its low cost and ability to be administered in the absence anesthesia staff may be of particular value. The body of knowledge can be further strengthened with the addition of good quality, randomized controlled trials with specific outcomes to be identified.

Appendix 1

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Agah, J., Baghani, R., Tali, S. S., & Tabarraei, Y. (2014). Effects of continuous use of Entonox in comparison with intermittent method on obstetric outcomes: A randomized clinical trial. *Journal Of Pregnancy*, 1-5. doi:10.1155/2014/245907	To compare the complications induced by both intermittent and continuous administration of Entonox	100 patients who delivered in Monini Hospital in Iran in 2013. Inclusion criteria were singleton pregnancy, cephalic presentation, and term gestation. Exclusion criteria were macrosomia, maternal contracted pelvis, repeat cesarean section, nonreassuring FHR, SPO2 less than 95%, head injury, and severe asthma.	Randomized Clinical Trial 50 women inhaled Entonox during contractions and put it aside in between them while 50 women used Entonox continuously.	Labor progression, fetal condition, and maternal O2 saturation as well as maternal and newborn outcomes and maternal pushing collaboration were recorded.	Length of second stage of labor, assisted birth, uterine atony, and Apgars all had no statistically significant differences. Perineal lacerations were less frequent in the continuous group and maternal pushing collaboration and satisfaction was also higher in the continuous group.	Continuous method of administration is also safe and mothers may be allowed to make their choice. Further investigation is needed to strengthen the findings.	Level I Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Annequin, D., Carbajal, R., Chauvin, P., Gall, O., Tourniaire, B., & Murat, I. (2000). Fixed 50% nitrous oxide oxygen mixture for painful procedures: A French survey. *Pediatrics*, *105*(4), e47-e47. http://dx.doi.org/10.1542/peds.105.4.e47	To assess the use and safety of Nitrous Oxide in the pediatric settings in France.	1,019 participants from 31 centers across France from September 1st 1996 through November 1st, 1996. All children 18 years or less who received a nitrous oxide administration for painful or invasive procedure outside the operating theater were included in the survey.	Nitrous oxide was administered to children during painful procedures. Surveys were completed following treatment by nurses, patients, and family members.	Self-assessment was reported as well as procedural pain evaluation by nurse and parents, team satisfaction, and child agreement for future use of nitrous oxide. Behavioral reactions were noted in an absent-present manner including crying, facial reactivity, withdrawal, restlessness, and additional restraint needed.	Median pain evaluation was a 9 on a 0-100 VAS and 1 for both nurses and parents on a 0-10 numerical scale. 93% of children said they would accept Nitrous Oxide again for a similar procedure. 56.7% of staff rated their satisfaction as very satisfied. All side effects were minor and transient. No single serious side effect was noted during the study	Analgesia obtained during procedures is good but not efficacious in all patients. Failures in pain relief should be detected early and patient should be switched to another analgesic method.	Level III Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Berlit, S., Tuschy, B., Brade, J., Mayer, J., Kehl, S., & Sütterlin, M. (2013). Effectiveness of nitrous oxide for postpartum perineal repair: A randomised controlled trial. *European Journal Of Obstetrics & Gynecology & Reproductive Biology*, *170*(2), 329-332. doi:10.1016/j.ejogrb.2013.06.025	To compare the effectiveness of self-administered 50% nitrous oxide and conventional infiltrative anesthesia with 1% prilocaine hydrochloride in postpartum perineal repair.	100 women with childbirth related injuries at the University Medical Centre Mannheim between November 2012 and February 2013. Exclusion criteria included epidural analgesia, multiple pregnancies, fourth degree perineal laceration, and age below 18.	Prospective Randomized Controlled Trial The study group contained 48 women who self-administered nitrous oxide 5-10 minutes prior to the start of the procedure. The control group received up to 20mls of locally infiltrated prilocaine.	Data concerning anesthesia, maternal parameters, duration of suturing, neonatal head circumference and weight, women's' tolerance of the mask, side effects, and need for more anesthesia.	Pain experienced during suturing and patient's satisfaction were not statistically different between the two groups. Nitrous oxide allowed for the avoidance of infiltrative pain and edema that may impair the repair process caused which could be caused by the infiltration of lidocaine.	Larger investigations concerning the topic should be performed as nitrous oxide self-administration during postpartum genital tract suturing seems to be a satisfactory and effective alternative to infiltrative anaesthesia for the majority of women	Level I Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Burgos, J., Cobos, P., Osuna, C., de Mar Centeno, M., Fernández-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. http://dx.doi.org/10.1515/jpm-2013-0046	To analyze the effect of using inhaled nitrous oxide for analgesia in external cephalic version at term	300 women with singleton pregnancy in breech presentation at term undergoing an ECV.	Prospective Comparative Study 50: 50 mix of Nitrous Oxide and oxygen was administered using a face mask for 3 minutes before beginning the ECV and continuous through the procedure for 2-4 minutes. This was administered to half of the sample. The other half underwent ECV with no analgesia.	Thirty minutes after the procedure the pain scale was assessed by a gynecologist who did not participate in the procedure. Success rate of the procedure, pain, and obstetric and perinatal outcomes were all assessed.	The success rate was 52.3% in the Nitrous Oxide group and 52.7% in the control group. The median level of pain was statistically lower in women given nitrous (6 vs. 7 in the control group). There were no significant differences in rate of complications or outcomes and there were no severe complications secondary to Nitrous Oxide inhalation	Further studies are needed which eliminate the bias in the use of consecutive cohort groups as opposed to a randomized trial. A study with a larger sample would also be helpful in eliminating errors due to a B error.	Level II Grade A

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Carstoniu, J., Levytam, S., Norman, P., Daley, D., Katz, J., & Sandler, A. N. (1994). Nitrous Oxide in early labor safety and analgesic efficacy assessed by a double-blind, placebo-controlled study. *Anesthesiology*, 80(1), 30–35. doi:10.1097/00000542-199401000-00008	To test the effects of nitrous oxide on the pain of labor contractions and on maternal SpO2 after labor contractions.	26 women who were admitted in labor to the delivery suite at a Toronto Hospital who had requested pain relief. Exclusion criteria included age <18 years; maternal cardiorespiratory disease; any evidence of fetal distress or abnormal heart rate pattern; any condition affecting the accuracy of pulse oximetry; or the use of opioid or regional	Randomized, double-blind, crossover, placebo-controlled study The two groups self-administered either 50% nitrous oxide or compressed air for 5 contractions and then the groups swapped gas they were using for the next set of 5 contractions.	Subjects were trained in the use of a visual analog pain scale. Baseline values were obtained. Pain scale and oxygen levels were measured with each type of gas.	There were no statistically significant differences in pain when nitrous oxide as compared to compressed air was administered. SpO2 was significantly higher after nitrous oxide administration.	The study supports the safety of the use of intermittent self-administered nitrous oxide with regard to maternal oxygenation. More research is necessary before a conclusive statement about the efficacy of nitrous oxide in labor can be made. Particular issues that need further attention include a multidimensional pain assessment; the use of	Level I Grade B

		analgesia.				nitrous oxide at the end of the first stage or during the second stage of labor; administration of nitrous oxide in a manner ensuring that the peak analgesic effect coincides with contractions; and continuous nitrous oxide administration	

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Chi, C., Lee, C. A., England, A., Hingorani, J., Paintsil, J., & Kadir, R. A. (2009). Obstetric analgesia and anaesthesia in women with inherited bleeding disorders. *Thromb Haemost*, *101*(6), 1104-1111. http://dx.doi.org/10.1160/th08-10-0694	To review the use of obstetric analgesia and anaesthesia in women with inherited bleeding disorders and their associated complications.	63 women with inherited bleeding disorders who had 80 pregnancies between January 1 2000 and December 31 2005. Women delivered at Royal Free Hospital in London.	Retrospective Review Haemophilia and obstetric case notes were reviewed retrospectively.	Clinical data was collected including type of bleeding disorder, labor and delivery data, method of pain relief and any complications attributable to the anesthesia.	Entonox was used in 61% of the labors and no complications were noted.	Each case must be assessed individually depending on the type of bleeding disorder. However Entonox appears to be a safe option for analgesia in women with bleeding disorders unlike other methods which may be contraindicated.	Level V Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Collins, M. (2015). A case report on the anxiolytic properties of nitrous oxide during labor. *Journal of Obstetric, Gynecologic, & Neonatal Nursing*, *44*(1), 87-92. http://dx.doi.org/10.1111/1552-6909.12522	To review the anxiolytic effects of Nitrous Oxide.	A 30 year old G3P2002 in labor at 40.6 weeks in the United States. History of 2 prior SVDs and unremarkable pregnancy other than estimated fetal weight about 600 grams larger than her previously largest child.	Case Study	A description of the woman's labor course before and after the nitrous oxide was provided as well as a statement from the woman regarding her experience using the nitrous oxide and how she felt it affected her.	The woman in this case experienced labor stalling that might have been associated with her unspoken and unresolved fear of giving birth to a child anticipated to be significantly larger than her previous two. In this case, the anxiolytic effect of nitrous oxide was the most helpful property and the woman's stalled labor quickly resolved with the used of nitrous oxide.	The adverse effects of fear in labor are well documented and inhalation of nitrous oxide may have an anxiolytic effect and reduces catecholamines. Research addressing the psychosocial aspects of nitrous oxide in labor is crucial.	Level V Grade A

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
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. http://dx.doi.org/10.1055/s-0034-1368606	To investigate the acceptance of the inhaled analgesia of inhaled nitrous oxide and oxygen by midwives and pregnant women during labor	66 pregnant women who received inhaled nitrous oxide and oxygen during labor on request and after prior assessment of suitability and the midwives attending their births.	Observational The midwife completed a questionnaire after the birth.	The patient satisfaction was documented based on the patient's subjective statements on tolerance, side effects, and whether she would choose this method of analgesia again. Pain intensity before and after receiving nitrous was assessed using a numerical rating scale.	A statistically significant reduction of pain was achieved with nitrous oxide and oxygen. The inhaled analgesia was mostly used by women who refused epidural analgesia. The likelihood of using it again was rated higher for patients who tolerated it well and used it in the second stage of labor and when bearing down. Midwives satisfaction depended on how it was	Inhaled nitrous oxide is a safe and effective method for pain relief during delivery and is accepted well by both women and their midwives. It can also be used postpartum.	Level III Grade B

					accepted by the women.		

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Duarte, R., McNeill, A., Drummond, G., & Tiplady, B. (2008). Comparison of the sedative, cognitive, and analgesic effects of nitrous oxide, sevoflurane, and ethanol. *British Journal of Anaesthesia*, *100*(2), 203-210. http://dx.doi.org/10.1093/bja/aem369	To compare the sedative, cognitive, and analgesic effects of nitrous oxide, sevoflurane, and ethanol to elucidate their mechanisms of action and allow therapeutic choices between the agents.	4 female and 4 male volunteers aged 19-28 years and weighing about the same who were healthy, light to moderate social drinkers and were not taking any medications that might have interfered with CNS function or drug absorption or elimination.	Nested within-subjects design with four sessions and treatments were given in a double-blind and random sequence. Participants attended 4 sessions, In each session they received one of the following: ethanol, a placebo, nitrous oxide, and sevoflurane. Performance and pain threshold testing were carried out before treatment and	Speed and accuracy were measured using psychomotor tests; von Frey filaments were used to measure touch and pain sensitivity; subjective mood, reaction time and memory were also measured.	All treatments caused the same degree of overall abnormal feelings, but sevoflurane caused more obtunding and nitrous oxide was more analgesic. Ethanol caused a marked feeling of drunkenness, but little drowsiness or analgesia. The effect of nitrous oxide affected the pan significantly greater than for any other treatment.	Further study to quantify the profiles of drug actions on performance and subjective effects is important in elucidating mode of action, measuring actions, and predicting effects in clinical use.	Level II Grade C

			twice during the treatment period.				

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Harrison, R. F., Shore, M., Woods, T., Mathews, G., Gardiner, J., & Unwin, A. (1987). A comparative study of transcutaneous electrical nerve stimulation (TENS), entonox, pethidine+ promazine and lumbar epidural for pain relief in labor. *Acta Obstetricia et Gynecologica Scandinavica*, *66*(1), 9-14. http://dx.doi.org/10.3109/00016348709092945	To compare analgesic effect, labor outcome, safety, and consumer satisfaction between transcutaneous electrical nerve stimulation, Entonox, Pethidine + Promazine and lumbar epidural.	170 Primigravida women attending Rotunda Hospital in Dublin from June to December 1983. All were primigravida and selected at random.	Nonexperimental Descriptive Comparative The patients were allowed to choose which method they wanted to try with 50 choosing TENS, 20 Entonox, 20 Pethidine + Promazine, and 50 lumbar epidural. They were also not restricted to the initial method they choose and were allowed to use an additional method as needed.	Collected data included pain thresholds using a Monsanto gun, assessment of pain during labor and assessment of pain relief, duration of labor, type of delivery, infant weight and Apgars, and post-delivery comments regarding choice of pain management.	99% of women who choose an epidural found it fully effective. Partial relief was reported by 90% in the Entonox group, 96% in the TENS group, and 54% in the Pethidine + Promazine group. 82% of patients in the TENS group, 80% in the Pethidine + Promazine group, and 5% of patients in the Entonox group required an addition method of pain relief.	The efficacy of Epidurals outweigh any possible side effects and Entonox appears suited to those able to cope with the earlier part of labor drug free. Tens has potential but development of materials suited to the quality of labor pain is needed.	Level III Grade B

					Women using Entonox alone had the shortest labors while women using epidurals had the longest. Operative delivery was much more common in the epidural group. There were no differences noted in cord pH or Apgar scores. Midwives and patients all gave high consumer satisfaction scores for all methods except Pethidine + Promazine.		

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Henry, A., & Nand, S. E. (2004). Intrapartum pain management at the Royal Hospital for Women. *Australian & New Zealand Journal Of Obstetrics & Gynaecology*, *44*(4), 307-313. doi:10.1111/j.1479-828X.2004.00231.x	To explore the use of, and women's satisfaction with, intrapartum pain management at Royal Hospital for Women in Sydney Australia.	496 women who delivered at the Royal Hospital for Women in Sydney Australia between October 2002 to January 2003. Women were excluded if they were less than age 17, non-English speaking, undergoing Cesarean section where no labor occurred, had any major neonatal morbidity, homebirths, and those with active psychiatric illness at the time of labor.	Cross-sectional Women who underwent labor were handed a survey in the first 24 hours post-partum to be complete by the end of the first post-partum week. Additional data was collected from women's charts if they completed the survey.	The survey contained 46 items separated into demographic information, intrapartum pain management use and women's satisfaction with use, and knowledge and attitudes towards intrapartum pain management. Additional data collected from the chart included information about antenatal care, place of delivery, and information on use of pain management	In comparing the usefulness of nitrous oxide with other pain management options, nitrous had very similar ratings regarding is usefulness as compared to natural methods which included massage, hot pack, bath/shower, or any other "nominated non-pharmacological method", although a slightly larger number of women reported they found nitrous	Similar future studies would be better to recruit from multiple hospitals to increase generalizable data.	Level III Grade B

				and timing.	to be not at all helpful as compared to natural methods. Natural methods would 'definitely' or 'probably' be used again by 79% of women compared to 65% who said they would use the nitrous oxide again.		

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Jones, P. L., Rosen, M., Mushin, W. W., & Jones, E. V. (1969). Methoxyflurane and nitrous oxide as obstetric analgesics. II.—A comparison by self-administered intermittent inhalation. *BMJ*, *3*(5665), 259-262. http://dx.doi.org/10.1136/bmj.3.5665.259	To compare the efficacy and side effects of Methoxyflurane and Nitrous Oxide.	50 patients with 25 in each group. The sample consisted of healthy, uncomplicated labors and vaginal deliveries.	Randomized Controlled Trial Patients were randomized into one of the two groups. During the first stage of labor, mothers were instructed to breath from the mask during each contraction and during the second they were instructed to take few breaths before bearing down.	The anesthetist measured the responses of the mother to each contraction, of the degree of restlessness between contractions according to a defined scale. At the end of labor the opinions of the midwife and the mother were sought The opinion of the mother was also sought at 36 to 48 hours after delivery. Pain relief, blood loss, side effects, memory of the labor and delivery,	Objective assessment by the anesthetists showed the methoxyflurane is the more effective analgesic. Nausea and vomiting were significantly less with the methoxyflurane.	Further study is needed to evaluate the efficacy of nitrous oxide	Level I Grade B

				smell of the nitrous oxide, dreams, and any other sensations were recorded. Apgars of the newborn were also recorded.			

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Khadem, N., Zirak, N., Soltani, G., Sahebdelfar, N., Sepehri Shamloo, A., & Ebrahimzadeh, S. (2013). Comparison of epidural versus entonox for labor analgesia in nulliparous women. *نشریه جراحی و تروما*, *1*(1), 1-5. Retrieved form http://www.ijs.ir/	To compare the efficacy of epidural versus Entonox methods for labor analgesia in nulliparous women	84 nulliparous women admitted to Imam Reza Hospital	Randomized Controlled Trial Women were randomly divided into two groups. 42 women used Entonox in the active phase of labor at the beginning of each contraction and 42 women received an epidural.	Pain was rated using a scale of 0 to 10.	Pain score was lower in all stages with epidural than with Entonox. There was no statistical difference between length of labor, cesarean rate, and Apgar scores.	Epidural is recommended for painless delivery but Entonox is safe and may be considered when regional analgesia is not performed.	Level I Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Lindholm, A., & Hildingsson, I. (2015). Women's preferences and received pain relief in childbirth–A prospective longitudinal study in a northern region of Sweden. *Sexual & Reproductive Healthcare*, *6*(2), 74-81. http://dx.doi.org/10.1016/j.srhc.2014.10.001	To describe what pain relief methods pregnant women preferred when asked in late pregnancy and to identify factors associated with preferred and received pain relief methods.	Pregnant Swedish-speaking women were recruited at the routine ultrasound visit in gestational week 17-18 at three hospitals in the northern region of Sweden. 1506 women consented to participate. 1,212 completed the first survey, 1,042 completed the second, and 936 completed the third survey.	Prospective Longitudinal Three questionnaires were used. The first was completed after the first visit after agreeing to participate in the study, the second was sent to women's homes at 32-34 weeks, and the third was sent to their homes at 2 months after birth.	The first questionnaire was used to collect basic demographic data. The second addressed women's preferences for pain relief and fear of birth using a 4 point Likert scale. The third questionnaire assessed methods actually used, information about the birth, and a question about birth experience being either positive or negative which was	Nitrous oxide was the most preferred and used pain relief method. Women who gave birth vaginally used nitrous oxide more often than women with spontaneous onset labor who ended with an emergency cesarean section. The 38% of women who rated their birth as "less positive" were strongly more likely to have had an epidural	Caregivers need to discuss with pregnant women about their pain relief preferences for labor and birth but also about pros and cons with the available methods as certain methods such as epidural is associated with a less positive birth experience.	Level III Grade B

				also measured using a 5 point Likert scale.			

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Mcguinnes, C., & Rosen, M. (1984). Enflurane as an analgesic in labour. *Anaesthesia*, *39*(1), 24-26. http://dx.doi.org/10.1097/00132582-198412000-00028	To compare the efficacy of enflurane 1% in air with Entonox.	20 women in labor who were in early normal labour	Random, Quasi-experimental crossover When uterine contractions became regular, each woman was randomly given one of the analgesic agents (Entonox or enflurane 1%) for three consecutive contractions, then given the other agent for three contractions.	When uterine linear analogue scores for pain were completed before and after each agent. Drowsiness and nausea were also assessed by linear analogue scores.	When Entonox was used, median pain scores were reduced from 61/100 when nothing was used to 52/100. Drowsiness occurred significantly less with Entonox than with enflurane 1%. No untoward effects were recorded with either agent.	Self-administered inhalational analgesics are safe because excess drowsiness is self-limiting. Further studies are needed to evaluate the effectiveness of different concentrations and to look for evidence of changes in the progress of labor or the neurobehavioral pattern of the newborn.	Level II Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Morgan, B., Bulpitt, C., Clifton, P., & Lewis, P. (1982). Effectiveness of pain relief in labour: survey of 1,000 mothers. *British Medical Journal (Clinical Research Edition)*, *285*(6343), 689-690. http://dx.doi.org/10.1136/bmj.285.6343.689	To compare the relative effectiveness of different methods of obstetric analgesia in a consecutive series of 1,000 women	1,000 women who delivered at Queen Charlotte's Hospital in London over a period of four months.	Cross-sectional interview	Patients were asked to rate pain from 0-100 on a 10 cm linear analogue scale.	Women who had an epidural had the lowest mean pain score (29 +/- 3.7) followed by meperidine plus epidural (30 +/- 3.8), epidural plus entonox (57 +/- 3.4), meperidine (58 +/- 3.1), entonox (61 +/- 3.1), pudendal block (68 +/- 1.9), miscellaneous (69 +/- 3.3), and no analgesia (70 +/- 2.6).	The relationship between maternal attitudes to pain in labor and its relation to a satisfactory experience appear to be important and need to be studied further. Pt's should be counselled that modern methods can relieve, although not totally abolish pain in labor and the promise of a totally painless labor is unrealistic and not warranted.	Level III Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Onody, P., Gil, P., & Hennequin, M. (2006). Safety of inhalation of a 50% nitrous oxide/oxygen premix. *Drug Safety*, *29*(7), 633-640. http://dx.doi.org/10.2165/00002018-200629070-00008	To analyze the factors that affect tolerance of the 50% Nitrous Oxide/Oxygen administration in wide range of clinical indications.	35,828 data sheets from 191 French hospital Pediatric and Adult units.	4 year Prospective Survey License of use for the product required the completion of a data sheet after each administration. Data sheets were supplied with the gas cylinders and had to be completed for each administration regardless of the occurrence or not of an adverse event.	Type of adverse event was described. Patient demographics, description of the premix including brand, route, starting date and time, indications for use, description off any concomitant drugs and full details of each adverse event including body site and severity, duration, correlation of disappearance and recurrence of the reaction with stopping and	A total of 1,581 (4.4%) adverse events were reported which were mostly gastrointestinal and neuropsychiatric disorders. The main factors associated with adverse events were age 11-18, concomitant drug administration and longer duration of inhalation. There were 27 reported serious adverse events, though only 9 of them could possibly be	The survey confirms the pharmacological safety of 50% Nitrous Oxide in a wide variety of clinical indications. There's a need for rational training of medical personnel in its administration.	Level III Grade A

				reintroducing the drug, recovery and sequelae conditions.	attributed to the Nitrous oxide. Concomitant drug association and insufficient patient surveillance were attributed to 14 of the serious adverse events.		

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
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. http://dx.doi.org/10.5812/ircmj.3470	To assess maternal expectations and experience of labor analgesia with nitrous oxide.	98 pregnant women with gestational age 37-42 weeks, uncomplicated pregnancies, and pregnant with at least their second child in active phase of labor in the maternity ward in Shahid Yahyanejiad Hospital in Babol from 2008-2009.	Randomized Clinical Trial Mothers inhaled the gas at the beginning of the pain and stopped when the pain of each contraction ended and continued until the 2nd stage of labor. One group received gas and the other did not.	A questionnaire was used to gather information about severity of pain, efficacy, expectations, experiences, and satisfaction using the gas and also any related complications	Most of the women receiving the gas had less pain and were satisfied with it. In the Entonox group, 40.82% had severe pain and 10.2% had very severe pain while in the control group, 55.1% had severe pain and 25.6% had very severe pain. 63% of the side effects were rated as mild.	Planning and establishment of a consultation system to provide information about various methods of labor analgesia, especially gas is necessary to increase the tendency of pregnant women to undergo natural delivery without bearing severe labor pains.	Level I Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Pita, C., Pazmiño, S., Vallejo, M., Salazar-Pousada, D., Hidalgo, L., Pérez-López, F., & Chedraui, P. (2012). Inhaled intrapartum analgesia using a 50-50 % mixture of nitrous oxide-oxygen in a low-income hospital setting. *Archives Of Gynecology & Obstetrics*, *286*(3), 627-631. doi:10.1007/s00404-012-2359-6	To present current information about the safety and risks of the use of nitrous oxide for both anesthesia and the low-dose nitrous oxide/oxygen combination that is used for analgesia, with emphasis on concerns that are related to effects on labor, birth, breastfeeding, the well-being of the mother and neonate, and possible occupational risks for individuals who care for women during	126 women with singleton pregnancies 35 weeks or more, in active phase of labor, cephalic presentation who delivered between July 2011 and June 2011 at Enrique C. Sotomayor Obstetrics and Gynecology Hospital in Guayaquil, Ecuador	Prospective observational pilot study Women were asked to inhale 50-50% nitrous oxide-oxygen during contractions and room air between contractions.	Pain perception was measured using a 10 point Visual Analog Scale. Scores were measured at baseline, 1 hour after initiation, and during episiotomy repair. Progression and duration of labor, maternal vital signs, and fetal well-being was also assessed hourly. Route of delivery, mixture consumption, adverse effects, degree of satisfaction, and	One hour after initiating procedure, pain decreased by 56.2% while cervical dilation and effacement increased by 28.4% and 21.7%. Vaginal delivery was achieved in 96.9% of cases. The main adverse effect was dizziness (43.7%) and was rated as mild and tolerable. 96% answered that they would recommend the method and 92.9% graded it as good/excellen	Inhaled intrapartum analgesia using 50-50% nitrous-oxygen provided rapid pain alleviation. It is an appealing, effective and safe method for management of pain during labor. Nitrous oxide is most useful at institutions with infrastructure and personnel limitations.	Level II Grade B

	labor			maternal/neonatal outcome data were also recorded.	t		

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Rosenstein, M., Flood, P., Thiet, M. P., Nakagawa, S., Bishop, J., & Cheng, Y. (2014). 598: The use of nitrous oxide analgesia during labor at a single institution in the United States. *American Journal of Obstetrics and Gynecology*, *1*(210), S294-S295. http://dx.doi.org/10.1016/j.ajog.2013.10.631	To describe the neonatal and maternal outcomes associated with the use of Nitrous Oxide at a US hospital	The sample included 6,192 laboring women from a single US hospital between 2007-2012. 14% of them used nitrous oxide and of those 42% also used an epidural.	Cohort Study Data was collected from the medical records of women enrolled in the study after they had given birth	Neonatal admission was the primary outcome. Secondary maternal and neonatal outcomes were also collected and compared against nonusers.	Nitrous oxide users were more likely to be nulliparous and less likely to receive oxytocin, deliver via C-section, or develop chorioamnionitis. There was no significant difference in the odds of NICU admission, acidemia, 5 minute Apgar score less than 7, or postpartum hemorrhage.	Nitrous oxide is a labor analgesic that is safe for the neonate and is not associated with adverse maternal outcomes.	Level III Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Stefani, S. J., Hughes, S. C., Schnider, S. M., Levinson, G., Abboud, T. K., Henriksen, E. H., ... & Johnson, J. (1982). Neonatal neurobehavioral effects of inhalation analgesia for vaginal delivery. *Anesthesiology*, *56*(5), 351-355. http://dx.doi.org/10.1097/00132582-198212000-00020	To assess the possible Neurobehavioral effects of Nitrous Oxide or Enflurane on the neonate.	61 healthy full term parturients and their newborns.	Randomized Controlled Trial Parturients were divided into 3 groups. Group 1 had 21 patients and received no inhalation analgesia. Group 2 had 22 patients and had received .3-.8% enflurane and Group 3 had 18 patients and had received 30-50% Nitrous Oxide	Two examiners who were unaware of the nature and duration of analgesia evaluated the neonates at 15 minutes, 2 hours, and 24 hours using the NACS (Neurologic and Adaptive Capacity Score)and ENNS (Early Neonatal Behavioral Score).	All groups were essentially similar with respect to method of delivery, administration of narcotics, and use of local anesthetics, duration and effectiveness of analgesia, 5 minute Apgar scores, and acid-base status. There was no difference in any item on either the NACS or ENNS.	The results confirm the safety and effectiveness of inhalation analgesia for vaginal delivery and demonstrate the absence of adverse neonatal neurobehavioral effects up to 24 hours after birth. Nitrous oxide is a good option for women in labor.	Level I Grade B

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Talebi, H., Nourozi, A., Jamilian, M., Baharfar, N., & Eghtesadi-Araghi, P. (2009). Entonox for labor pain: a randomized placebo controlled trial. *Pakistan Journal of Biological Sciences: PJBS*, *12*(17), 1217-1221. http://dx.doi.org/10.3923/pjbs.2009.1217.1221	To investigate the effectiveness of nitrous oxide on pain of labor contractions and maternal SaO2.	534 ASA I and II parturients between September 2004 to 2006. Ages were from 16 to 35 years of age, pregnant with first or second child and in active phase of labor. Patients with fetal distress, any maternal cardiorespiratory condition, or history of taking opioids were excluded as well as patients who did not tolerate Entonox.	Randomized Placebo Controlled Trial Patients were randomized to receive either a pre-prepared mixture of 50% nitrous oxide and oxygen or 50% oxygen. The utilized intermittent self-administration.	Pain was rated with a VAS. O2 saturation, FHR, Mean Arterial Blood Pressure, Apgar scores, and side effects were recorded.	During the first three measurements, the SaO2 was significantly higher in the control group, yet there was no difference among groups in the next measurements. The MAP was comparable except the first two measurements in which the control group was higher. Pain scores were significantly lower in the Nitrous Oxide group throughout the study. There were no	Data indicates that using 50% Nitrous Oxide provides significant pain relief and is associated with few side effects. It can be quickly implemented during advanced painful labor. The study had limitations including the difficulty in timing appropriately the administration of nitrous oxide and it widely fluctuating bloodstream levels and also the failure to	Level I Grade A

					significant differences in 1st and 5th minute Apgar scores. Side effects were significantly higher among patients in the Nitrous Oxide group. Dizziness occurred in 22.6%of the Nitrous group and Drowsiness occurred in 15.4% compared to 0% in the control group.	evaluate patient's assessments of pain relief during delivery and 36-48 hours later.	

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Waldenström, U. (1999). Experience of labor and birth in 1,111 women. *Journal Of Psychosomatic Research*, *47*(5), 471-482. doi:10.1016/S0022-3999(99)00043-4	To increase our understanding of women's birth experience.	1,230 women of low medical risk who were recruited from the greater Stockholm area in early pregnancy. They were allocated to care in an in-hospital birth center or standard care. 1,148 women returned the follow-up questionnaire and the final sample was 1,111 after women were excluded for fetal loss and for cesarean section with no labor.	Cross Sectional Data was collected by a questionnaire in early pregnancy and a follow-up questionnaire two months after delivery.	The first questionnaire included demographic information as well as information about anxiety via the Karolinska Scales of Personality and about expectations going into birth The second questionnaire included details about the birth, and assessed women's feelings about their birth as rated on a 1-7 scale as far if their experience was negative	Of women who had nitrous oxide, 57% reported positive or very positive birth experience compared with 49% of women who had meperidine and 34% of women who had epidural analgesia. Overall, the use of nitrous oxide was associated with a less positive birth experience compared to the use of no medications. This is hypothesized to be correlated to	Pharmacological pain relief reduces pain, but its effect on the overall birth experience is in question and is an important field for further research.	Level III Grade B

				or positive.	personality traits, which affect women's inclination to nitrous oxide as well as their satisfaction with birth.		

Citation	Purpose	Sample	Design	Measurement	Results/Conclusion	Recommendations	Level and Quality
Waldenström, U., & Irestedt, L. (2006). Obstetric pain relief and its association with remembrance of labor pain at two months and one year after birth. *Journal of Psychosomatic Obstetrics & Gynecology*, *27*(3), 147-156. http://dx.doi.org/10.1080/01674820500433432	To investigate the association between use of pain relief during labor, and specifically epidural analgesia, and long-term memory of labor pain.	A national sample of 2,482 Swedish women with vaginal delivery or emergency cesarean section preceded by labor were followed from early pregnancy to one year after birth.	Longitudinal Cohort Study Three postal questionnaires were used. One in early pregnancy and one two months after birth and one year after birth.	Socio-demographic information, level of worry about the approaching birth, and expectations of labor pain; intensity of pain actually experienced, delivery data	Nitrous oxide was the most commonly used method of pain relief. 37.6% rated it as very effective compared to 83.7% epidural and 41.4% that used Pethidine. High rates of nitrous oxide use was associated with remembering less pain.	Further study is needed to try to explain the amnesic effect seen with nitrous oxide and to have more consistent conditions throughout the study.	Level II Grade B

References

Adams, S., Eberhard-Gran, M., & Eskild, A. (2012). Fear of childbirth and duration of labour: A study of 2,206 women with intended vaginal delivery. *BJOG: An International Journal of Obstetrics & Gynaecology*, *119*(10), 1238-1246. doi:10.1111/j.1471-0528.2012.03433.x

Agah, J., Baghani, R., Tali, S. S., & Tabarraei, Y. (2014). Effects of continuous use of Entonox in comparison with intermittent method on obstetric outcomes: A randomized clinical trial. *Journal of Pregnancy*, 1-5. doi:10.1155/2014/245907

AHRQ (2011). Evidence-based practice center systematic review protocol. Project title: Nitrous oxide for the management of labor pain. Retrieved from http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=675&pageaction=displayproduct

Akerman, N & Dresner, M. (2009). The management of breakthrough pain during labour. *CNS Drugs*, 23(8), 66-679, doi: 10.21265/00023210-200923080-00004

Anderson, D. (2011). A review of systemic opioids commonly used for labor pain relief. *Journal of Midwifery & Women's Health*, *56*(3), 222-239. doi:10.1111/j.1542-2011.2011.00061.x

Andersen, L. B., Melvaer, L. B., Videbech, P., Lamont, R. F., & Joergensen, J. S. (2012). Risk factors for developing post-traumatic stress disorder following childbirth: a systematic review. *Acta Obstetricia Et Gynecologica Scandinavica*, *91*(11), 1261-1272. doi:10.1111/j.1600-0412.2012.01476.x

Annequin, D., Carbajal, R., Chauvin, P., Gall, O., Tourniaire, B., & Murat, I. (2000). Fixed 50% nitrous oxide oxygen mixture for painful procedures: A French survey. *Pediatrics*, *105*(4), e47-e47. http://dx.doi.org/10.1542/peds.105.4.e47

American College of Nurse-Midwives. (2010). From the American College of Nurse-Midwives: Nitrous oxide for labor analgesia. *Journal of Midwifery & Women's Health*, 55(3), 292–296

American College of Nurse-Midwives. (2012). *Core competencies for basic midwifery practice*. Retrieved from http://www.midwife.org/index.asp?bid=59&cat=2&button=Search&rec=50

Berlit, S., Tuschy, B., Brade, J., Mayer, J., Kehl, S., & Sütterlin, M. (2013). Effectiveness of nitrous oxide for postpartum perineal repair: A randomised controlled trial. *European Journal of Obstetrics & Gynecology & Reproductive Biology*, *170*(2), 329-332. doi:10.1016/j.ejogrb.2013.06.025

Bistoletti, P., Lagercrantz, H., & Lunell, N. O. (1980). Correlation of fetal heart rate patterns with umbilical artery pH and catecholamines during last hour of labor. *Acta Obstetricia et Gynecologica Scandinavica*, *59*(3), 213-216. http://dx.doi.org/10.3109/00016348009155398

Burgos, J., Cobos, P., Osuna, C., de Mar Centeno, M., Fernández-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. http://dx.doi.org/10.1515/jpm-2013-0046

Carstoniu, J., Levytam, S., Norman, P., Daley, D., Katz, J., & Sandler, A. N. (1994). Nitrous Oxide in early labor safety and analgesic efficacy assessed by a double-blind, placebo-controlled study. *Anesthesiology*, 80(1), 30–35. doi:10.1097/00000542-199401000-00008

Chi, C., Lee, C. A., England, A., Hingorani, J., Paintsil, J., & Kadir, R. A. (2009). Obstetric analgesia and anaesthesia in women with inherited bleeding disorders. *Thromb Haemost*, *101*(6), 1104-1111. http://dx.doi.org/10.1160/th08-10-0694

Collins, M. (2015). A case report on the anxiolytic properties of nitrous oxide during labor. *Journal of Obstetric, Gynecologic, & Neonatal Nursing: Clinical Scholarship for the Care of Women, Childbearing Families, & Newborns*, *44*(1), 87-92. doi:10.1111/1552-6909.12522

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. http://dx.doi.org/10.1055/s-0034-1368606

Dearholt, S. L. & Dang, D. (2012). Johns Hopkins nursing evidence-based practice model and guidelines. Indianapolis, IN: Sigma Theta Tau International.

Duarte, R., McNeill, A., Drummond, G., & Tiplady, B. (2008). Comparison of the sedative, cognitive, and analgesic effects of nitrous oxide, sevoflurane, and ethanol. *British Journal of Anaesthesia*, *100*(2), 203-210. http://dx.doi.org/10.1093/bja/aem369

Grass, J. A. (2005). Patient-controlled analgesia. *Anesthesia & Analgesia*, *101*(5S), S44-S61. http://dx.doi.org/10.1213/01.ane.0000177102.11682.20

Harrison, R. F., Shore, M., Woods, T., Mathews, G., Gardiner, J., & Unwin, A. (1987). A comparative study of transcutaneous electrical nerve stimulation (TENS), entonox, pethidine+ promazine and lumbar epidural for pain relief in labor. *Acta Obstetricia et Gynecologica Scandinavica*, *66*(1), 9-14. http://dx.doi.org/10.3109/00016348709092945

Halpern, S. H., Levine, T., Wilson, D. B., MacDonell, J., Katsiris, S. E., & Leighton, B. L. (1999). Effect of labor analgesia on breastfeeding success. *Birth*, *26*(2), 83-88. http://dx.doi.org/10.1046/j.1523-536x.1999.00083.x

Henry, A., & Nand, S. E. (2004). Intrapartum pain management at the Royal Hospital for Women. *Australian & New Zealand Journal of Obstetrics & Gynaecology*, *44*(4), 307-313. doi:10.1111/j.1479-828X.2004.00231.x

Jones, P. L., Rosen, M., Mushin, W. W., & Jones, E. V. (1969). Methoxyflurane and nitrous oxide as obstetric analgesics. II.—A comparison by self-administered intermittent inhalation. *BMJ*, *3*(5665), 259-262. http://dx.doi.org/10.1136/bmj.3.5665.259

Khadem, N., Zirak, N., Soltani, G., Sahebdelfar, N., Sepehri Shamloo, A., & Ebrahimzadeh, S. (2013). Comparison of epidural versus entonox for labor analgesia in nulliparous women. نشریه جراحی و تروما, 1(1), 1-5. Retrieved form http://www.ijs.ir/

King, T., Brucker, M., & Fahey, J. (2013). *Varney's nurse midwifery*. Sudbury, MA: Jones and Bartlett Publishing.

Ko, J. Y., & Leffert, L. R. (2009). Clinical implications of neuraxial anesthesia in the parturient with scoliosis. *Anesthesia & Analgesia*, *109*(6), 1930-1934. http://dx.doi.org/10.1213/ane.0b013e3181bc3584

Kuczkowski, K. M. (2007). Labor analgesia for pregnant women with spina bifida: What does an obstetrician need to know?. *Archives of Gynecology and Obstetrics*, *275*(1), 53-56. http://dx.doi.org/10.1007/s00404-006-0147-x

Lederman, R. P., Lederman, E., & McCann, D. S. (1985). Anxiety and epinephrine in multiparous women in labor: relationship to duration of labor and fetal heart rate pattern. *American Journal of Obstetrics and Gynecology*, *153*(8), 870-877. http://dx.doi.org/10.1016/0002-9378(85)90692-1

Leighton, B. L., & Halpern, S. H. (2002). The effects of epidural analgesia on labor, maternal, and neonatal outcomes: A systematic review. *American Journal of Obstetrics and Gynecology*, *186*(5), S69-S77. http://dx.doi.org/10.1067/mob.2002.121813

Levinson, G., & Shnider, S. M. (1979). Catecholamines: The effects of maternal fear and its treatment on uterine function and circulation. *Birth*, *6*(3), 167-174. http://dx.doi.org/10.1111/j.1523-536x.1979.tb01329.x

Likis, F. E., Andrews, J. C., Collins, M. R., Lewis, R. M., Seroogy, J. J., Starr, S. A., ... & McPheeters, M. L. (2014). Nitrous oxide for the management of labor pain: a systematic review. *Anesthesia & Analgesia*, *118*(1), 153-167. http://dx.doi.org/10.1097/01.aoa.0000455280.655.3

Lindholm, A., & Hildingsson, I. (2015). Women's preferences and received pain relief in childbirth–A prospective longitudinal study in a northern region of Sweden. *Sexual & Reproductive Healthcare*, *6*(2), 74-81. http://dx.doi.org/10.1016/j.srhc.2014.10.001

Mcguinnes, C., & Rosen, M. (1984). Enflurane as an analgesic in labour. *Anaesthesia*, *39*(1), 24-26. http://dx.doi.org/10.1097/00132582-198412000-00028

Morgan, B., Bulpitt, C., Clifton, P., & Lewis, P. (1982). Effectiveness of pain relief in labour: survey of 1,000 mothers. *British Medical Journal (Clinical Research Edition)*, *285*(6343), 689-690. http://dx.doi.org/10.1136/bmj.285.6343.689

Nilsson, C., Bondas, T., & Lundgren, I. (2010). Previous birth experience in women with intense fear of childbirth. *Journal of Obstetric, Gynecologic, & Neonatal Nursing: Clinical Scholarship for the Care of Women, Childbearing Families, & Newborns*, *39*(3), 298-309. doi:10.1111/j.1552-6909.2010.01139.x

Nursing Theory. (2015). *Goal attainment*. Retrieved from http://www.nursing-theory.org/theories-and-models/king-theory-of-goal-attainment.php

Onody, P., Gil, P., & Hennequin, M. (2006). Safety of inhalation of a 50% nitrous oxide/oxygen premix. *Drug Safety*, *29*(7), 633-640. http://dx.doi.org/10.2165/00002018-200629070-00008

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. http://dx.doi.org/10.5812/ircmj.3470

Pita, C., Pazmiño, S., Vallejo, M., Salazar-Pousada, D., Hidalgo, L., Pérez-López, F., & Chedraui, P. (2012). Inhaled intrapartum analgesia using a 50-50 % mixture of nitrous oxide-oxygen in a low-income hospital setting. *Archives of Gynecology & Obstetrics*, *286*(3), 627-631. doi:10.1007/s00404-012-2359-6

Poole, J. (2003). Analgesia and anesthesia during labor and birth: Implications for mother and fetus. *JOGNN: Journal of Obstetric, Gynecologic & Neonatal Nursing*, *32*(6), 780-793. http://dx.doi.org/10.1177/0884217503258498

Posner, G., Black, A., Jone, G., & Dy, J. (2013). *Oxorn-Foote Human Labor & Birth*. (6th Ed.) New York, NY: McGraw Hill.

Rooks, J. P. (2007, May). Use of nitrous oxide in midwifery practice–complementary, synergistic, and needed in the United States. *Journal of Midwifery & Women's Health*. pp. 186-189. http://dx.doi.org/10.1016/j.jmwh.2007.02.017

Rooks, J. P. (2012). Labor pain management other than neuraxial: What do we know and where do we go next?. *Birth: Issues in Perinatal Care*, *39*(4), 318-322. doi:10.1111/birt.12009

Rosenstein, M., Flood, P., Thiet, M. P., Nakagawa, S., Bishop, J., & Cheng, Y. (2014). 598: The use of nitrous oxide analgesia during labor at a single institution in the United States. *American Journal of Obstetrics and Gynecology*, *1*(210), S294-S295. http://dx.doi.org/10.1016/j.ajog.2013.10.631

Sinusas, K. & Gagliardi, A. (2001). Initial management of breastfeeding. *American Family Physician, 64*(6), 981-989. Retrieved from http://www.aafp.org/afp/2001/0915/p981.html

Stefani, S. J., Hughes, S. C., Schnider, S. M., Levinson, G., Abboud, T. K., Henriksen, E. H., ... & Johnson, J. (1982). Neonatal neurobehavioral effects of inhalation analgesia for vaginal delivery. *Anesthesiology*, *56*(5), 351-355. http://dx.doi.org/10.1097/00132582-198212000-00020

Stewart, L. S., & Collins, M. (2012). Nitrous oxide as labor analgesia. *Nursing for Women's Health*, *16*(5), 398-409. http://dx.doi.org/10.1213/01.ane.0000445607.05453.f5

Talebi, H., Nourozi, A., Jamilian, M., Baharfar, N., & Eghtesadi-Araghi, P. (2009). Entonox for labor pain: a randomized placebo controlled trial. *Pakistan Journal of Biological Sciences: PJBS*, *12*(17), 1217-1221. http://dx.doi.org/10.3923/pjbs.2009.1217.1221

Waldenström, U. (1999). Experience of labor and birth in 1,111 women. *Journal of Psychosomatic Research*, *47*(5), 471-482. doi:10.1016/S0022-3999(99)00043-4

Waldenström, U., & Irestedt, L. (2006). Obstetric pain relief and its association with remembrance of labor pain at two months and one year after birth. *Journal of Psychosomatic Obstetrics & Gynecology*, *27*(3), 147-156. http://dx.doi.org/10.1080/01674820500433432