

Nitrous Oxide as Pain Relief for Women in Labor

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Introduction

Labor and childbirth can be a very frightening and anxious time in a woman's life. Pain is considered a normal, natural and expected part of childbirth and for that reason, it is vitally important to provide women access to different approaches to pain management. Healthcare professionals must be aware of all the options available to women for pain management because it is crucial that women feel they have a choice in what they use for their body. While every woman will experience pain differently, they should be able to have a choice of which measures they use to cope with the pain and demands of labor and they should understand the basic physiology behind why they are experiencing pain. "Pain is defined as 'an unpleasant sensation caused by noxious stimulation of the sensory nerve endings' or 'as a state in which an individual experiences and reports the presence of severe discomfort or an uncomfortable sensation'" (Lennon, 2018, p.637).

The pain women experience during labor and childbirth is caused by a combination of physical and psychological factors. Physiologically, the feedback system that exists between your hormones, endorphins and pain receptors enable your body to continue to release oxytocin. Oxytocin is the hormone that "initiates uterine contractions and cervical dilation, and allows the fetus to enter the pelvis, causing distention and stretching of the pelvic floor and vagina" (Lennon, 2018, p.637). The result of all the influences is a sensation of pain. The psychological component of pain during labor is the way in which the woman perceives the pain and discomfort. Perceptions of pain are influenced by many external factors such as culture, background, expectations, experience, fatigue, fear and anxiety (Lennon, 2018). In addition to understanding the physiology behind the pain, women must understand the options available to them to help manage that pain.

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There are both pharmacologic and non-pharmacologic pain relief measures that can be taken in order to reduce pain and improve comfort of laboring women. Often, a combination of pharmacologic and non-pharmacologic methods is effective at reducing and relieving pain and discomfort. There are many methods of pain relief for women in labor. They are generally considered to be in one of two major classes; analgesics and anesthetics. An analgesic is a drug that relieves pain but still allows for function and movement of muscle. An anesthetic relieves pain by decreasing sensation, so you cannot feel anything, including pain. Furthermore, pain relieving drugs for labor can be classified into systemic, regional or local. “Systemic medications affect the entire body. Local medications affect only a small area of the body. Regional medications affect a region of the body, like the region below the waist” (American College of Obstetricians and Gynecologists (ACOG), 2017). Opioids are the most common form of systemic analgesics used during labor and they are typically given through an IV. Opioids can depress breathing and heart rate in both mother and fetus and can cause drowsiness, nausea and itching. “An epidural block is the most common type of pain relief used for childbirth in the United States” (ACOG, 2017). The epidural is an example of regional anesthesia used in pregnant women. Side effects of an epidural when an opioid is used include nausea, itching, changes in breathing and drowsiness. Other side effects of an epidural can include fever, headache, decreased blood pressure and soreness. Local anesthetics are used in specific body areas and are often used for repair of an episiotomy or other tissues after birth. For local anesthetics, the medication is injected into the nerves and causes numbness and reduced sensation, so pain is not felt.

“Nitrous oxide is a tasteless and odorless gas used as a labor analgesic in some hospitals” (ACOG, 2017). Nitrous oxide, more commonly known as laughing gas, is most well-known for

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its use in the dental field however it is becoming increasingly popular as a tool for women to manage their labor pains. In high doses, such as in the dental field, nitrous oxide acts as an anesthetic. In lower doses, it acts as an anxiolytic, which helps to reduce anxiety and an analgesic which helps to reduce pain (Collins, 2015). Historically, nitrous oxide was used in the United States for labor pain management but never to a large extent. Currently, nitrous oxide is not widely used in the United States, however it is used in a vast majority of other well-developed countries especially in Europe. “Inhaled N₂O for labor analgesia has remained popular throughout Europe, with reported use in up to 60% of laboring women” (Collins, Fiore, Boudreau & Hewer, 2018, p. 72). In the United States, nitrous oxide has been used less commonly and most women choose opioid or other methods of pain management. “From 1975 to 1985, N₂O was used in about 6% of laboring patients in the United States, with numbers diminishing greatly in the late 1980s” (Collins, Fiore, Boudreau & Hewer, 2018, p. 72). With the new research and knowledge we have today about nitrous oxide and its uses as labor analgesia, there is a growing interest from women and a number of hospitals in the United States have begun to offer it to laboring women (Collins, Fiore, Boudreau & Hewer, 2018, p. 72). Although it is not a very well-known method of pain management, there are many midwives, physicians and healthcare professionals who strongly support its implementation into hospitals in America.

According to the *Journal of Midwifery & Women’s Health*, “Nitrous oxide labor analgesia is safe for the mother, fetus, and neonate and can be made safe for caregivers. It is simple to administer, does not interfere with the release and function of endogenous oxytocin, and has no adverse effects on the normal physiology and progress of labor” (Rooks, 2011, p. 557). The mode of action of nitrous oxide is not clear, but we do know that it “works by

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increasing the release of endorphins, corticotropins and dopamine that are produced in the mother's brain" (Stewart & Collins, 2012, p.402). This means that nitrous oxide works by increasing the release of natural opioids from the brain without having to introduce outside medications or synthetic drugs into the body. Nitrous oxide could revolutionize pain management. Unlike epidurals that can disrupt progress of labor and opioid analgesics that can have detrimental effects on the mother and fetus as well as the outcome, nitrous oxide is a safe and effective way to help women cope with the pain of childbirth. It also does not disrupt fetal alertness in utero which can lead to better outcomes and potentially higher APGAR scores after birth. In the United States, many women are limited to having to choose opioids and other drug agents given through epidural because there is a lack of alternative option, nitrous oxide could give women another choice.

One of the most commonly used brands of medical nitrous oxide in areas outside of the United States is Entonox. Entonox is a combination of 50% nitrous oxide and 50% oxygen that can be used in a hospital setting during labor. "Entonox has never been approved by the US Food and Drug Administration (FDA) for use in the United States; the only delivery apparatus used for this purpose in the United States is Nitronox" (Collins, Starr, Bishop, & Baysinger, 2012, p. e127). Nitronox is a delivery system that, "combines 50% N₂O and 50% oxygen in a set concentration that cannot be altered" (Collins, Starr, Bishop, & Baysinger, 2012, p. e127). In order to protect healthcare workers who may face exposure to abnormally high concentrations of nitrous oxide for extended periods of time, "scavenging equipment is set up through wall suction to remove exhaled nitrous oxide from the environment to decrease occupational exposure" (Houser, Debuty & Beal, 2018, p. 15). Entonox is typically self-administered either intermittently or continuously. This allows the woman the freedom to decide when she wants to

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use the analgesic and when she wants to stop using it to try something different. Entonox can provide independence for the laboring woman and it allows freedom to move around the room unlike an epidural or other pain relief methods. Nitrous oxide also has a very quick onset of 30-50 seconds and if the woman wishes to discontinue use, it can easily be reversed by simply breathing normal room air for around 5 minutes instead of breathing into the mask.

Overall, there are many advantages and benefits to using nitrous oxide for pain management in labor and women in the United States and around the world deserve to have as many options as possible to choose from to ensure that they feel comfortable and satisfied with their pain management regimen. Women in labor should have bodily autonomy and be able to have help in relieving their pain in a way that works with what they want in their birth plans and what their expectations are for labor and childbirth.

Significance in Nursing

Pain is one of the most common problems that nurses have to manage during their care of patients. Whether the patient is in pain from a surgery or cancer, a broken bone or delivering a baby, pain remains at the center of patient problems. Patients in all areas of nursing experience pain and it is crucial to find ways to manage that pain effectively and efficiently. Pain is considered as the fifth vital sign which indicates that it is a vitally important part of nursing care. Although it is seen as a normal body process to feel pain, it can greatly hinder healing, progress and overall well-being. “Chronic pain can lead to a chronic stress reaction that causes an increase in blood pressure and heart rate. This stress reaction can lead to harmful health effects, such as a reduced ability to fight off illnesses and diseases” (Cleveland Clinic, 2017). For that reason, this topic is incredibly important. Women in labor experience pain and discomfort through all stages of labor and after birth. As nurses, it is our responsibility to help patients cope

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with the pain they are experiencing and provide them with the most comfort and support that we can. It is also important to provide patients with options for their own pain management.

Providing people with choices can help them feel more independent and can therefore positively influence their health and well-being. Being in pain can hinder progression of labor and increase fear and anxiety about giving birth. Nitrous oxide has the properties necessary to help women feel less anxious, more relaxed and it can help them experience less pain and discomfort. Also, adding nitrous oxide to the pain management regimens available to patients in the hospital allows people to have more say in how they manage their pain and it may allow women to cope better with the things they may be experiencing in any and all stages of labor.

The purpose of this literature review is to examine both the benefits and risks associated with the use of nitrous oxide as a method of pain relief for women in labor. Additionally, we will examine any known contraindications, patient satisfaction and implementation methods associated with the use of nitrous oxide in this patient population. This literature review will evaluate the current scientific evidence with the goal of understanding whether nitrous oxide is a valid and viable option for women experiencing labor pain.

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Background

Pain

“Pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage” (Londhey, 2015, p. 5). It is a sensation that can range from mild, localized discomfort to agony. Pain also has emotional, psychological and spiritual components in addition to the physical components. The physical part of pain results from nerve stimulation. Pain may be contained to a discrete area, such as when you experience an injury, or it can be more diffuse, as in disorders like fibromyalgia where the pain is felt throughout the entire body or a wide range of areas. Pain is also a term used specifically for painful uterine contractions that occur in childbirth known as labor pains. Pain is a protective mechanism that occurs when tissues are damaged. Your body has a natural internal reaction to remove pain stimulus. The pain receptors are free nerve endings and they are present in superficial layers of skin, periosteum, arterial walls, joint surfaces, falx cerebri and the tentorium. The pain receptors are stimulated by mechanical, thermal and chemical stimuli (Londhey, 2015, p. 5).

Physiologically pain can be classified into 2 types: fast pain and slow pain. Fast pain is felt quickly, usually within 0.1 sec. It is also described as sharp, acute, electric or pricking pain. This type of pain is commonly felt in superficial tissues and rarely felt in deeper tissues. “Fast pain pathway is stimulated by mechanical or thermal pain stimuli and carried by A δ fibers at velocities between 6 and 30m/sec” (Londhey, 2015, p. 5). Sharp pain makes the person aware of the damaging influence and react immediately to remove himself or herself from the stimulus. AN example of this would be touching something hot and immediately moving your hand away when you feel the burning pain. The other kind of pain is slow pain. Slow pain is also called burning, aching, throbbing, gnawing, nauseating or chronic pain. It is present in superficial skin

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as well as deeper tissues. “The slow pain pathway is mainly stimulated by chemical stimuli (but also by mechanical and thermal) and carried by type C fibers at velocities between 0.5 and 2 m/sec” (Londhey, 2015, p. 5). Chemicals such as bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine and proteolytic enzymes are responsible for generating the feeling of pain. Prostaglandins and substance P enhance the sensitivity of the nerve endings without causing any direct excitation to them. The factors that cause pain include heat, lactic acidosis from tissue ischemia, contusion of tissues, bacterial infection, muscle spasm from mechanical stimulation and compression of blood vessels which can cause ischemia (Londhey, 2015, p.5).

Analgesia System

The pain threshold is the amount of pain each person individually can manage and deal with. It varies from person to person and the reaction to pain is highly variable. There is a natural internal system of the brain that works to suppress input of pain signals. This is called the analgesia system. The neurotransmitters released by the analgesia system are enkephalin and serotonin. “Enkephalins inhibit pre and post synaptic C fibers and A δ fibers when they synapse in dorsal horns, thus blocking the pain signals at initial entry into the spinal cord. Activation of the analgesia system by nervous signals entering the periaqueductal gray and periventricular areas or inactivation of pain pathways by analgesics almost totally suppress the pain signals entering through the peripheral nerves. The large type A β sensory fibres responsible for carrying touch sensation can depress transmission of pain signals from the same area” (Londhey, 2015, p. 7). Therefore, when these are stimulated simultaneously, there is suppression of pain. This system is the rationale and the basis of pain relief measures we attempt to achieve by applying liniments, massage, acupuncture and acupressure (Londhey, 2015, p. 7).

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Pain in Labor

Physical Aspects of Labor Pain. Labor pain is a very complex, subjective variable type of pain. No two births will be the same and no two women will experience labor pain in the same way. There are several factors that affect a woman's perception of pain in labor which also makes each experience very unique. It has been consistently found however, that labor pain is ranked quite high on the pain rating scale when compared with other painful experiences. Labor pain typically has two components; visceral and somatic. "Visceral labor pain occurs during the early first stage and the second stage of childbirth. With each uterine contraction, pressure is transmitted to the cervix causing stretching and distension and activating excitatory nociceptive afferents. These afferents innervate the endocervix and lower segment from T10 – L1" (Labor & Maguire, 2008, p. 15). Somatic pain is the second component of labor pain which occurs in addition to the visceral pain described above. Somatic pain occurs in the late first stage and the second stage of labor. "It arises due to afferents that innervate the vaginal surface of the cervix, perineum and vagina and occurs as a result of stretching, distension, ischemia and injury (tearing or iatrogenic) of the pelvic floor, perineum and vagina" (Labor & Maguire, 2008, p. 16). This pain manifests when the fetus begins to descend down further into the pelvis. During the active stage of labor, the uterus more regularly and rhythmically and the contractions become more intense. "The intensity of labor pain increases with greater cervical dilatation and correlates well with the intensity, duration and frequency of uterine contractions" (Labor & Maguire, 2008, p. 16). Pain experienced in early labor is visceral pain and it is referred to T10-T12 dermatomes. This means that the pain is felt in the lower abdomen, sacrum and back. Visceral pain in early labor is usually dull in character and it is not always sensitive to opioid drugs. Responses of pain to opioids depends on the route of administration. "Somatic pain occurs closer to delivery, is

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sharp in character and easily localized to the vagina, rectum and perineum. It radiates to the adjacent dermatomes T10 and L1 and compared to visceral pain, is more resistant to opioid drugs” (Labor & Maguire, 2008, p. 16).

Psychological Aspects of Labor Pain. Labor is a very emotional experience and the pain associated with labor presents a psychological challenge for many patients. “Studies have shown that women who had continuous intra-partum support were less likely to have intra-partum analgesia or to report dissatisfaction” (Labor & Maguire, 2008, p. 16). Some studies have also suggested that an underlying anxiety trait can result in a higher uptake of epidural analgesia as well as influence the efficacy of the analgesic effect the epidural block has on the patient. Some evidence also suggests “attitudes to pain relief in labor depend on personal aspirations, cultural factors and peer group influences” (Labor & Maguire, 2008, p. 17). A woman’s ability to cope with pain experienced in labor is as important if not more important than the actual level of pain they are experiencing. The ability to cope with pain may be rated as more important than the level of pain experienced. “In one survey, only 9% of women wanted the most pain free labor that drugs can give me. The majority, 67%, wanted the minimum quantity of drugs to keep the pain manageable. What seems to be important is that women are more likely to be satisfied with pain relief if they felt they had been in control during their labor” (Labor & Maguire, 2008, p. 17).

Pain Management in Labor

Women experience pain in different ways. Therefore, it is important that proper education occurs between patients and providers regarding pain management techniques and strategies that will be most successful for relieving labor pain depending on the case and circumstances. Some of the most common options available to women experiencing labor pain

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include epidurals, spinal blocks, analgesics, general anesthesia, inhalational anesthetics and other complementary methods such as breathing techniques, massage, visualization and water therapies. An epidural is the most common type of pain relief used during labor. When you receive an epidural, a small catheter is inserted into the lower part of the back. Numbing medication is delivered through the catheter and works to numb the lower half of the body, typically from the navel and below. An epidural allows you to remain awake and alert throughout the labor and birth, however the patient is bed bound since their lower body is numbed. Epidurals are considered a very safe option for women, however, as with any medication there are side effects. The epidural can cause a decrease in maternal blood pressure which can decrease fetal heart rate. In order to prevent this, additional intravenous fluids may be ordered, or the patient may need an additional medication to maintain blood pressures. Some women experience a degree of soreness or tenderness in their lower back at the insertion site, but this discomfort does not typically last more than a few days. Another side effect is a headache. Although it is rare, sometimes the needle can pierce the covering on the spinal cord causing a headache that can last for a few days. The spinal block is another analgesic option for women that can be used alone or in combination with an epidural. This procedure is similar to that of an epidural, but this goes deeper into the back and actually enters the spinal canal. The spinal block works immediately and lasts for a few hours. This method of pain relief also numbs the entire lower half of the body and is often used during planned cesarean sections.

Analgesics can also provide pain relief and they are pain medications given through an intravenous line or intramuscularly. These medications can be opioids or non-opioids and are used to temporarily relieve pain but do not eliminate it completely. General anesthesia is used in emergency cesarean section procedures or in women with other urgent medical problems.

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General anesthesia causes the patient to lose consciousness, so the woman is not awake and alert during the birth of the child. In addition to these pharmacological methods of pain relief, many women choose to use non-pharmacological or complementary methods to assist with the management and relief of their labor pains. Common complementary methods include massage, deep and slow breathing through contractions, visualization by the woman of herself somewhere peaceful or water therapies such as soaking in a tub or taking a warm shower can help soothe some of the tension. Inhalational anesthetics, such as nitrous oxide, are another method of pain management women may choose and this is the main method of analgesia this review aims to discuss (American Society of Anesthesiologists, 2020).

Inhalational Anesthetics

With the exception of nitrous oxide, inhaled anesthetics do not provide any significant analgesia. Instead, they produce immobility and amnesia. “Inhaled anesthetics produce immobility via actions on the spinal cord. There is consensus that inhaled anesthetics produce anesthesia by enhancing inhibitory channels and attenuating excitatory channels” (Open Anesthesia, 2020). Common inhalational anesthetics include fluroxene, sevoflurane, desflurane and isoflurane. Inhaled anesthetics can have side effects that affect many different body systems. Cardiovascular system effects include a decrease in mean arterial pressure because they reduce systemic vascular resistance. Inhaled anesthetics can also cause an increase in heart rate and sevoflurane, desflurane and isoflurane specifically diminish baroreceptor responses. This can cause fluctuations in blood pressures without any form of compensation. With inhalational anesthetics, any sudden changes in concentration can cause a more profound cardiovascular effect. Additionally, all inhalational anesthetics cause a prolonged QT interval. The respiratory effects of inhalational anesthetics can include a decrease in tidal volume and increased frequency

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of respirations. This can lead to increased dead space ventilation which will result in an increase in PaCO₂. Intracranial pressure can be increased when inhaled agents are used for anesthesia and autoregulation of these pressures becomes impaired. Inhaled anesthetics also cause EEG changes which can include initial increases in amplitude and synchrony which is then followed by periods of electrical silence at increased doses. Isoflurane, sevoflurane and desflurane can cause severe hepatic injury. Lastly, “other than nitrous oxide (which increases skeletal muscle tone), inhaled anesthetics either do not affect, or in some cases lower skeletal muscle tone” (Open Anesthesia, 2020). This indicates that voluntary control of muscles can become impaired with the use of some inhalational anesthetics.

“Nitrous oxide is the oldest anesthetic agent in clinical use” (Satuito & Tom, 2015, p. 43). Nitrous oxide belongs to a class of anesthetics called inhalational anesthetics and it is the least potent anesthetic in this class. “These are excellent hypnotics, and at higher concentrations, they provide varying degrees of analgesia and skeletal muscle relaxation” (Becker & Rosenberg, 2008, p. 124). Gases are distributed and absorbed based on a pressure gradient, moving from areas of high pressure to areas of low pressure. “Inhalational anesthetics, including nitrous oxide-oxygen, are absorbed and distributed as the result of pressure gradients in the lungs and equilibrate when the tension of inspired gas equals that in alveoli, blood, and tissues” (American Dental Association, 2019). Inhalational anesthetics are also dependent on solubility. Gases, such as nitrous oxide, have low solubility in the blood allowing for a very rapid onset of action. “Gases that have low solubility in blood and adipose tissue, such as nitrous oxide, will achieve blood tension and equilibrate more rapidly; this provides the driving force for inhalation agents to enter the brain, where anesthetic action occurs” (American Dental Association, 2019). In fact, nitrous oxide has the fastest onset among all inhaled agents. Inhaled agents also have the most

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rapid elimination because the same principles used for the uptake and distribution are used during elimination. That means that when the inhaled agent is stopped, the gas tends to move back into the alveoli in the lungs to be expired during normal breathing (Becker & Rosenberg, 2008). “Systemic elimination occurs with pulmonary exhalation; its low solubility allows nitrous oxide to be removed rapidly from the body” (American Dental Association, 2019).

Nitrous oxide can be easily distinguished from other inhalational anesthetics because it provides different systemic effects. “All inhalational agents are respiratory depressants and share a tendency increase respiratory rate but decrease tidal volume” (Becker & Rosenberg, 2008, p. 126). Nitrous oxide is an exception to this rule in that it does not decrease ventilation. Nitrous oxide also produces no reduction in mean arterial pressure, unlike many other inhaled agents, and has very little to no impact on vital physiologic functions. At subanesthetic levels, nitrous oxide produces mild analgesia, a net increase in minute ventilation, has little influence on stroke volume, heart rate and cardiac output and enables the maintenance of stable blood pressure (Becker & Rosenberg, 2008).

History of Nitrous Oxide

Nitrous oxide is a colorless and odorless gas. Nitrous means an element containing nitrogen and oxide means an element containing oxygen. Nitrous oxide is made up of one part oxygen and two parts nitrogen. “Nitrous oxide was first synthesized by Joseph Priestley in 1772. It was initially used as a dental analgesic and has been used extensively in a wide range of surgical procedures for both anesthesia and analgesia” (BOC Healthcare, 2019). Around 1800, a scientist in London, Humphrey Davy, was the first to describe the anesthetic effects of nitrous oxide. He was also the first person to suggest its use during surgical procedures and coined the name “laughing gas”. His advice, however, was not taken seriously and while people would use

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and abuse nitrous oxide in order to experience its euphoric effects, it wasn't seriously considered for use as anesthesia until Horace Wells began his experiments. Horace Wells was an American dentist who began exploration into the nitrous oxide after observing a man from a traveling circus inhale the nitrous oxide and proceed to become bruised and had a cut on his leg. Wells noticed that the man did not seem to notice the pain until the nitrous oxide began to wear off. He later convinced a fellow dentist to extract one of Wells' wisdom teeth while he was under the influence of nitrous oxide. After finding it effective at relieving pain, he introduced it to his own dental practice, marking the beginning of the use of nitrous oxide as a form of anesthetic (British Journal of Hospital Medicine, 2015). "In 1863 nitrous oxide anesthesia came into general use, when Gardner Quincy Colton successfully began to use nitrous oxide in all his "Colton Dental Association" clinics" (Academy of Dental Learning, 2017, p. 7). Until the 1860's, nitrous oxide was used alone as an inhalational anesthetic and patients were receiving 100% concentration of the gas. Oxygen was then added to the gas mix and it allowed Colton and his associates to perform over 75,000 extractions in more than 25,000 patients using nitrous oxide as an anesthetic. "Now with the efficacy and safety demonstrated by large numbers of successful procedures, the use of nitrous oxide rapidly became the preferred anesthetic method in dentistry" (Academy of Dental Learning, 2017, p. 7). Every year in North America, approximately 45 million dental patients undergo anesthesia with nitrous oxide being used in approximately half of these procedures. "Nitrous is the most used gaseous anesthetic in the world, commonly administered for the purpose of decreasing the amount of more potent and usually more toxic agents during general anesthesia cases" (Academy of Dental Learning, 2017, p. 8).

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Nitrous Oxide Side Effects

Adverse Effects. As with any medication, there are some negative side effects of nitrous oxide when used at the concentrations needed for dental procedures. The major adverse effects of nitrous oxide deal with its metabolism, pressure/volume toxicity and oxygen toxicity.

“Nitrous oxide irreversibly oxidizes the cobalt atom of vitamin B12, inhibiting the activity of the cobalamin-dependent enzyme methionine synthase” (Academy of Dental Learning, 2017, p. 16).

Loss of this enzyme causes a blockage in the synthesis of methionine which is essential for myelin sheath creation and DNA synthesis. “In adults with untreated B12 deficiency exposed to nitrous or those who chronically abuse N₂O leading to depletion of body stores of cobalamin, a myeloneuropathy is seen which is identical to subacute combined degeneration of the spinal column as seen in pernicious anemia” (Academy of Dental Learning, 2017, p. 17). For these reasons, patients with suspected B12 deficiency (history of B12 supplementation, post gastrectomy, ileal malabsorption) or anemia should not receive nitrous oxide. The other major cause of adverse events from nitrous oxide is due to pressure/volume complications. Nitrous oxide is 34 times more soluble in blood than nitrogen. It will therefore diffuse from the blood into any closed air-filled cavity in the body at a faster rate than nitrogen can be diffused out. “In a cavity with thick or noncompliant walls, the pressure inside such a cavity will immediately begin to increase. On the other hand, if the nitrous diffuses into a compliant, thin-walled air-filled space such as a pulmonary cyst or a loop of incarcerated bowel, the elevation in pressure will lead to distention of the structure” (Academy of Dental Learning, 2017, p. 17). The major example of nitrous diffusing into a poorly compliant cavity is the eyeball. The third adverse issue with nitrous oxide administration is oxygen toxicity. “Nitrous oxide administration should be avoided in patients who have received therapy with Bleomycin, an anti-neoplastic antibiotic,

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which is known to cause pulmonary toxicity” (Academy of Dental Learning, 2017, p. 17). In those patients who have received bleomycin, acute respiratory distress syndrome has occurred. This is thought to be caused by fluid overload and inspiration of high concentrations of oxygen during the procedure. Post-inhalation hypoxia (lack of oxygen) is also a potential problem associated with nitrous oxide use. “For this reason, the standard of care is to administer 100% oxygen for at least 5 minutes to all patients at the conclusion of inhalation anesthesia with N₂O /O₂” (Academy of Dental Learning, 2017, p. 18). This has been shown to completely prevent the post-inhalation hypoxia. Overall, acute and chronic adverse effects of nitrous oxide on the patient are rare and nausea and vomiting are the most common adverse effects, occurring in 0.5% of patients (Academy of Dental Learning, 2017, p. 18).

Positive Effects. The benefits of nitrous oxide in dentistry include the simplicity of administration, the anxiolytic capacity and the safety of its use. Nitrous oxide is administered through a mask that is placed over the mouth, nose or both. The scavenging system is used to reduce the amount of nitrous oxide released into the room air when it is exhaled by the laboring woman. The scavenging system collects the nitrous oxide for disposal which reduces the unnecessary environmental or occupational exposure to excess amounts of nitrous oxide. Once the system is set up to deliver the nitrous oxide-oxygen mixture, the rest of administration is straight forward patient education (Stewart & Collins, 2012). Nitrous oxide is an option that is offered to many dental patients to help make them more comfortable during procedures and feel less anxious about the dental work they are going to have done. The nitrous oxide should make you feel calm and comfortable during the procedure and any of its effects will wear off within minutes of removing the mask. Nitrous oxide also has a long history of safety and efficacy. It has a very rapid onset of action and it can be discontinued just as quickly as it is started. It takes

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less than one minute to feel results when inhaling the nitrous oxide and its effects can be reversed by simply breathing normally for about a minute. Nausea, dizziness and drowsiness tend to be the most common side effects, however due to its rapid excretion from the body, any adverse effects are short lived. Nitrous oxide also produces no reduction in mean arterial pressure, allowing for the maintenance of stable blood pressures, it does not decrease ventilation and has very little influence on stroke volume, heart rate and cardiac output (Becker & Rosenberg, 2008).

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Methods

A literature review was performed to identify the benefits and risks of nitrous oxide as a method of pain relief for women in labor. Databases used were Medline, CINAHL, PubMed, Cochrane and Google Scholar. Databases were searched for peer reviewed articles of both research studies and literature reviews. All articles were published between 2007 and 2019. In order to find relevant, helpful and supportive articles for this literature review, keywords were used in the search. Keywords included: *nitrous oxide, labor, pain, pain management, analgesia, anesthesia, Entonox.*

The inclusion criteria for the articles that will be discussed in this literature review are:

- Articles that are research studies must have IRB approval
- All articles must be either research studies or literature reviews
- Articles must focus on the use of nitrous oxide for women in labor
- Articles that include other pain management methods should be focused on nitrous oxide
- Articles should be focused on the use of nitrous oxide in hospital and medical settings rather than dental settings

The exclusion criteria are:

- Articles that concentrate on nitrous oxide use in dentistry
- Articles that focus on the use of nitrous oxide for pain other than in labor (ex: cancer patients)
- Articles that are more than 13 years old

All articles that were found from the relevant databases were first assessed to determine if they were applicable to the topic at hand. The abstracts of the articles selected were read and

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those that were found to be constructive were reviewed further and read entirely. Articles that met all inclusion criteria, used concrete methodologies with standardized results and were found to have applicable and useful information were included in the sample for this literature review.

The overall search provided 35 articles to be reviewed and utilized in the writing of this review. There were no exclusion criteria for articles based in areas of the world outside of the United States. Many of the articles utilized in this review were conducted or reviewed in areas such as Iran and countries in Europe. Nitrous oxide is not as widely used in the United States as it is in other parts of the world so it would be helpful for healthcare officials and government policymakers to consider the methods in which other countries have implemented nitrous oxide into their hospital policies. Modeling the protocols we can use in the United States off of countries where nitrous oxide is working successfully could be an important step in providing women another pain relief option. Another important point to include is that the majority of these articles have experts in the field working on the research and review or literature. Medical doctors, certified nurse midwives, nursing and midwifery professors, anesthesia professionals and other research experts were involved in all of the articles used in the review.

Since the goal of this literature review is to determine if nitrous oxide is a safe, reliable and valid option for women to use for pain relief in labor, it is important that the producers of the research being used are experts in the fields of anesthesia, midwifery, obstetrics and gynecology. Everyone in these specialty areas has received extensive education about pharmacology, obstetrics and healthcare in general which are all crucial to answering the research question being asked in this literature review.

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Results/Findings

Advantages

After reviewing the research available about nitrous oxide as a new method of pain relief for women in labor, it is evident that there are many advantages to its use. It provides women experiencing labor pain another option and supports a woman's right to make choices about her body and her plan of care. Some of the most obvious benefits found during research surrounded topics including ease of administration, cost, onset and excretion from the body, influence on maternal outcomes, influence on fetal outcomes, influence on labor pattern and cost.

Administration. Nitrous oxide is administered through a mask that is placed over the mouth, nose or both. The apparatus used for administration is a portable gas blender and scavenging system. The scavenging system is used to reduce the amount of nitrous oxide released into the room air when it is exhaled by the laboring woman. The scavenging system collects the nitrous oxide for disposal which reduces the unnecessary environmental or occupational exposure to excess amounts of nitrous oxide. Once the system is set up to deliver the nitrous oxide-oxygen mixture, the rest of administration is straight forward patient education. Since nitrous oxide must only be self-administered by the laboring woman, it is important to teach her how to use the apparatus and when to use it for best results. "Entonox which is administered by a self-use mask can be used intermittently or continuously. In the intermittent method the parturient breathes in the mask during contractions and puts it aside between them while in the continuous method she uses the mask permanently" (Agah, Bohemi, Tali & Tabarrael, 2014, p. 2).

In addition to educating the patient, it is also important to explain to family members or friends who may be in the room with the woman that they must not assist the woman in administering the nitrous oxide as this is one of the built-in safety mechanisms of this method of pain management. This allows for self-regulation of nitrous oxide intake and reduces the risk of

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toxicity from inhaling too much. “Side effects are maternal drowsiness, nausea and vomiting when inhaled analgesia is used too long or extensively, especially if the rule of self-administration is violated” (Klomp, van Poppel, Jones, Lazet, Di Nisio & Lagro-Janssen, 2012, p. 4). It is crucial that family members and healthcare staff understand the rules of self-administration and understand that the patient is the only person who can be in control of the nitrous oxide administration. “Encouraging the woman to inhale slowly and deeply for 30 seconds prior to the onset of the contraction will achieve the most effective results” (Stewart & Collins, 2012). The peak effect of nitrous oxide analgesia occurs around 50 seconds after beginning its administration. The peak of the pain women feel during labor occurs 30 seconds after the uterine contractions start. “So, for maximum perception of painless effect, the mother should use the mask at least 30s before beginning of contraction” (Agah, Bohemi, Tali & Tabarrael, 2014, p. 2). The synchronization of nitrous oxide administration and uterine contractions takes some adjusting for many women, which is another reason education is so important.

Patient Controlled. The fact that nitrous oxide is patient controlled is an advantage itself. “A patient-controlled analgesia (PCA) pump is a computerized machine that releases a drug for pain at the press of a button” (Cleveland Clinic, 2015). In the case of nitrous oxide administration, the release of the medication is through the mask, instead of the push of a button. For self-administration of nitrous oxide, “the patient must place the mask over the nose and mouth with sufficient force to create a seal and inhale with enough force to initiate the gas release” (Pinyan, Curley, Keever & Baldwin, 2017, p. 161). This method also allows for the built-in safety feature of self-administration to do its job. “An integral safety feature of nitrous oxide use is that when the woman has physiologically reached her limit of nitrous oxide intake, she will no longer be able to hold the mask up to her face for more, thus self-regulating the

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intake” (Stewart & Collins, 2012, p. 405). Women are often fearful and anxious during labor and being able to control the timing of their analgesic allows them to feel more in control of the situation and what is happening with their bodies. Self-regulation and self-control of pain management also encourages body autonomy and independence which is beneficial for all people and all patients. Nitrous oxide also allows for independence in the sense that women can move freely while using nitrous oxide, unlike with an epidural. An epidural causes numbness in the lower half of the body and forces women to remain in bed with a catheter. With inhaled nitrous oxide, women can be more mobile rather than being stuck in bed throughout their labor. They can walk around their room or the unit and they have the freedom to be more independent during their labor. In addition to the ease of administration and the benefit of patient-controlled anesthesia, nitrous oxide is also a safe option for both mother and baby.

Safety. Nitrous oxide has a history of safety and efficacy in the world of obstetrics. It has a very rapid onset of action and it can be discontinued just as quickly as it is started. It takes less than one minute to feel results when inhaling the nitrous oxide and its effects can be reversed by simply breathing normally for about a minute. “A major advantage of N₂O is that it has a rapid onset and offset profile and can be started quickly, with the added benefit of maternal clearance within 30 to 60 seconds” (Collins, Fiore, Boudreau & Hewey, 2018, p. 74). The rapid N₂O clearance also allows for the option to change to another form of pain management if the laboring woman is not satisfied with the analgesia provided by N₂O. This prevents build up in fetal or maternal tissues and prevents any possibility of toxicity. Also, since maternal satisfaction is a goal of pain relief during labor, an additional advantage of nitrous oxide is “the rapid N₂O clearance also allows for the option to change to another form of pain management if the laboring woman is not satisfied with the analgesia provided by N₂O” (Collins, Fiore,

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Boudreau & Hewey, 2018, p. 74). Nausea, dizziness and drowsiness tend to be the most common side effects, however due to its rapid excretion from the body, any adverse effects are short lived.

Nitrous oxide also produces no reduction in mean arterial pressure, allowing for the maintenance of stable blood pressures, it does not decrease ventilation and has very little influence on stroke volume, heart rate and cardiac output (Becker & Rosenberg, 2008). This is important for women with a history of cardiac issues or women who may have experienced cardiac issues as a result of their pregnancy. “It does not cause diffusion hypoxia (an abrupt, short-lasting decrease in alveolar oxygen when room air is inhaled following high-dose nitrous oxide anesthesia), interfere with oxytocin function, have an impact on spontaneous vaginal birth rate, increase risk for complications, have an impact on Apgar scores, impair ability to breastfeed, depress neonate respiration rate, or require intensive monitoring. It can also be safely used with other forms of analgesia” (Pinyan, Curlee, Keever & Baldwin, 2017, p. 161). There has not been evidence to show a difference in cesarean section rates or rates of postpartum complications such as hemorrhage or infection when using nitrous oxide as opposed to a different form of analgesia. “Women using nitrous oxide remain awake and alert, with complete motor and sensory function throughout use” (Stewart & Collins, 2012, p. 402). Therefore, there is not delay in initiation of skin to skin contact between the mother and baby and it does not cause any delay in breastfeeding which is beneficial for both the mother and the baby.

In the fetus, “nitrous oxide crosses the placenta to concentrate in the fetus at about 80 percent of the maternal serum level” (Stewart & Collins, 2012, p. 403). Much like in the mother, nitrous oxide can be rapidly excreted from the lungs once respirations begin. This ensures there is no respiratory or central nervous system depression at birth. According to several studies,

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there is no statistically significant difference in APGAR scores, behavioral scores of the newborn, incidence of meconium or cord blood gases. “It does not have an impact on spontaneous vaginal birth rate, increase risk for complications, have an impact on Apgar scores, impair ability to breastfeed, depress neonate respiration rate, or require intensive monitoring. It can also be safely used with other forms of analgesia” (Pinyan, Curlee, Keever & Baldwin, 2017, p. 161). “Nitrous oxide does not inhibit the release of oxytocin, infant alertness, the need for neonatal resuscitation, or breastfeeding” (Collins, Fiore, Boudreau & Hewey, 2018, p. 74).

Additionally, “nitrous oxide does not affect infant alertness during the early bonding period between a mother and her newborn, it does not affect breastfeeding and it does not increase the need for neonatal resuscitation” (American Pregnancy Association, 2015). This is important for the newborn because skin to skin contact provides many benefits for bonding, breastfeeding and transitioning to the outside world. “The American Academy of Pediatrics recommends that all breastfeeding babies spend time skin-to-skin right after birth” (Cleveland Clinic, 2018). Having the baby on the chest helps to initiate breastfeeding and allows for easy access when the infant needs to be breastfed, especially when the newborn is sleepy. “Compared with babies who are swaddled or kept in a crib, skin-to-skin babies stay warmer and calmer, cry less, and have healthier blood sugar levels” (Cleveland Clinic, 2018). Overall, nitrous oxide allows for pain relief during labor without causing detrimental maternal or fetal effects.

Progress of Labor. In a typical labor, there are three stages. Stage one includes the early and active labor, stage two includes the birth of the baby and stage three includes the delivery of the placenta. “The first stage of labor and birth occurs when you begin to feel regular contractions, which cause the cervix to open (dilate) and soften, shorten and thin (effacement)” (Mayo Clinic, 2020). Oxytocin is the hormone that “initiates uterine contractions and cervical

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dilation, and allows the fetus to enter the pelvis, causing distention and stretching of the pelvic floor and vagina” (Lennon, 2018, p. 637). In other words, oxytocin is the driving force behind labor. It causes the contractions that push the fetus into the birth canal, and it helps prepare the mother's body for childbirth. Some well-known and commonly used methods of pain relief disrupt the natural oxytocin produced by the body. The disruption of oxytocin can therefore disrupt the progression of labor once it has been initiated. Nitrous oxide is a method of pain management that does not inhibit the release of oxytocin (Collins, Fiore, Boudreau & Hewey, 2018, p. 74). It also does not interfere with oxytocin function (Pinyan, Curlee, Keever & Baldwin, 2017, p. 161). With nitrous oxide, the natural release of oxytocin is not affected. That means that nitrous oxide, “has no adverse effects on the normal physiology and progress of labor” (American Pregnancy Association, 2015). When oxytocin is not interrupted during labor, cervical dilation and effacement can proceed naturally, thus reducing the need for additional treatments, interventions or therapies to dilate and efface the cervix. Therefore, the natural process of labor is not interrupted.

Cost. With the healthcare system in the United States today, cost is an important factor to consider. Nitrous oxide is considered to be an inexpensive and cost-effective method of pain management for women experiencing labor pain. “Since the use of Entonox, especially in intermittent form, reduces labor pain without causing complications for the mother, and also is associated with more maternal satisfaction, this gas can be used during labor in order to reduce the number of cesarean deliveries occurring due to labor pain and as a result, the complications of surgery and anesthesia and its high costs can be decreased” (Attar, Feizabadi, A., Jarahi, Feizabadi, L. & Sheybani, 2016, p. 3330). The simplicity and effectiveness of nitrous oxide is beneficial for the cost of its use as well. “It is much simpler and less expensive to use than

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epidural analgesia and does not result in complications that require additional treatments and both mother and baby days of hospitalization” (Rooks, 2007, P. 5). Epidurals tend to be a common choice for pain management however, “epidural anesthesia is expensive, costing anywhere from \$1,000 and \$4,000 depending on the setting” (Hauser, DeButy & Beal, 2018, p. 12).

In a nurse directed model for implementation of nitrous oxide, a cost benefit analysis was performed. “The initial expenditure for the NO/O demand-flow system was approximately \$5,000” (Pinyan, Curlee, Keever & Baldwin, 2017). The nitrous oxide only cost \$1 per patient and it cost \$10 for the mask and tubing used for administration. This cost analysis included their total apparatus costs for all patients as well as how much it cost for nurse education and their total expenditure for nitrous oxide was just over \$10,000 for 466 patients. In addition to the cost of the nitrous oxide and administration apparatus, there are often added expenses when an anesthesiologist or certified registered nurse anesthetists (CRNA) is involved in the administration of anesthesia. In this nurse directed model, there are no additional expenses placed on the patients to cover administering the nitrous oxide since it is the patient themselves who are administering the gas. “The supplies and bedside anesthesia staff-time required for anesthesia care at the bedside for nitrous oxide use are less than that required for epidural placement and monitoring, and therefore theoretically less costly” (Stewart & Collins, 2012, p. 403). Overall, nitrous oxide has been considered an inexpensive and effective option to help relieve labor pain but more cost analyses should be performed. Since there are many people in the United States with poor or no health insurance, it is important to consider costs when planning care for individuals in the hospital.

Disadvantages

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Occupational Exposure. Some hospital staff on labor and delivery units have questioned the safety of their exposure to nitrous oxide after stories arose about fertility issues among other healthcare professionals exposed to nitrous oxide on the job. Most current data in the United States regarding fertility issues linked to nitrous oxide use have been based on samples in the dental profession. Nitrous oxide used in dentistry is different than nitrous oxide used in labor and delivery. Dose and duration of exposure are the two most important factors to consider. The dose used in a dental office or during a dental procedure is much higher than that used for women in labor. Additionally, dental hygienists are in much closer contact to the exhaled nitrous oxide from patients than on a labor and delivery unit of a hospital. Additionally, hospital rooms currently in the United States have much better ventilation systems than dental rooms and therefore, there is less exposure to nitrous oxide in the ambient air around staff. Also, with the new scavenging apparatus for nitrous oxide administered for women in labor, an even smaller amount of exhaled nitrous is entering the air and thus less occupational exposure occurs. “No U.S. studies have examined workplace exposure on labor and delivery units” (Stewart, L. S., & Collins, M., 2012). Finally, the safeguards we gave here in the United States work to help limit exposure and protect hospital staff. “Per the U.S. Occupational Safety and Health Administration (OSHA, n.d.), exposure limit is 25 to 50 parts per million (ppm), whereas the European limit is generally set at 100 ppm” (American College of Nurse-Midwives, 2010). “Current standards in the United States for management of waste anesthetic gases call for limiting occupational exposure to N₂O to not more than an 8-hour time-weighted average (TWA) concentration of 25 ppm” (American College of Nurse Midwives, 2011). This means that the limited exposure nurses and hospital staff may experience has not been proven to cause any

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adverse health effects. Much like any drug, extensive research and testing should be done to ensure complete safety.

Environmental. In the United States today, the environmental impact of nearly everything is being evaluated to ensure it is safe to use and not detrimental to the environment. “As with any inhaled medical gas, there is concern over environmental dispersion of nitrous oxide waste” (Stewart, L. S., & Collins, M., 2012). Gas emissions can be toxic to the environment and with the new push towards saving the environment it is important that all things being introduced undergo evaluation. “Although medical use of nitrous oxide composes less than 1 percent of environmental emissions of nitrous oxide, it is a potent greenhouse gas” (Stewart, L. S., & Collins, M., 2012). There are many other sources of nitrous oxide emission such as dairy farms, fertilizers and power stations that cause much more significant and detrimental issues in the environment.

Implementation/ Accessibility. Implementation of any new procedures, supplies, medications or treatments in the medical world can be difficult. In the United States, there are many obstacles to the introduction of something new into the medical field because we work hard to protect patients from harm and maintain safe working environments for hospital and healthcare staff. Nitrous oxide is beginning to be reintroduced into modern hospitals for women in labor and the implementation process can be challenging, demanding and time-consuming. Compared with the total number of hospitals across the country, very few have successfully reimplemented nitrous oxide into their pain management options. Policies and procedures must first be developed and then those policies must be approved, and the projects can finally be implemented. The long process to introducing nitrous oxide could be a disadvantage because the longer it takes to bring nitrous oxide into every hospital, the longer women will have to choose

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pain management techniques that do not include nitrous oxide. In addition to implementation, accessibility could be an issue. First, if implementation is not occurring in all hospitals, people living in regions where nitrous oxide is not used will not have that option to choose it. Also, women in underdeveloped countries have limited access to any form of pain management during labor so it is an area to be further investigated as to how we can make nitrous oxide universally available. Finally, women who do not wish to give birth in a hospital setting or those who are unable to give birth in a hospital due to personal, financial or insurance reasons would also not have access to nitrous oxide. It is important that all women have access to a choice for themselves in how they wish to manage their pain and nitrous oxide should be able to be one of those choices. The reality, however, is that no matter what you do to provide equal accessibility, there always seems to be some people who have easier and cheaper access.

Contraindications

Much like other medical treatments and interventions, nitrous oxide is not best suited for every patient. There are some important contraindications to the use of nitrous oxide that healthcare providers must be aware of in order to provide safe patient care. “Clearly, inability to use a nasal mask is an absolute contraindication to the use of nitrous oxide” (Becker & Rosenberg, 2008, p. 129). These patients generally either cannot breathe through their nose adequately or cannot tolerate sustained placement of the mask. Some examples could include patients with a sever phobia or patients who may be cognitively impaired. Patients with a deviated septum, nasal polyps, upper respiratory infections, allergic rhinitis and severe sinusitis may also be advised against the use of inhaled nitrous oxide for pain relief (Becker & Rosenberg, 2008, p. 129). “Absolute contraindications to the administration of nitrous oxide include the presence of a potential space the gas could fill such as with pneumothorax, intraocular surgery,

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bowel obstruction or middle ear surgery. Other conditions that contraindicate nitrous oxide usage are increased intracranial pressure, increased intraocular pressure and pulmonary hypertension” (Stewart & Collins, 2012, p. 404). Additionally, women should be checked for vitamin B12 deficiency prior to the use of nitrous oxide. Additional contraindications include “documented vitamin B12 deficiency, or oxygen impairment” (Collins, 2014, p. 89). “Documented vitamin B12 deficiency (pernicious anemia) and taking B12 supplementation and/or a decreased vitamin B12 functioning (cobalamin functioning), such as Crohn’s disease, celiac disease, gluten intolerance, pernicious anemia, history of bariatric surgery, and/or a strict vegan diet a condition that affects the ability to oxygenate the blood, defined as O₂ saturation consistently <95% on room air” (Hauser, DeButy & Beal, 2018, p. 14), may be reasons to choose a pain management strategy that does not involve nitrous oxide as these conditions could be worsened with N₂O use.

Patient Perspectives

Much like any new pain reliever, there are mixed reviews and different perspectives on the use of nitrous oxide for labor pain management. Some women may feel it works well to control and ease their pain while others may find it to be minimally effective. Pain relief is dependent upon many factors. Physical, mental and social influences can change effectiveness and satisfaction with any treatment. Despite some varying opinions, “studies have shown that the majority of pregnant women receiving Entonox gas were satisfied with the analgesic effects and reported good experiences” (Pasha, et. al., 2012, p. 795). “Although nearly half of the women in our study who delivered with nitrous oxide analgesia alone reported low or intermediate analgesic effectiveness, satisfaction scores were uniformly high in this group, with only a minority (48, or 7%) reporting a satisfaction score <8” (Richardson, Lopez, Baysinger, Shotwell & Chestnut, 2017, p. 551). Women in some studies were as likely to report high

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satisfaction as women using other pharmacologic pain relief methods. Additionally, many women chose to continue with nitrous oxide although other forms of analgesia were available to them. This shows that patient satisfaction with their treatment depends on more than just the pain relief. Pain relief is a contributing factor to patient satisfaction but other factors such as independence, ease of use, cost, side effects and personal beliefs can affect the way patients feel about a treatment. Patient satisfaction should be a top priority when it comes to labor and maternal care and part of providing satisfactory care is the ability to give women options to choose what they want in their healthcare. Nitrous oxide provides women with another choice.

Author/Article Title	Purpose	Type of Study/Sample Size	Main Outcomes
Agah et. al., 2014 Effects of Continuous Use of Entonox in Comparison with Intermittent Method on Obstetric Outcomes: A Randomized Clinical Trial	To compare the complications induced by two methods to find out whether it is safe to permit the mothers to use Entonox continuously or not	50 parturient used Entonox intermittently and 50 cases used it continuously during labor. Randomized clinical trial	This study showed the mean duration of second stage of labor had no significant difference ($P = 0.3$). Perineal laceration was less in continuous group significantly ($P = 0.04$). Assisted vaginal birth was not different significantly ($P = 0.4$). Uterine atony had no significant difference in two groups ($P = 0.2$). Maternal collaboration in pushing and satisfaction were higher in continuous group significantly ($P = 0.03$), ($P < 0.0001$). Apgar score of neonates at first and fifth minute was acceptable and not different significantly in two groups ($P = 0.3$). Conclusions. Our study demonstrated continuous method is also safe. So, it seems reasonable to set mothers free to choose the desired method of Entonox usage
Agah et. al., 2014 Maternal Side-Effects of Continuous vs. Intermittent Method of Entonox During Labor: A Randomized Clinical Trial	The aim of this study is to demonstrate whether continuous method is as safe as intermittent method.	Research study, One hundred admitted women for vaginal delivery were included in this study randomized clinical trial	The maternal side effects of Entonox had no significant difference in two groups ($p > 0.05$). Mothers' satisfaction rate in continuous group was more than the intermittent group significantly ($p < 0.001$). Meantime of active phase of labor had no significant difference between two groups ($p = 0.2$).
Attar, et, al., 2016 Effect of Entonox on reducing the need for Pethidine and the Relevant Fetal and Maternal Complications for Painless Labor	The aim of this study was to evaluate the analgesic effects of Entonox during labor on reducing the need for pethidine (Meperidine) and fetal-maternal complications	Research study, conducted on pregnant women, participants were randomly allocated to receive inhaled Entonox gas ($n = 200$) or inhale Oxygen ($n = 200$) as a control group double-blind randomized clinical trial	In our study, Entonox significantly reduced pain during delivery without significant increase in maternal and neonatal complications. Complications such as nausea, vomiting, dizziness, and drowsiness were reported in 25% of the Entonox group and 23% in the control group ($p = 0.640$). Mean of pain severity score during labor in the Entonox and control groups was 4.5 ± 1.2 and 5.2 ± 1.4 , respectively ($p < 0.001$). Pethidine requirement, significantly was lower in the Entonox group (31.6 ± 11.8 versus 35.7 ± 12.4 ; $p < 0.001$).
Becker & Rosenberg, 2008 Nitrous Oxide and the Inhalation Anesthetics	The purpose of this CE article is to provide an overview of inhalation anesthetics in general and to address nitrous oxide more specifically in comparison.	Continuing Education article	Nitrous oxide is the most commonly used inhalation anesthetic in dentistry and is commonly used in emergency centers and ambulatory surgery centers as well. When used alone, it is incapable of producing general anesthesia reliably, but it may be combined with other inhalation and/or intravenous agents in deep sedative/general anesthetic techniques. However, as a single agent, it has impressive safety and is excellent for providing minimal and moderate sedation for apprehensive dental patients. To gain a full appreciation of the

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			pharmacology, physiologic influences, and proper use of nitrous oxide, one must compare it with other inhalation anesthetics. The purpose of this CE article is to provide an overview of inhalation anesthetics in general and to address nitrous oxide more specifically in comparison.
British Journal of Midwifery, 2018 Pain management in labor and childbirth: Going back to basics	Discuss the importance of understanding pain management options.	Peer reviewed article, Double blind peer review Literature review	Midwives need to equip themselves with the knowledge needed to assist the women to make informed choices. Midwives can provide this information during antenatal interactions, making every encounter matter and ensuring that the women is aware of the physiological processes that occur during pregnancy and birth and knows what to expect. This should equip the woman with a variety of choices to help her manage the pain of labor
Caton et. al., 2002 The Nature and Management of Labor Pain: Executive Summary (Caton et. al., 2002)	This report describes the background and process for a rigorous project to improve understanding of labor pain and its management, and summarizes the main results and their implications	Literature review	The experience of labor pain is a highly individual reflection of variable stimuli uniquely received and interpreted through an individual woman's emotional, motivational, cognitive, social, and cultural circumstances. Choice among a variety of methods and individualization of pain-related care is desirable. Although formerly more widely available in the United States, relatively few laboring women appear to have access to nitrous oxide currently. A large proportion of women appear to obtain adequate pain relief and to be satisfied with this method. As women self-administer it, they can maintain a sense of control and reduce burdens on staff. Effects appear to reverse rapidly when women stop inhaling the drug. It does not appear to interfere with labor physiology. Use of co-interventions that require monitoring and management and increase risks to the mother and fetus/infant appears to be limited. Once incorporated into practice, the technique is simple and inexpensive.
Collins, 2014 A Case Report on the Anxiolytic Properties of Nitrous Oxide during Labor	To discuss the anxiolytic properties of nitrous oxide	Case report/literature review	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 children. Inhalation of N ₂ O with its resultant anxiolytic effect causes a decreased catecholamine response (Gillman et al., 1988), and in this case the woman's stalled labor was quickly resolved. N ₂ O is a valuable option for labor analgesia, with notable anxiolytic effects that may prove as important as its analgesic effects. Women should have access to this safe and efficacious method of analgesia

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<p>Collins et. al., 2018</p> <p>Nitrous Oxide for the Management of Labor Analgesia</p>	<p>This article reviews nitrous oxide and explores current practice standards for use of nitrous oxide in managing labor analgesia</p>	<p>Literature review</p>	<p>The effects of inhaled N₂O are both analgesic and anxiolytic, an invaluable combination in the practice of obstetrics that is safe in all 3 phases of labor. Nitrous oxide is pharmacologically fast in onset and clearance, making it valuable in the treatment of breakthrough pain and anxiety. In the United States, the most common means of analgesic management continues to be continuous labor epidurals and opiate administration, both intravenously and intramuscularly.³⁴ Providing additional options (i.e., inhaled N₂O) help to improve the overall experience, particularly for women desiring less invasive and low-commitment interventions</p>
<p>Collins, Starr, Bishop & Baysinger, 2012</p> <p>Nitrous Oxide for Labor Analgesia: Expanding Analgesic Options for Women in the United States</p>	<p>This article discusses the use of N₂O for pain management during labor, including its history, properties, clinical indications, and use and environmental safety issues.</p>	<p>Management Update Literature review</p>	<p>Nitrous oxide (N₂O) is a commonly used labor analgesic in many Western countries, but is used infrequently in the United States. The University of California at San Francisco has been offering N₂O for labor analgesia for more than 30 years. Vanderbilt University Medical Center recently began offering N₂O as an option for pain relief in laboring women. Many women report that N₂O provides effective pain relief during labor and argue that it should be made more widely available in the United States. This article discusses the use of N₂O for pain management during labor, including its history, properties, clinical indications, and use and environmental safety issues. Practical issues regarding implementation of N₂O service in a medical center setting are also discussed.</p>
<p>Czech et. al., 2018</p> <p>Pharmacological and Non-Pharmacological Methods of Labor Pain Relief—Establishment of Effectiveness and Comparison</p>	<p>To evaluate the effectiveness of pharmacological and non-pharmacological pain relief methods and to compare them.</p>	<p>Research study, 258 women were included in the study. They were divided into six groups depending on chosen method of labor pain relief. interviewed using a questionnaire and the visual analogue scale for pain.</p>	<p>Epidural analgesia is the gold standard of labor pain relief; however, water birth was found to be associated with the highest satisfaction level of the parturient women. The contentment of childbirth depends not only on the level of experienced pain, but also on the care provided to the parturient during pregnancy and labor</p>
<p>Dammer et. al., 2014</p> <p>Introduction of Inhaled Nitrous Oxide and Oxygen for Pain</p>	<p>. This study aimed to investigate the acceptance of the inhaled analgesia of inhaled nitrous oxide</p>	<p>Observational study, 66 pregnant women</p>	<p>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 inhaled nitrous oxide and oxygen again was reported as higher for patients who tolerated it well (p=0.0129) and used it in the second stage of</p>

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Management during Labor– Evaluation of Patients and Midwives Satisfaction	and oxygen by midwives and pregnant women during labor		labor ($p=0.0003$) and when bearing down ($p=0.0008$). Inhaled nitrous oxide and oxygen is an effective method for pain management during labor and is accepted well by women in labor and by midwives.
Galeotti et. al., 2016 Inhalation Conscious Sedation with Nitrous Oxide and Oxygen as Alternative to General Anesthesia in Precooperative, Fearful, and Disabled Pediatric Dental Patients: A Large Survey on 688 Working Sessions	To evaluate the effectiveness and tolerability of nitrous oxide sedation for dental treatment on a large pediatric sample.	472 noncooperating patients (ages 4-17) were treated under conscious sedation. Observational Survey	688 conscious sedations were carried out. The success was 86.3%. Adverse effects occurred in 2.5%. 1317 dental procedures were performed. Inhalation conscious sedation represented an effective and safe method to obtain cooperation, even in very young patients, and it could reduce the number of pediatric patients referred to hospitals for general anesthesia.
Hauser, DeButy & Beal, 2018 Implementation of an evidence-based practice change to offer nitrous oxide during labor	The aim of this evidence-based practice change was to implement use of nitrous oxide as a pain management option during labor and to examine women's satisfaction with that option.	Evidence-based practice change guided by the model for evidence-based practice change.	Nitrous oxide was offered to 26% of eligible women. Most of the 55 women who used nitrous oxide during the implementation period reported satisfaction with it and indicated that they would consider nitrous oxide for future labor. Our experience implementing a practice change to offer nitrous oxide to laboring women indicated that use of nitrous oxide was feasible in this setting and that women were receptive to this option, were satisfied with its use and would use nitrous oxide for a future labor.
Honarmandpour et. al., 2015 Effects of Entonox in Comparison with Lidocaine on Pain Severity during Episiotomy Incision in Nulliparous Women: A	This study aimed to compare the effects of Entonox and lidocaine on pain intensity during episiotomy incision in nulliparous women	Research study, conducted on 120 term nulliparous women, who met the inclusion criteria. Randomized control trial	In this study, no significant difference was observed between the intervention and control groups regarding pain intensity ($P=0.52$). Moreover, no significant difference was observed in the satisfaction level of the two groups ($P=0.70$). According to the results of this study, Entonox could be used as an effective and noninvasive alternative to lidocaine to reduce pain during episiotomy incision without significant side effects.

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Randomized Control Trial			
Illuzzi et. al., 2018 Nitrous oxide's revival in childbirth	To discuss nitrous oxide as a method of pain relief for women in labor	Peer reviewed article Literature review	Nitrous oxide increases dopamine, norepinephrine, and endogenous opioid release, decreasing pain perception and producing a sense of euphoria and sometimes psychedelic effects, Nitrous oxide has no effect on cord blood gases, Apgar scores, or neonatal behavior but there are no extensive long-term studies on infants and children exposed to the gas during labor. Nitrous oxide remains a popular modality for pain management for women around the globe. It can be used exclusively, or as an adjunct to other methods. Contraindications, side effects, and complication rates are low. Nitrous oxide may increase patient satisfaction by giving women a greater sense of control during labor in an era when more women are seeking this type of birthing experience.
Klomp, Van Poppel, Jones, Lazet, Di Nisio & Lagro-Janssen, 2012 Inhaled analgesia for relieving pain during labour.	To examine the effects of all modalities of inhaled analgesia on the mother and the newborn for mothers who planned to have a vaginal delivery.	Literature review	Inhaled analgesia appears to be effective in reducing pain intensity and in giving pain relief in labour. However, substantial heterogeneity was detected for pain intensity. Furthermore, nitrous oxide appears to result in more side effects compared with flurane derivatives. Flurane derivatives result in more drowsiness when compared with nitrous oxide. When inhaled analgesia is compared with no treatment or placebo, nitrous oxide appears to result in even more side effects such as nausea, vomiting, dizziness and drowsiness. There is no evidence for differences for any of the outcomes comparing one strength versus a different strength of inhaled analgesia, comparing different delivery systems or comparing inhaled analgesia with TENS
Labor & Maguire, 2008 The Pain of Labour	To look at different types of pain and pain experienced during labor.	Literature review	Labour is an emotional experience and involves both physiological and psychological mechanisms. The pain of labour is severe but despite this its memory diminishes with time. Labour pain has two components: visceral pain which occurs during the early first stage and the second stage of childbirth, and somatic pain which occurs during the late first stage and the second stage. The pain of labour in the first stage is mediated by T10 to L1 spinal segments, whereas that in the second stage is carried by T12 to L1, and S2 to S4 spinal segments. Pain relief in labour is complex and often challenging without regional analgesia. Effective management of labour pain

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			plays a relatively minor role in a woman's satisfaction with childbirth.
Lennon, 2018 Pain management in labour and childbirth: Going back to basics	To look at different pharmacological and non-pharmacological methods of pain management used in childbirth and labor.	Literature review	As rates of anxiety, tocophobia and post-traumatic stress syndrome increase, there is a need for health professionals to reflect, review and rethink how women could be better prepared for labour and birth. Women need to fully understand the choices available and to have the support to enable them to deal with the pain and challenges of labour. All pregnant women should be helped to understand the physiology of labour and birth so that they are aware of what is happening to their bodies and what they and their midwife might do or avoid to keep birth normal. Information must incorporate discussions on both pharmacological and non-pharmacological methods of pain relief, which must be current, contemporary and evidence-based to enhance the woman's ability to make informed choices about her intrapartum care. How the woman copes with this process depends on not only the confidence she has in her own body but also on the support of her caregivers. The care setting, as well as any pre-existing fears, previous experiences and expectations all heavily influence a woman's positive or negative birth experience.
Londhey, 2015 Pathophysiology of Pain	To look at the pathophysiology of pain and the different pain pathways.	Supplement to journal of the association of physicians of India	Pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage. It is a sensation that can range from mild, localized discomfort to agony. Pain has both physical and emotional components. The physical part of pain results from nerve stimulation. Pain may be contained to a discrete area, as in an injury, or it can be more diffuse, as in disorders like fibromyalgia. Pain is also a term specifically used to denote a painful uterine contraction occurring in childbirth known as labour pains. With this background, it is necessary to have the basic understanding of the neuroanatomy and physiology of pain to tackle it in a reasonable way in the era of evidence- based- medicine.
Macintyre, 2001 Safety and efficacy of patient-controlled analgesia	To determine the safety and effectiveness of patient-controlled analgesia	Literature review	PCA can be a very effective and safe method of pain relief and may allow easier individualization of therapy compared with conventional methods of opioid analgesia. However, it is not a 'one size fits all' or a 'set and forget' therapy and original prescriptions may need to be adjusted if maximal benefit is to be given to all patient. Conventional methods of analgesia could be as effective as PCA in many patients.

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			However, in many busy hospital wards, staff numbers, time, attitudes, and knowledge may serve to limit the efficacy of nurse administered pain relief. It is, therefore, likely that the popularity of PCA will continue and that PCA will remain a commonly used method of analgesia.
Najefian et. al., 2013 The Effect of Nitrous Oxide (Entonox) on Labor Pain Relief During Delivery Stages	aimed to evaluate the effect of Entonox on the intensity of labor pain during delivery stages	clinical trial study was conducted among 200 pregnant women with the gestational age of (37-41 weeks) Randomized clinical study	Mean duration of active phase in the Entonox and control groups was 4.07 ± 3.2 and 5.28 ± 4.7 hours respectively. The association was significantly different between two groups ($p = 0.03$). The mean of pain severity during three consequent contractions in the trial and control groups was 5.18 ± 1.29 and 8.99 ± 1.98 respectively which was significantly different ($p < 0.005$). Entonox is more effective to reduce pain during labor and delivery. Entonox is cheap, safe and easily available for pain relieving labor. It has no severe side effect on mother and not any side effect on neonate.
Parsa et. al., 2017 The Effect of Entonox on Labor Pain Relief among Nulliparous Women: A Randomized Controlled Trial	This study investigated the effect of Entonox on pain relief and length of labor in nulliparous women.	Research study, conducted among 120 nulliparous women (60 in intervention and 60 in control group) Randomized control trial	Entonox provides significant pain relief and it can quickly be implemented during painful labor. There were significant differences between two groups on labor pain at the first, second, third and fourth hours after intervention. Duration of labor in the intervention group (64.80 minutes) was significantly shorter than the control group (98.33 minutes).
Pasha et. al., 2012 Maternal Expectations and Experiences of Labor Analgesia with Nitrous Oxide	The purpose of this study was to assess maternal expectations and experience of labor analgesia with nitrous oxide.	Clinical trial study, 98 women	This study has shown that using Entonox gas caused less labor pain, favorable expectations and experiences and more maternal satisfaction. nox users in active phase of labor was moderate level (46.94%), while being severe for the control group (55.10%); 40.82% of the mothers in Entonox group had a severe pain and 10.20% had a very severe pain, whereas in the control group 55.10% of the mothers experience a severe pain and 26.53% of whom had very severe pain. Many pregnant women using Entonox gas received efficacy of Entonox gas in a different level and had less labor pain, and only 2% of them were unsatisfied
Pinyan, Curlee, Keever & Baldwin, 2017	This quality improvement project involved development and implementation of	Quality Improvement Project	Approximately one half of the patients who have given birth at the hospital since initiation of the project have used nitrous oxide during labor. The majority of women who participated in a survey after birth found it helpful during mild-to-moderate labor pain. No adverse

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A Nurse-Directed Model for Nitrous Oxide Use During Labor	a nurse-driven, self-administered, demand-flow nitrous oxide program as an option for pain relief for laboring women in a rural community hospital		effects have noted in either the mother or the baby following nitrous oxide use. Initiation and management of nitrous oxide by registered nurses is a safe and cost-effective option for labor pain. It may be especially beneficial in hospitals that do not have 24/7 in-house anesthesia coverage
Pita et. al., 2012 Inhaled intrapartum analgesia using a 50–50 % mixture of nitrous oxide–oxygen in a low-income hospital setting	To analyze the benefits of an inhaled analgesia procedure over intrapartum pain and the degree of satisfaction of using this method	Pilot study, 126 women	Inhaled intrapartum analgesia using a N2O–O2 50–50 % mixture provided rapid pain alleviation. It is an appealing, effective and safe method for the management of pain during labor, most useful at institutions with infrastructure and personnel limitations
Richardson et. al., 2016 Nitrous Oxide During Labor: Maternal Satisfaction Does Not Depend Exclusively on Analgesic Effectiveness	to compare the relationship between analgesic effectiveness and patient satisfaction with analgesia in women who delivered vaginally using nitrous oxide, neuraxial analgesia or both	standardized survey was recorded on the first postpartum day for all women who received anesthetic care for labor and delivery - 6507 women	Patients who received nitrous oxide alone were as likely to express satisfaction with anesthesia care as those who received neuraxial analgesia, even though they were less likely to report excellent analgesia. Although pain relief contributes to the satisfaction with labor analgesia care, our results suggest that analgesia is not the only contributor to maternal satisfaction.
Richardson et. al., 2017 Should Nitrous Oxide Be Used for Laboring Patients?	To discuss the use of nitrous oxide and whether it should be implemented in healthcare or not.	Literature review	Unlike neuraxial labor analgesia, N2O provides highly variable labor analgesia, ranging from very poor to very good. Despite this variability, parturient who choose to use N2O where neuraxial analgesia is an option (including after trying N2O) report satisfaction like that reported by women who use neuraxial analgesia. Parturient using N2O report higher satisfaction than subsets of parturient who experience inadequate neuraxial labor analgesia. Regarding safety, parturient and neonatal adverse effects occur at rates similar to other techniques and may be no more frequent than in patients who undergo labor and delivery without analgesia. Environmental exposure and health risk to health care providers are minimal when proper scavenging of exhaled gas and adequate ventilation are used.

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			Costs of administering N2O appear similar to other alternatives for labor pain relief. Costs may be lower than for neuraxial techniques because non-anesthesia trained nursing staff can monitor nitrous oxide analgesia safely. N2O analgesia provides a useful alternative for pain relief in parturient who decline neuraxial labor analgesia or who have contraindications to neuraxial blocks and may offer advantages over patient-controlled systemic opioid administration and non-pharmacological techniques.
Rooks, 2007 Nitrous Oxide for Pain in Labor—Why Not in the United States?	To discuss the benefits of nitrous oxide and why it should be implemented in the United States	Literature review/editorial	Nitrous oxide can be started and stopped at any point during labor, according to the needs and preferences of the woman. It takes effect in about 50 seconds after the first breath and the effect is transient—essentially gone when no longer needed. Although nitrous oxide provides much less complete pain relief than an epidural, it is enough for many women. It is eliminated through the lungs rather than the liver, and so does not accumulate in the mother's or baby's body. Nitrous oxide has significant cost advantages. It is much simpler and less expensive to use than epidural analgesia and does not result in complications that require additional treatments and both mother and baby days of hospitalization.
Rooks, 2011 Safety and Risks of Nitrous Oxide Labor Analgesia: A Review	This review of the safety and risks of nitrous oxide (N2O) labor analgesia presents results of a search for evidence of its effects on labor, the mother, the fetus, the neonate, breastfeeding, and maternal-infant bonding.	Literature review	Nitrous oxide analgesia is safe for mothers, neonates, and those who care for women during childbirth if the N2O is delivered as a 50% blend with O2, is self-administered, and good occupational hygiene is practiced. Because of the strong correlation between dose and harm from exposure to N2O, concerns based on effects of long exposure to high anesthetic-level doses of N2O have only tenuous, hypothetical pertinence to the safety of N2O/O2 labor analgesia. Nitrous oxide labor analgesia is safe for the mother, fetus, and neonate and can be made safe for caregivers. It is simple to administer, does not interfere with the release and function of endogenous oxytocin, and has no adverse effects on the normal physiology and progress of labor
Rooks, 2010 Use of Nitrous Oxide in Midwifery Practice – Complementary,	To discuss safety. Efficacy and necessity of nitrous oxide for labor pain management.	Literature review	N2O is not right for every woman, but it is wonderful for some women, and as stated above, more effective for parous women than for women having their first child. It is particularly helpful for women experiencing rapid labor, transition, second stage labor and while suturing the perineum. It is also helpful for women who want to avoid an epidural or women who must wait for an epidural.

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Synergistic and Needed in the United States			
Sanders et. al., 2014 An exploration of the benefits and drawbacks of intrapartum pain management strategies	To explain the advantages and disadvantages of pain management strategies in labor	Literature review	The benefits and drawbacks of each strategy are highly individualized and subject to change. Individualized antenatal discussing and planning is imperative for managing women's expectations of labor pain and in facilitating maternal satisfaction and choice. Entonox, 50% Nitrous Oxide (N ₂ O) and 50% Oxygen (O ₂), is the most widely used form of inhalation analgesia in modern midwifery practice (Jones et al, 2013), and is frequently perceived as the first step on the ladder of analgesic options
Satuito & Tom, 2016 Potent Inhalational Anesthetics for Dentistry	This article reviews the history, similarities, differences, and clinical applications of the most popular inhalational agents used in contemporary dental surgical settings.	Continuing Education article	Nitrous oxide and the volatile inhalational anesthetics have defined anxiety and pain control in both dentistry and medicine for over a century. From curious experimentation to spectacular public demonstrations, the initial work of 2 dentists, Horace Wells and William T. G. Morton, persists to this day in modern surgery and anesthesia. This article reviews the history, similarities, differences, and clinical applications of the most popular inhalational agents used in contemporary dental surgical settings.
Sheyklo, et. al., 2017 Effect of Entonox for pain management in labor: A systematic review and meta-analysis of randomized controlled trials	The aim of this study was to systematically review studies addressing the effect of Entonox for pain management in labor.	Systematic review/meta-analysis of randomized controlled trials	Finally, 14 articles were included in the study. Pain relief standard difference in mean between-groups was -1.01 (95% CI: -1.59 to -0.43, Q=148.5, df=8, p=0.02, I ² =76) this difference was significant (p<0.05). The overall Apgar score standard difference in mean between-groups (Entonox vs. comparison) was 0.12 (95% CI: 0.01 to 0.23, Q=109.4, df=16, p=0.00, I ² =85.3) this difference was significant (p<0.05). The results of mothers' satisfaction rate show that mothers in Entonox group has a high level of satisfaction rate. According to results of studies published in Iran, it seems that Entonox is an effective method for pain relief in vaginal delivery, as well as for improving infant Apgar score and mothers' satisfaction rate. Pain relief through Entonox can be used as a strategy for cesarean section reduction plan in Iran.
Shuman, 2016 Nitrous Oxide: Use and Safety	The focus of this clinical study is to provide the dental professional with the steps needed to deliver	Clinical study	Nitrous oxide is a valuable agent that assists patients who are anxious and fearful. It has an excellent safety record when used for anxiolysis and conscious sedation. There are, however, certain parameters that must be followed to ensure that every patient receives the proper and correct mode of treatment in this area.

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	nitrous oxide in a safe and efficacious manner		
Stewart & Collins, 2012 Nitrous Oxide as Labor Analgesia: Clinical Implications for Nurses	Describe maternal and fetal pharmacologic effects of nitrous oxide and procedures are best suited for nitrous oxide use. Discuss nitrous oxide delivery	Continuing Nursing Educational Article	Nitrous oxides pharmacologic makeup and minimal maternal and fetal side make it an appropriate alternative for labor analgesia for many women. With the reintroduction of self-administered nitrous oxide into U.S. hospitals, a working knowledge of safe and evidence-based nursing care of the laboring woman using nitrous oxide is essential. An understanding of the history of nitrous oxide use, as well as how the current practices have evolved, will assist labor and delivery nurses to optimize the benefits of self-administration of nitrous oxide. Either alone or in combination with nonpharmacologic pain management therapies, nitrous oxide offers laboring women a feasible alternative to existing modalities. Educating women about analgesic options and including them in the decision-making process empowers them and ultimately leads to satisfying birth experiences.

Table 1. ARTICLE TABLE

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Discussion

Outcomes

The findings of this literature review have shown the wide variety of pain management techniques and medications available to women experiencing labor pain. Current popular pain management methods women use, especially in the United States, include pharmacological interventions such as epidurals and opioids, as well as nonpharmacological methods such as acupuncture, water therapy, massage therapy and breathing techniques. While nitrous oxide is a significantly less popular choice in the United States, this review has shown that it is widely used in other parts of the world. The purpose of this literature review was to examine the benefits and risks associated with the use of nitrous oxide as a method of pain relief for women in labor and to look at contraindications for its use and patient satisfaction with its use.

Some of the benefits associated with nitrous oxide use from this review include ease of administration, cost, onset and excretion from the body, influence on maternal outcomes, influence on fetal outcomes, influence on labor pattern and cost. Some of the disadvantages of nitrous oxide that were found in this review include the risks associated with occupational exposure, the environmental impact of nitrous oxide, the difficulty associated with implementation of new policies into hospitals and the challenges of ensuring all women have equal access to nitrous oxide as an option for pain management. As with any medical intervention, there are contraindications to consider before administering nitrous oxide. Some of these include inability to hold the face mask, inability to tolerate the face mask, vitamin B12 deficiency, problems with oxygenation and the presence of a potential space the gas could fill such as with pneumothorax, intraocular surgery, bowel obstruction or middle ear surgery (Stewart & Collins, 2012, p. 404). Although there was not an abundance of patient perspectives found for this literature review, there were a few articles that included how the women felt the

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nitrous oxide worked for reducing or managing their labor pain. One example of this was, “studies have shown that the majority of pregnant women receiving Entonox gas were satisfied with the analgesic effects and reported good experiences” (Pasha, et. al., 2012, p. 795). Overall, nitrous oxide appears to be a very valid option that could be beneficial for many women experiencing labor pain if it were to be made more available in the United States. Researchers and healthcare workers should continue to collect data on this subject and create conversations regarding the use of nitrous oxide in order to continue to push for its implementation universally.

Implications in Nursing Practice and Education

Nurses working in hospitals, clinics and primary care settings, especially those who work in obstetrics and gynecology specialties, should use the information provided in this literature review and work to apply it to their nursing practice. Nurses working in labor and delivery and postpartum specialties deal with managing the pain their patients are experiencing every day. These nurses, like all nurses, must work hard to advocate for their patients and to provide the best care possible. One of the best ways for nurses to do this is to speak up about the use of nitrous oxide and its benefits. Nurses have the power to implement change in their facilities and it is important that they use that power to help with this issue. Women who are experiencing labor pain deserve to have that pain relieved in a way that works well for them and their birth goals. Nitrous oxide is a way to give women an option that doesn't include opioids or an epidural and won't force them to rely on non-pharmacologic methods to manage their pain. If nurses take this information to their managers and healthcare officials at their care settings, more hospitals may begin working to implement nitrous oxide as a pain management method available to all women who meet the necessary criteria.

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Another important role that nurses perform is education. Educating patients is a crucial part of the responsibilities of a nurse. Therefore, it is vital that nurses working in specialty areas such as obstetrics understand the information provided in this literature review. Labor nurses need to be aware of the benefits, risks and contraindications associated with the use of nitrous oxide in women in labor. Nurses should be educated on patient controlled anesthesia and the rules associated with that so they can be sure to provide adequate information to women and their family members about how nitrous oxide will be delivered and ensure they understand that the patient is the only one allowed to hold the mask. It is also important that nurses are educated on the equipment used to dispense nitrous oxide to ensure that there is safe and successful administration. Once nitrous oxide is implemented into more and more hospitals, it will then also be important to bring education regarding nitrous oxide to nursing schools as well. New nurses should be made aware of the use and benefits of nitrous oxide so they can provide their patients with the same level of care and education.

Implications for Further Research

As with any research problem, there is always room for improvement. “Opportunities for research related to N₂O include occupational exposure and effects on those caring for women using N₂O; fetal/neonatal effects; maternal satisfaction; institutional and system factors that may act as an impedance to initiation; and initiation by nursing staff versus other types of providers (respiratory therapy or anesthesia, for example)” (Collins, 2015, p. 91). Occupational exposure was a common theme throughout this review that seemed to be of concern. The use of scavenging equipment to remove excess nitrous oxide from the air when the woman exhales has been successfully implemented. However, it is important that research is conducted to ensure that equipment is functional and sufficient to keep healthcare workers safe. “Research is needed

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on occupational risks of providing care to women using N₂O/O₂ labor analgesia in well-ventilated hospitals or birth centers with active scavenging built into the equipment that provides the gas mixture to the woman” (Rooks, 2011, p. 563). For the scavenging equipment, it is also important to conduct research on how many breaths the woman needs to exhale into the scavenging equipment to reduce the amount of nitrous oxide exposure healthcare workers experience (Rooks, 2011, p. 563).

Additionally, nitrous oxide has not been commonly used in the United States which provides another future research project. “Because N₂O/O₂ labor analgesia has not been widely used in the United States in recent years, most of the research has been done elsewhere, yet interest in use of N₂O during labor is expanding and new research is needed” (Rooks, 2011, p. 563). Regulations for research in the United States can be different than that of other countries so it is important that research is conducted in America to ensure hospitals can begin implementation as soon as possible. Legislation and government can also be helpful for the future research of nitrous oxide. “Legislation mandating the widespread availability of all safe and viable analgesia options for labor and birth would certainly increase the opportunity for the growth of this modality” (Collins, 2015, p. 91). Government policies can help hospitals, healthcare workers and researchers override the impediment of further research. Often, reasons for halting research are due to reasons unrelated to what is in the best interest of the women in labor and have more to do with the best interest of the hospital and institutional economic concerns (Collins, 2015, p. 91). Lastly, education would be an area for further research to be conducted. Since nurses and providers would be providing the majority of the education about nitrous oxide to the women interested in choosing it, it would be crucial to ensure that education is sufficient and standardized so that all women receive the same information and the best

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information possible. “Patient safety is a key component of nitrous oxide self-administration. As with any new intervention, nurses must have thorough education and demonstrate competency before providing care for women using nitrous oxide” (Stewart & Collins, 2012, p. 405).

Conclusion

This literature review attempted to summarize the currently known benefits, risks and contraindications associated with the use of nitrous oxide as a method of pain management for women in labor. It also aimed to look at patient satisfaction and identify where future research may be needed. After reviewing the articles, it has been determined that nitrous oxide is a safe and effective pain management option for many women experiencing labor pain around the world. It should be highly considered for future research projects so that implementation can begin in all hospitals in the United States. It is important for all patients, especially women in labor, to feel in control of their care and to have a sense of autonomy over their bodies and nitrous oxide is a great way to do that for women.

Future research studies should focus on occupational exposure associated with the use of inhaled nitrous oxide and the use of scavenging equipment to remove excess nitrous oxide from the air when the woman exhales. Although it appears to have been successfully implemented, it is important that research is conducted to ensure that equipment is functional and sufficient to keep healthcare workers safe. Additional areas of research can include researching its use in the United States, the development of government policies to help hospitals, healthcare workers and researchers override the impediment of further research and education methods for nurses and providers to ensure that knowledge is sufficient and standardized so that all women receive the same information and the best information possible.

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Labor and childbirth can be a very frightening and anxious time in a woman's life. Pain is considered a normal, natural and expected part of childbirth and for that reason, it is vitally important to provide women access to different approaches to pain management. Healthcare professionals must be aware of all the options available to women for pain management because it is crucial that women feel they have a choice in what they use for their body. While every woman will experience pain differently, they should be able to have a choice of which measures they use to cope with the pain and demands of labor. Nitrous oxide provides women experiencing labor pain another option and supports a woman's right to make choices about her body and her plan of care.

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References

- Agah, J., Baghani, R., Safiabadi Tali, S. H., & Tabarraei, Y. (2014). Effects of continuous use of Entonox in comparison with intermittent method on obstetric outcomes: A randomized clinical trial. *Journal of Pregnancy*, 2014, 1-5. DOI: 10.1155/2014/245907
- American College of Nurse Midwives - Nitrous Oxide for Labor Analgesia. (2011). Retrieved from https://www.midwife.org/acnm/files/acnmlibrarydata/uploadfilename/000000000080/nitrous_oxide_12_09.pdf
- American Dental Association. (2019). Nitrous oxide. Retrieved from <https://www.ada.org/en/member-center/oral-health-topics/nitrous-oxide>
- American Pregnancy Association. (2015). Nitrous oxide during labor. Retrieved from <https://americanpregnancy.org/labor-and-birth/nitrous-oxide-labor/>
- American Society of Anesthesiologists. (2020). Labor pain. Retrieved from <https://www.asahq.org/whensecondscount/pain-management/types-of-pain/labor/>
- Attar, A. S., Feizabadi, A. S., Jarahi, L., Feizabadi, L. S., & Sheybani, S. (2016). Effect of Entonox on reducing the need for Pethidine and the relevant fetal and maternal complications for painless labor. *Electronic Physician*, 8(12), 3325-3332 DOI: <http://dx.doi.org/10.19082/3325>
- Becker, D. E., & Rosenberg, M. (2008). Nitrous oxide and the inhalation anesthetics. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2614651/>
- BOC Healthcare. (2019). Medical nitrous oxide. Retrieved from <https://www.bochealthcare.co.uk/en/products-and-services/products-and-services-by-category/medical-gases/medical-nitrous/medical-nitrous-oxide.html>
- Caton, Corey, Frigoletto, Hopkins, Lieberman, Mayberry, . . . Young. (2002). The Nature and

NITROUS OXIDE AS PAIN RELIEF FOR WOMEN IN LABOR

Management of Labor Pain: Executive summary. *American Journal of Obstetrics and Gynecology*, 186(5), S1-S15. DOI:10.1067/mob.2002.123102

Cleveland Clinic. (2017). Chronic pain: Living with chronic pain. Retrieved from

<https://my.clevelandclinic.org/health/diseases/11977-chronic-pain-living-with-chronic-pain>

Cleveland Clinic. (2015). Patient-controlled analgesia pump. Retrieved from

<https://my.clevelandclinic.org/health/drugs/12057-patient-controlled-analgesia-pump>

Cleveland Clinic. (2018). Skin-to-skin contact for you & baby. Retrieved from

<https://my.clevelandclinic.org/health/articles/15276-skin-to-skin-contact-for-you--baby>

Collins, M. R., Starr, S. A., Bishop, J. T., & Baysinger, C. L. (2012). Nitrous oxide for labor analgesia: Expanding analgesic options for women in the United States. *Reviews in Obstetrics and Gynecology*, 5(3/4), e126-e131. DOI: 10.3909/riog0190]

Collins, M. (2015). A case report on the anxiolytic properties of nitrous oxide during labor. *Journal of Obstetrics, Gynecology and Neonatal Nursing*. 44, 87-92. DOI: 10.1111/1552-6909.12522

Collins, S., Fiore, A. T., Boudreau, J. A., & Hewer, I. (2018). Nitrous oxide for the management of labor analgesia. *American Association for Nurse Anesthetists Journal*. 86(1), 72-80. Retrieved from https://www.aana.com/docs/default-source/aana-journal-web-documents-1/journal-course-6-nitrous-oxide-for-the-management-of-labor-anesthesia-february-2018.pdf?sfvrsn=442d42b1_4

Czech, I., Fuchs, P., Lorek, M., Tobolska-Lorek, D., Drosdzol-Cop, A., & Sikora, J. (2018).

NITROUS OXIDE AS PAIN RELIEF FOR WOMEN IN LABOR

Pharmacological and non-pharmacological methods of labour pain relief—establishment of effectiveness and comparison. *International Journal of Environmental research and Public Health*. 15(2792), 1-11. DOI: 10.3390/ijerph15122792

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. *Geburtsh Frauenheilk*. 74, 656–660
DOI: <http://dx.doi.org/10.1055/s-0034-1368606>

Ellis, H. (2015). Horace Wells: Pioneer of nitrous oxide anaesthesia. *British Journal of Hospital Medicine*. 76(1), 56. DOI: <https://doi.org/10.12968/hmed.2015.76.1.56>

Galeotti, Angela, Bernardin, G., Vincenzo, Fabrizio, G., Gentile, . . . Tiziana. (2016). Inhalation

Conscious sedation with nitrous oxide and oxygen as alternative to general anesthesia in preoperative, fearful, and disabled pediatric dental patients: A large survey on 688 working sessions. *BioMed Research International*. 2016, 1-6. DOI:
<http://dx.doi.org/10.1155/2016/7289310> Retrieved from

Hauser, T., DeButy, K., & Beal, C. C. (2018). Implementation of an evidence-based practice change to offer nitrous oxide during labor. *Nursing for Women's Health*. 23(1), 11-20. DOI:
<https://doi.org/10.1016/j.nwh.2018.12.001>

Honarmandpour A, Abbaspour Z, Ziaghani S, Javadifar N. (2016). Effects of entonox in comparison with lidocaine on pain severity during episiotomy incision in nulliparous women: A randomized control trial. *Journal of Midwifery and Reproductive Health*. 5(1), 791-799
DOI: <http://dx.doi.org/10.19082/3325>

Illuzzi, J. L., Telfer, M. L., Rubin, P., & Cnm. (2018). Nitrous oxide's revival in childbirth.

NITROUS OXIDE AS PAIN RELIEF FOR WOMEN IN LABOR

Retrieved from <https://www.contemporaryobgyn.net/pregnancy-and-birth/nitrous-oxides-revival-childbirth>

Klomp, T., Van Poppel, M., Jones, L., Lazet, J., Di Nisio, M., & Lagro-Janssen, A. (2012). Inhaled analgesia for relieving pain during labour. *The Cochrane Library*. 2012(9). Retrieved from https://www.cochrane.org/CD009351/PREG_inhaled-analgesia-for-relieving-pain-during-labour

Labor, S. & Maguire, S. (2008). The pain of labor. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4589939/pdf/10.1177_204946370800200205.pdf

Lennon, R. (2018). Pain management in labour and childbirth: Going back to basics. Retrieved from <https://www.magonlinelibrary.com/doi/full/10.12968/bjom.2018.26.10.637>

Londhey, Vikram A. (2015) Pathophysiology of pain. *Journal of the Association of Physicians of India*. 2015. Retrieved from http://www.japi.org/february_2015_special_issue_pain/01_pathophysiology_of_pain.pdf

Macintyre, & E., P. (2001). Safety and efficacy of patient-controlled analgesia. Retrieved from <https://academic.oup.com/bja/article/87/1/36/304220>

Mayo Clinic. (2020). Stages of labor and birth: Baby, its time! Retrieved from <https://www.mayoclinic.org/healthy-lifestyle/labor-and-delivery/in-depth/stages-of-labor/art-20046545>

Najefian, M., Cheraghi, M., Pourmehdi, Z., & A., Dadgari Nejad. (2013). The effect of nitrous oxide (ENTONOX) on labour pain relief during delivery stages. *International Journal of Pharmacy & Therapeutics*. 4(4), 242-246. Retrieved from

NITROUS OXIDE AS PAIN RELIEF FOR WOMEN IN LABOR

<https://www.researchgate.net/publication/256081871> The effect of nitrous oxide ENT ONOX on labour pain relief during delivery stages

Open Anesthetics. (2017). Inhaled anesthetics (pharmacology). Retrieved from

https://www.openanesthesia.org/inhaled_anesthetics_pharmacology/

Parsa, P., Saeedzadeh, N., Roshanaei, G., Shobeiri, F., & Hakemzadeh, F. (2017). The effect of Entonox on labour pain relief among nulliparous women: A randomized controlled trial. 11(3), QC08-QC118. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/28511452>

Pasha, H., Basirat, Z., Hajahmadi, M., Bakhtiari, A., Faramarzi, M., & Salmalian, H. (2012). Maternal expectations and experiences of labor analgesia with nitrous oxide. 14(12),792-797. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3587869/>

Pinyan, T., Curlee, K., Keever, M., & Baldwin, K. (2017). A nurse-directed model for nitrous oxide use during labor. 42(3), 160-166. Retrieved from https://www.nursingcenter.com/journalarticle?Article_ID=4115312

Pita, C. P., Pazmiño, S., Vallejo, M., Salazar-Pousada, D., Hidalgo, L., Pérez-López, F. R., . . . Enrique C. Sotomayor Hospital. (2012). Inhaled intrapartum analgesia using a 50–50 % mixture of nitrous oxide–oxygen in a low-income hospital setting. Retrieved from <https://link.springer.com/article/10.1007/s00404-012-2359-6>

Richardson, M. G., Lopez, B. M., Baysinger, C. L., Shotwell, M. S., & Chestnut, D. H. (2017). Nitrous oxide during labor: Maternal satisfaction does not depend exclusively on analgesic effectiveness. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/28002168>

Rooks, J. P. (2007). Nitrous oxide for pain in labor--Why not in the United States? *Wiley Online Library*. 34(1). Retrieved from <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1523-536X.2006.00150.x>

NITROUS OXIDE AS PAIN RELIEF FOR WOMEN IN LABOR

Rooks, J. P. (2010). Use of nitrous oxide in midwifery practice—Complementary, synergistic, and needed in the United States. *Journal of Midwifery & Women's Health*. 52(3), 186.

Retrieved from <https://onlinelibrary.wiley.com/doi/abs/10.1016/j.jmwh.2007.02.017>

Rooks, J.P. (2011). Safety and risks of nitrous oxide labor analgesia: A review. 56(6), 557-565.

Retrieved from

[http://www.porterinstrument.com/~porterin/dentalcontent/app/webroot/files/datasheets/Safety-and-Risks-of-Nitrous-Oxide-Labor-Analgesia-JMWH-\[2011\].pdf](http://www.porterinstrument.com/~porterin/dentalcontent/app/webroot/files/datasheets/Safety-and-Risks-of-Nitrous-Oxide-Labor-Analgesia-JMWH-[2011].pdf)

Sander, R., & Lamb, K. (2014). An exploration of the benefits and drawbacks of intrapartum pain management strategies. *British Journal of Midwifery*. 22(9), 642-649. DOI:

10.12968/2014/22.9.642

Satuito, M., & Tom, J. (2015). Potent inhalational anesthetics for dentistry. 63, 42-49. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4751520/>

Sheyklo, S. G., Hajebrahimi, S., Moosavi, A., FatPournaghi-Azar, F., AzamiAghdash, S., &

Ghojazadeh, M. (2017). Effect of Entonox for pain management in labor: A systematic review and meta-analysis of randomized controlled trials. 9(2), 6002-6009 Retrieved from

https://www.researchgate.net/publication/322201847_Effect_of_Entonox_for_pain_management_in_labor_A_systematic_review_and_meta-analysis_of_randomized_controlled_trials

Shuman, I. (2016). Nitrous oxide: Use and safety.

Stewart, L. S., & Collins, M. (2012). Nitrous oxide as labor analgesia: Clinical implications for nurses. 2012, 400-409. Retrieved from [https://nwhjournal.org/article/S1751-](https://nwhjournal.org/article/S1751-4851(15)30697-8/fulltext)

[4851\(15\)30697-8/fulltext](https://nwhjournal.org/article/S1751-4851(15)30697-8/fulltext)

NITROUS OXIDE AS PAIN RELIEF FOR WOMEN IN LABOR

Women's health care physicians: Medications for pain relief during labor and delivery. (2017).

Retrieved from <https://www.acog.org/Patients/FAQs/Medications-for-Pain-Relief-During-Labor-and-Delivery>