

Safety and Risks of Nitrous Oxide Labor Analgesia: A Review

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Introduction: 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. Concerns about apoptotic damage to the brains of immature mammals exposed to high doses of N₂O during late gestation, possible cardiovascular risks from hyperhomocysteinemia caused by N₂O, a hypothesis that children exposed to N₂O during birth are more likely to become addicted to amphetamine drugs as adults, and possible occupational risks for those who provide care to women using N₂O/O₂ labor analgesia are discussed in detail.

Methods: Research relevant to the 4 special concerns and to the effects of N₂O analgesia on labor and the mother-child dyad were examined in depth. Three recent reviews of the biologic, toxicologic, anesthetic, analgesic, and anxiolytic effects of N₂O; 3 reviews of the safety of 50% N₂O/oxygen (O₂) in providing analgesia in a variety of health care settings; and a 2002 systematic review of N₂O/O₂ labor analgesia were used.

Results: 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.

Discussion: 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. J Midwifery Womens Health 2011;56:557-565 © 2011 by the American College of Nurse-Midwives.

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INTRODUCTION

Nitrous oxide (N₂O) is a weak anesthetic at high doses and an analgesic and anxiolytic at low doses.^{1,2} Everything about the effectiveness, safety, and risks of N₂O is related to dose, which is a product of the concentration and duration of its use or other exposure. This article presents current information about the safety and risks of the use of N₂O for both anesthesia and the low-dose nitrous oxide/oxygen combination (50% N₂O/O₂) that is used for analgesia, with emphasis on concerns that are especially relevant to effects on labor, birth, breastfeeding, the well-being of the mother and neonate, and possible occupational risks for individuals who care for women during labor. First, the safety and risks of high-dose use of N₂O when used for anesthesia and, second, the safety and risks of N₂O/O₂ when used for analgesia are reviewed. The third, smaller section reviews occupational safety and risks. Although the second section is most pertinent to labor analgesia, decisions to allow N₂O/O₂ labor analgesia in specific hospitals require agreement by anesthesiologists, who tend to be most aware of concerns about adverse effects of N₂O used for anesthesia. Since N₂O/O₂ labor analgesia is currently used in only a few US hospitals,³ many anesthesiologists practicing in the United States have not had experience with it.

Nitrous oxide was used for labor analgesia in the United States more widely in the past but never as extensively as in many other countries.³ Knowledge about N₂O/O₂ labor analgesia and interest in using it in the United States has recently

increased; additional hospitals have begun to offer it, and others plan to when new equipment becomes available.⁴ At the same time, there is growing concern about current use of high doses of N₂O to augment anesthesia during surgery.⁵⁻⁸

BACKGROUND

Nitrous oxide belongs to a large category of drugs that decrease the excitability of brain cells.¹ Anesthetic doses can depress the central nervous system to the point of unconsciousness, but as the weakest inhaled anesthetic, N₂O is always paired with a stronger agent when used for anesthesia.¹ Its analgesic effectiveness is thought to result from increasing the release of endogenous endorphins, dopamine, and other natural opioids in the brain and neuromodulators in the spinal cord.^{1,2,9,10} It also increases the release of prolactin and decreases the release of cortisol, reducing the hormonal response to stress.¹¹ Effects on consciousness may include detachment, dizziness, euphoria, fatigue, hallucinations, hazy memory of events, headache, nightmares, pleasure, relaxation, sedation, and a sense of warmth.^{1,9,12-15} The percentage of women who report hazy memory of labor varies, but women report hazy memories of giving birth less frequently than they do haziness about labor.^{9,12} Unique characteristics of N₂O/O₂ labor analgesia are responsible for many of its safety advantages. Nitrous oxide enters and is eliminated from the body through the lungs. Less than 1% is metabolized, it is not stored in the body, and greater than 99% is exhaled unchanged.^{1,9,16,17} Laboring women control the dose of N₂O/O₂ by how they inhale it and how long they use it, especially whether they use it continuously (during and between contractions) or

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intermittently (for a minute preceding and during contractions but not between them).^{9,16}

Although N₂O is not a potent analgesic at doses provided during labor, it helps women relax, gives them a sense of control, and reduces their perception of pain, even though they may still be aware that pain is present.^{3,9,12,16} The effects vary from woman to woman. Some women do not like how it makes them feel; some want a stronger analgesic. However, N₂O/O₂ is effective enough for many women and can fill currently unmet needs for labor analgesia.^{3,9,14,16,18,19}

Safe practice for N₂O/O₂ labor analgesia requires that: 1) the N₂O is administered with oxygen (O₂) and the N₂O concentration does not exceed 50%; 2) it is self-administered, and the laboring woman holds the mask or mouthpiece without any assistance; and 3) the N₂O/O₂ delivery equipment uses a demand valve to stop the supply when the woman is not inhaling and uses scavenging equipment to capture the exhaled N₂O.^{9,12,16} These measures help ensure that a woman using N₂O/O₂ analgesia cannot overdose or become hypoxic, and they protect health care workers from contaminated air.^{1,9}

LITERATURE REVIEW

This review is based on the following: 1) 2 international reviews of the biologic and toxicologic effects of N₂O that integrated findings from laboratory, clinical, and epidemiologic studies and that emphasized the use of N₂O for anesthesia and the effects of high doses^{1,20}; 2) a review of the biologic mechanisms involved in the anesthetic, analgesic, and anxiolytic actions of N₂O₂; 3) 3 reviews of the safety of 50% N₂O/O₂ for conscious analgesia administered by professionals primarily in health care settings other than labor^{13,15,21}; 4) Rosen's 2002 review of 50% N₂O labor analgesia⁹; 5) an authoritative text on risks related to maternal use of drugs during pregnancy and lactation¹⁷; and 6) documents produced by the US National Institute for Occupational Safety and Health and the Occupational Safety and Health Agency. Separate literature searches were conducted for evidence on effects of N₂O/O₂ analgesia on the physiology of normal labor, birth, breastfeeding, and mother-child bonding; effects on the mother, fetus, and neonate; and occupational risks for people who attend women using N₂O/O₂ labor analgesia. More weight was given to clinical than to laboratory studies, to randomized controlled trials (RCTs) than to observational clinical studies, and to studies of N₂O/O₂ labor analgesia provided according to current standards.

EFFECTS OF NITROUS OXIDE WHEN DELIVERED IN ANESTHETIC DOSES

Effects of Nitrous Oxide on Cobalamin (Vitamin B₁₂), Methionine Synthase, and Homocysteine

Nitrous oxide oxidizes a physiologically active form of cobalamin (vitamin B₁₂), thereby inactivating it. Cobalamin is used by the enzyme methionine synthase to convert homocysteine into methionine, which uses folate to synthesize myelin and the nucleic acids DNA and RNA.¹ When cobalamin is not available, methionine synthase cannot convert homocysteine, and plasma levels of homocysteine rise.²²

Except for the effects of N₂O on consciousness, nausea and vomiting, and neuro-apoptosis, all known adverse effects

of N₂O are due to inactivation of cobalamin. Extremely high doses of N₂O and/or long-term exposure (dose = concentration × duration of exposure) can reduce cobalamin function enough to cause adverse effects such as bone-marrow depression, macrocytic (megaloblastic) anemia, and neuropsychiatric disorders.¹ The effects reverse with time except when the dose is so high that it causes cell death, which has occurred in rats kept under barometric pressures that cause them to inhale concentrations of N₂O for greater than 6 hours.¹

Any condition that reduces cobalamin function, such as Crohn disease, celiac disease, gluten intolerance, pernicious anemia, long-term recreational abuse of N₂O, chronic malnutrition, or adherence to a strict vegan diet, increases risks of complications from exposure to N₂O.¹ Surgical patients who receive N₂O anesthesia for greater than 6 hours are at increased risk.¹ Royston et al²³ measured methionine synthase blood levels of 22 patients undergoing surgery with 70% N₂O anesthesia. The mean time to a 50% reduction was 46 minutes (range 30-99 min).

Hyperhomocysteinemia and Cardiovascular Disease Risk

Chronic hyperhomocysteinemia is an independent risk factor for premature peripheral, cerebral, and coronary vascular disease.²⁴ Use of N₂O anesthesia during surgery increases the incidence of postoperative hyperhomocysteinemia²⁵ and of subclinical myocardial ischemia (detected by cardiac monitoring) for as long as 2 days after carotid endarterectomy surgery.²⁶ Preoperative treatment with vitamin B complex can prevent increased plasma homocysteine levels after surgery with N₂O-based anesthesia.²⁷

Concern about the effect of N₂O on homocysteine motivated anesthesiologists from several countries to form the Evaluation of Nitrous oxide In a Gas Mixture for Anaesthesia (ENIGMA) Trials Group to study the effect of N₂O on the risk of cardiovascular disease during and after surgery.⁸ The ENIGMA study was a large (N = 3187), international RCT designed to compare short-term effects of providing anesthesia with and without N₂O for long surgeries.⁵ The primary purpose was to determine whether participants who underwent N₂O anesthesia had longer hospitalizations than those who had intravenous anesthesia and breathed 80% O₂ during surgery. Patients in the N₂O-free group had significantly lower rates of wound infection, better wound healing, and less severe nausea and vomiting, but there was no difference in the median duration of hospital stay.⁵ An accompanying editorial cited 2 large, well-designed RCTs that reported 40% to 50% reductions in surgical-site infections among patients who inhaled 80% O₂ during surgery and suggested that the between-group differences in wound healing and infection could have resulted from higher levels of O₂ in the blood and tissues of the N₂O-free participants.⁶ The editorialist warned that it would not be easy to replace the special roles of N₂O in easing children into anesthesia, providing analgesia during dental procedures, and helping women cope with pain during labor.⁶

Although the ENIGMA trial was not designed to detect effects on myocardial infarctions or perioperative deaths, both were more frequent in the group that breathed 70% N₂O during surgery.⁸ Neither difference was statistically significant,

but the higher rates (1.3% vs 0.7% for myocardial infarctions and 9 vs 3 postoperative deaths, $P = .10$)—made sense, given the association between hyperhomocysteinemia and cardiovascular disease in nonsurgical patients.⁸ Participants randomized to N₂O-based anesthesia in the ENIGMA trial were not treated with preoperative vitamin B.

A follow-up study evaluated long-term effects of N₂O anesthesia on the ENIGMA study participants (N = 2050) whose surgeries had not been related to cardiac disease.⁷ The median follow-up time was 3.5 years; the primary endpoint was survival. Although there were no between-group differences in the rates of stroke or death, 5.3% of the participants anesthetized with N₂O had myocardial infarctions, compared to 3.7% in the N₂O-free control group (odds ratio [OR] 1.59; 95% confidence interval [CI], 1.01-2.51; $P = .04$).⁸ The authors concluded that the “exact relationship between N₂O administration and serious long-term adverse outcomes will require confirmation by an appropriately designed large randomized controlled trial.”⁷

Despite associations between anesthetic doses of N₂O and hyperhomocysteinemia and between hyperhomocysteinemia and cardiovascular disease, there is no clear evidence that N₂O increases the risk of dying during or after surgery.^{7,8} The relationship between homocysteine and serious cardiovascular events and deaths is not linear or well-elucidated. A 2002 meta-analysis of 30 observational studies concluded that “elevated homocysteine is at most a modest independent predictor of ischemic heart disease and stroke risk in healthy populations.”²⁸ An RCT published in 2004 found that high doses of B vitamins given to stroke survivors for 2 years after a stroke lowered homocysteine levels, but the moderate reduction had no effects on vascular outcomes during 2 years of vitamin treatment.²⁹ Although a 2007 meta-analysis concluded that lowering homocysteine levels with folic acid may reduce the risk of stroke,³⁰ the 2 largest RCTs in the meta-analysis had essentially negative findings.^{29,31} ENIGMA-II will be a large, international RCT to determine whether avoiding N₂O anesthesia reduces deaths and major cardiovascular events for patients who are having noncardiac surgeries but are at risk of coronary artery disease.³²

Neuro-Apoptosis

Damage similar to that seen in fetal alcohol syndrome occurs in the brains of rat pups exposed to many drugs that inhibit transmission of excitatory stimuli during synaptogenesis, when the immature mammalian brain grows and develops very quickly.³³ Synaptogenesis comprises the last 3 to 4 months of gestation and the first 3 years after birth in humans but only the first 2 weeks after birth in rats. Exposing rodent pups to high doses of virtually any systemic anesthetic can cause apoptotic damage.^{33,34} The mechanism of neuronal damage is thought to be mistimed neuro-apoptosis, a type of natural cell death that is necessary for normal brain development. Nitrous oxide by itself does not cause apoptosis in neonatal rat brains at concentrations less than or equal to 75%.¹ The US Food and Drug Administration has called for primate studies and use of medical record data to better understand the cognitive and neurobehavioral effects of exposing pregnant women and young children to prolonged anesthesia.³⁴

Neurotoxic Effects

Neurotoxic effects other than neuro-apoptosis are thought to be caused by damage to the myelin sheath that protects neural axons.^{1,35} Both vitamin B₁₂ deficiency and long-term N₂O abuse can result in neurotoxic symptoms such as paresthesias, peripheral neuropathy, neuropsychiatric problems, irritability, mild memory impairment, dementia, depression, and psychosis.^{1,35} These recognized manifestations of vitamin B₁₂ deficiency are effectively treated with high doses of B vitamins.³⁶ Individuals with normal vitamin B₁₂ levels have stores that protect them unless the exposure is extremely great or repeated frequently, as in N₂O drug abuse. Even in cases of extreme vitamin B₁₂ deficiency pathology, most people recover with time and vitamin treatment.¹

EFFECTS OF NITROUS OXIDE/OXYGEN USED IN ANALGESIC DOSES

Nitrous Oxide/Oxygen Used in Many Health Care Settings

Collado et al¹³ searched the Cochrane Database of Systematic Reviews to identify 140 studies of adverse events associated with almost 48,000 administrations of 50% N₂O/O₂. Although few studies adhered to European standards for good clinical research, a 4-year prospective survey of 35,828 administrations of 50% N₂O/O₂ in 191 French pediatric and adult hospital units conducted under the conditions required for drug testing reported 27 “serious adverse events” experienced by 23 patients.³⁷ Nine adverse events—2 incidents of vomiting and 1 case each of consciousness disorder, bradycardia, vertigo, headache, nightmares, sweating, and somnolence—had a reasonable causal relationship with the N₂O, a rate of 3 serious adverse events per 10,000 administrations of 50% N₂O/O₂.³⁷ In a review of 12 RCTs, Faddy and Garlick²¹ found that adverse effects were rare and concluded that N₂O could be used safely by lay first responders such as mountain and mine rescue teams.

Effects of Nitrous Oxide/Oxygen on Labor Progress

Nitrous oxide affects several major hormones that are important during labor and birth including endorphins, prolactin, cortisol, and epinephrine/norepinephrine,¹ but it does not reduce the release or effectiveness of endogenous oxytocin and has no effects on uterine contractions or labor progress.^{9,16} Dr. J. Whitridge Williams, renown titan of early 20th Century American obstetrics, praised N₂O because it does not diminish the force of contractions or have any negative impact on labor progress.³⁸

In a study of 1300 Chinese women randomized to inhale either 50% N₂O or 50% O₂ during labor, the women who inhaled N₂O had shorter active phases of labor (153 min vs 187 min; $P < .05$) and fewer cesarean births (11.6% vs 19.3%; $P < .05$).¹⁴ In 2010, French physician Michel Odent suggested that inhibition of excitatory stimulation in the neocortex may support labor by inhibiting neocortical intervention in the involuntary physiological processes of birth.³⁹

Effects of Nitrous Oxide/Oxygen on the Mother

The greatest maternal risk of any inhaled anesthetic or analgesic is aspiration of stomach contents caused by loss of the

Table 1. Clinical Application: Use of 50% Nitrous Oxide/Oxygen for Labor Analgesia

Step	Description
Precautions	<ol style="list-style-type: none"> 1. Determine that there are no contraindications such as inability to hold face mask or mouth tube, impaired oxygenation, or hemodynamic instability. 2. Use with caution if other sedating drugs are administered during use of N₂O/O₂.
Preparation	<ol style="list-style-type: none"> 1. Inform the woman of potential side effects of nausea, vomiting, and/or dizziness. 2. Instruct on how to hold the mask or tube so it creates a seal; instruct on timing of inhalation. 3. Review with the woman and any labor support persons that only the woman can hold the mask. <ol style="list-style-type: none"> a. Sedation from N₂ is possible only if the woman continues to inhale the gas after she can no longer hold the mask tightly to her face or the tube tightly in her mouth. N₂O dissipates rapidly with exhalation, and the effects resolve very quickly. b. Self-administration gives the woman personal control of management of pain, and this control may potentiate the analgesic effect.
Procedure	<ol style="list-style-type: none"> 1. The woman holds the mask or tube in a manner that creates a seal. 2. She tries to start inhaling the gas 30 seconds before a contraction starts because the onset of action takes about 30 seconds; full analgesic effects occur in 50 seconds. It often takes 3 to 4 contractions to learn the best technique. 3. The woman should exhale into the mask to facilitate scavenging.
Intermittent vs continuous inhalation	<ol style="list-style-type: none"> 1. Intermittent inhalation 30 seconds prior to the onset of a contraction maximizes the peak effect of N₂O/O₂ so the peak analgesic effect occurs during the peak of the uterine contraction. 2. Continuous inhalation is easier to initiate but exposes the woman to N₂O between contractions, when the central nervous system effects of dizziness or dysphoria could be bothersome. These effects are not as noticeable during the pain of contractions.

Adapted with permission from Bishop JP, King TL. University of California San Francisco Nitrous Oxide for Labor Analgesia Protocol.

protective laryngeal reflexes during unconsciousness.⁹ Maternal loss of consciousness was reported during an early period when N₂O concentrations from 75% to 100% were sometimes used during labor.^{9,40} Rare instances of unconsciousness can occur with 50% N₂O/O₂ if someone other than the laboring woman holds the mask on the woman's face.¹² The procedure for using 50% N₂O/O₂ is described in Table 1. When a woman inhaling 50% N₂O/O₂ begins to become sedated, she is unable to hold the mask or mouth tube and breathe the gas mixture appropriately. Because N₂O is released from the blood through the lungs very rapidly, she recovers in a matter of minutes.

Nausea and Vomiting and Inner-Ear Pressure

The most common side effects of N₂O/O₂ labor analgesia are nausea and vomiting, which ranged from 5% to 36% in the studies in Rosen's review,⁹ and changes in consciousness such as dizziness or sedation.^{1,9,14} Vomiting is common during labor per se,⁹ but more common among women using N₂O/O₂ during labor than among patients using it for other reasons.¹³ It is also more common after use of N₂O-based anesthesia for surgery than after surgery without N₂O⁴¹ and among women who inhale N₂O/O₂ analgesia continuously instead of intermittently (44% vs 25%).⁴²

Nitrous oxide may cause emesis in part by pressure changes in the middle ear caused by diffusion of N₂O.¹⁵ In-

creased inner-ear pressure can result if there is an obstruction or compromise in the Eustachian tube.¹⁵ Upper respiratory infection, allergic rhinitis, and severe sinusitis are common enough that some women will have them when they arrive at a hospital in labor. Those conditions should be taken into consideration for women who want to use N₂O/O₂ analgesia. Recent ear surgery probably should be a contraindication.¹⁵

Hyperventilation Apnea, Diffusion Hypoxia, and Oxygen Desaturation

Because the fetus is dependent on maternal oxygenation, any reduction in the amount of O₂ in a laboring woman's blood is concerning. The degree of oxygen saturation (SaO₂) in the hemoglobin of arterial blood is expressed as the percentage of complete saturation (100%) as determined by pulse oximetry, which measures the percentage of all hemoglobin that is saturated (SpO₂). An SpO₂ of 98% is normal for pregnant women.⁴³ An SpO₂ less than 94% during 2 or more subsequent recordings has been defined as O₂ desaturation.⁴⁴ All pharmacologic methods of labor analgesia can cause O₂ desaturation. Opioids depress respiratory function, whether administered systemically or neuraxially (epidurals or spinals).⁴⁵ There have been 2 concerns about SpO₂ between contractions during N₂O/O₂ labor analgesia. First, many women hyperventilate during contractions, perhaps even more to maximize the effectiveness of N₂O/O₂. Hyperventilating 50%

O₂ (vs 21% in air) can reduce the carbon dioxide in a woman's blood below the level needed to stimulate breathing for some seconds after contractions.^{9,46} The second possible problem is a theoretical concern that N₂O/O₂ labor analgesia can cause "diffusion hypoxia" between contractions,^{9,46} as it sometimes does when N₂O anesthesia is stopped. Diffusion hypoxia is caused by the speed at which N₂O diffuses from blood into the lung alveoli of a person who stops inhaling it. If a laboring woman's lungs are filled with N₂O at the end of a contraction, a temporary lack of space for O₂-containing air to enter the alveoli could cause O₂ desaturation. Diffusion hypoxia does not occur during N₂O/O₂ labor analgesia.^{9,46}

Understanding the effects of specific analgesics on SpO₂ levels of laboring women is complicated because 1) some O₂ desaturation occurs during normal (unmedicated) labor, 2) effective labor analgesia tends to reduce desaturation by reducing hyperventilation and other O₂-sensitive responses to pain, and 3) most episodes of O₂ desaturation during labor have no effect on the Apgar score or other indices of the well-being of the neonate. Studies of the effect of N₂O/O₂ on SpO₂ are further complicated because most of them were conducted during the last century in countries where many women used opioids and N₂O/O₂ together. In a 1989 report of 33 healthy women using both meperidine (pethidine) and N₂O/O₂ during labor in the United Kingdom, almost half of the women (16/33) had at least 1 episode of O₂ desaturation exceeding 10 seconds, with SpO₂ less than 90% (mean 83.7%, range 60%-89%); 2 women had multiple episodes of hypoxia, with SpO₂ of less than 70%.⁴⁷

Rosen analyzed and summarized the best studies available on O₂ desaturation in women using N₂O/O₂ labor analgesia as of October 2000 and concluded that episodes of O₂ desaturation of closely monitored women using only N₂O/O₂ are infrequent, transient, not extreme, more common when 75% N₂O/O₂ is used, and are not reflected in poor Apgar scores.⁹ Few new studies have been published since Rosen's 2002 review. In 2005, Volmanen et al⁴⁸ did a randomized, double-blind, cross-over comparison of patient-controlled intravenous remifentanyl and N₂O/O₂ during the first stage of labor that was an exception. Twenty laboring women were followed, half in each group. The women who used remifentanyl judged it to be 3 times as effective as N₂O/O₂, but it caused more sedation. There were no differences in the incidence of SpO₂ less than 95% (1 in the N₂O/O₂ group and 2 in the remifentanyl group had an SpO₂ of <95% for more than 20 seconds but less than 1 minute).⁴⁸

Doses of N₂O as used in current labor analgesia have minimal toxicity and cause minimal depression of the cardiovascular system.^{9,17} However, some women use several analgesic methods during labor, and 22% of women who gave birth in US hospitals in 2005 received opioids at some time during labor.⁴⁹ A woman with opioids in her system when she starts to use N₂O/O₂ is at increased risk of O₂ desaturation; signs include rapid breathing, cyanosis, poor coordination, lethargy/lassitude, and executing poor judgment. Except for cyanosis, symptoms are relatively subjective and nonspecific, especially for a woman who is 1) in labor and 2) using N₂O. Cyanosis is a very late sign. These women should have increased attention and surveillance, with pulse oximetry if

possible (J. Bishop, CNM, MPH, University of California at San Francisco; M. Collins, CNM, RNC, Vanderbilt University School of Nursing; and Sarah Starr, MD, Vanderbilt School of Medicine; personal communication, July 2011). Oxygen desaturation should not be a concern for a woman using N₂O/O₂ without opioids in her blood.⁹

Effects of Nitrous Oxide/Oxygen on the Fetus, Newborn, and Breastfeeding

Nitrous oxide crosses the placenta; the concentration in the fetal circulation becomes about 80% of that in the mother's blood within 15 minutes.^{9,50} It has no effect on the fetal heart rate.⁵⁰ The large, Chinese, RCT (N = 1300) that compared intermittent inhalation of 50% N₂O/O₂ to 50% O₂ found no significant between-group differences in the incidence of meconium-stained amniotic fluid, Apgar scores, or blood-gas analyses of fetal umbilical-cord blood.¹⁴

Nitrous oxide is eliminated quickly and entirely by the neonate's lungs with the onset of breathing and does not depress its respirations.^{9,50} Studies have consistently found no negative effects on Apgar or neonatal-neurobehavioral scores of neonates exposed to N₂O while being born,^{9,50} whether the mother had used it for only 5 minutes or 5 hours.⁵⁰ The half-life of N₂O in the neonate after birth is less than 3 minutes.¹⁷ It has no adverse effect on the suckling behavior of neonates exposed to it while being born.⁵⁰ Some older nurses have told of routinely giving whiffs of O₂ to stimulate neonates whose mothers inhaled N₂O/O₂ while giving birth at a time when high concentrations were used and doctors or nurses held the masks against the mothers' faces. Although some newborns seemed depressed, those whose mothers had not also received opioids revived quickly with just a whiff of O₂. Many women who gave birth in hospitals in the United States during that period received several doses of opioids as well as N₂O.

Offspring of mice that breathed 5%, 15%, or 35% N₂O for 4 hours each day during the middle half of a normal 21-day gestation had diminished startle responses.⁵¹ The significance of that finding is not understood.⁵¹

Theory that Intrapartum Exposure to Nitrous Oxide While Being Born Increases the Risk that the Child Will Become Addicted to Amphetamines in Later Life

In 1987, investigators from the Karolinska Institute published the first of at least 8 research-based papers supporting a hypothesis that obstetric procedures, especially analgesic drugs administered during the 10 hours before birth, may be associated with increased risk of drug addiction and other self-destructive behavior when the child is older.⁵² Six papers were published in English. It began as an effort to explain higher rates of deaths from suicide and drug addiction in certain parts of Stockholm. Area of residence (associated with social factors during adolescence known to be associated with drug addiction) was a less powerful predictor of later drug addiction than the hospital in which the person was born, especially for amphetamine addicts.^{40,52,53} Certain hospitals in Stockholm were known for having given women even 100% N₂O during contractions for long periods during labor from about 1945 to 1966.^{40,54}

In 1988, the Karolinska group published a study that found a dose-dependent association between amphetamine addiction and intrapartum exposure to N₂O using data from the birth records of 200 amphetamine addicts born in Stockholm during that period.⁴⁰ Data from the records of 73 addicts were matched with those of 109 of their not drug-addicted siblings born during the same period. A logistical regression analysis was conducted in which the mothers' use of N₂O during labor competed with 12 other perinatal variables as possible confounders to explain why some of their children became amphetamine addicts and others did not. The relative risk of amphetamine addiction increased with duration of the mothers' intermittent use of 100% N₂O during labor, reaching 5.6 (95% CI, 1.6-16.9; *P* = .005) for children whose mothers had inhaled a high-concentration of N₂O for 4.5 or more hours compared to 25 minutes or less. The authors explained their findings as a possible effect of neurological "imprinting."⁴⁰ A similar study by the Karolinska group later found a similar relationship between intrapartum exposure to opioids and opiate addiction.⁵⁴

OCCUPATIONAL EXPOSURE RISKS

Dose is the critical determinant of risk from occupational exposure to N₂O, even though very high occupational exposures (eg, 1000 parts per million) are very low percentages (eg, one-tenth of 1%) of the ambient air. Concern about potential health risks from occupational exposure to inhaled anesthetics resulted in the development of national and provincial occupational exposure limits (OELs) for specific anesthetics. The United States, The Netherlands, and Ontario, Canada, all call for limiting N₂O exposure to an 8-hour time-weighted average concentration of 25 parts per million. Quebec's OEL is 50 parts per million, while N₂O OELs in the United Kingdom, Italy, Sweden, Norway, Denmark, and Alberta, Canada, allow 100 parts per million.¹ The US OEL was suggested by the National Institute for Occupational Safety and Health in the 1970s and is based on the precautionary principle instead of actual data.

Facilities in which N₂O/O₂ labor analgesia occurs and the equipment used to provide it are important determinants of the safety and risk of occupational exposure. Most US hospitals have good ventilation, and scavenging capability is built into all equipment used for N₂O/O₂ labor analgesia in the United States. *Scavenging* means that the equipment that provides N₂O/O₂ to the woman also provides constant negative pressure to capture her exhalations and suck them out of the room and ultimately out of the hospital. It requires the woman to exhale back into the mouth-tube or facemask for several breaths each time she stops inhaling N₂O/O₂. Scavenging is not done regularly or well in some countries.⁵⁵⁻⁵⁷ The work pattern of a midwife or nurse is also important, especially how frequently and long they are in close contact with women using N₂O/O₂.

The underlying cause of occupational health risk is inactivation of methionine synthase.¹ With very low exposures (true of occupational exposure in general), the only substantive concern is a possible effect on human reproduction. A study of 418 fertile, married dental assistants working in California during the 1980s found reduced fecundability (more menstrual cycles without contraception required to be-

come pregnant) among those working where N₂O was used without scavenging.⁵⁸ Each hour of exposure to unscavenged N₂O per week corresponded to a 6% reduction in the probability of conception in a menstrual cycle (*P* < .01). The air where they worked was estimated to contain greater than 1000 parts per million of N₂O. There was no relationship between fecundability and the number of hours worked by dental assistants providing N₂O/O₂ analgesia with scavenging.⁵⁸ N₂O-induced fertility problems occur in rats at 1000 parts per million but not at 500 parts per million or less.¹ Five-hundred parts per million is 20 times the US OEL of 25 parts per million.

A larger study (N = 3347) analyzed associations between several reproductive problems and exposure to N₂O and other occupational risks among Swedish midwives in the 1980s, resulting in 3 separate publications.⁵⁹⁻⁶¹ Approximately half of the midwives had some occupational exposure to N₂O during their most recent pregnancy, although most Swedish women use it for relatively short periods during labor. Scavenging and forced ventilation were not used in many Swedish hospitals during the 1980s. The probability of becoming pregnant during any menstrual cycle as compared to other midwives (the fecundability ratio) was reduced by 2-shift or 3-shift rotations to 0.78 (95% CI, 0.65-0.94).⁵⁹ There were no noticeable differences in the frequency of intercourse related to different work schedules, although midwives working full-time were less likely to become pregnant than those working part-time. There was no relationship between fecundability and N₂O/O₂ exposure except among 41 midwives who attended greater than 30 births per month in which N₂O was being used; their fecundability ratio was 0.64 (95% CI, 0.44-0.95). No effect was seen among midwives with less exposure to N₂O/O₂.⁵⁹

Frequent or permanent staff shortages were related to an increased risk of spontaneous abortions before 13 weeks of pregnancy. Spontaneous abortions after 12 weeks were associated with working nights (OR 3.33; 95% CI, 1.13-9.87) or rotating between 3 different shifts (OR 1.63; 95% CI, 0.95-2.81).⁶⁰ Use of N₂O/O₂ during greater than 50% of births attended was not associated with increased risk of spontaneous abortion (OR 0.95; 95% CI, 0.62-1.47).⁶⁰ Working nights was associated with an almost 7-fold increase in preterm (<37 wk) births (OR 5.6; 95% CI, 1.9-16.4).⁶¹ Exposure to N₂O was associated with a 77-g reduction in average birth weight (95% CI, -24 to -129 g) and an increase in the odds of neonates being small for gestational age (OR 1.8; 95% CI, 1.1-2.8).⁶¹

With occupational risk, the simple concept of dose equals concentration multiplied by duration of exposure is affected by restitution—the ability of the body to recover from subclinical effects on cells, which depends on the length of time between repetitive exposures.⁶² The following hypothetical example explains this process: A caregiver works in a poorly ventilated hospital where N₂O/O₂ is used without scavenging. Subclinical cellular changes begin while she is exposed to N₂O-contaminated air. When she leaves the hospital, the damage stops, and her body begins to repair the damaged cells. If she returns to an N₂O-polluted environment before restitution is complete, the pathological process resumes and may progress. If that happens repetitively, the damage can accumulate until it affects her fertility. If she remains unexposed for a sufficient period, her body will repair the damage.¹

It would be difficult to provide scavenging for N₂O/O₂ analgesia during a home birth because of the lack of a source of negative pressure (suction) to pull the woman's exhalations out of the room. However, it might not be necessary, depending on how often and long a specific birth attendant provides care to a woman using N₂O/O₂. Nitrous oxide can be helpful during a home birth, but women laboring at home tend to use it sparingly. A fan blowing at a right angle to the birthing woman and a window open by 2 inches create enough cross-current and fresh air circulation to keep exhaled gases out of the birth attendant's breathing zone.⁶³ A birth center could establish scavenging by attaching a plastic hose to the scavenging outlet of the machine that provides the gases and threading it through a small hole in an external wall to a protected outside area with an exhaust fan. The external atmosphere is also the ultimate destination for contaminated gases drawn out of labor rooms by central vacuum systems in hospitals. Nitrous oxide is nontoxic and can be released safely into the outside air. Most N₂O in the earth's atmosphere comes from natural processes, including denitrification of plant debris by bacteria in soils.⁶⁴ Humans evolved and live with some N₂O in the air.

Occupational exposure to N₂O has been significantly reduced over the last 25 years due to scavenging and ventilation.¹ Professionals who work with women using N₂O/O₂ can measure the extent of their exposure by wearing N₂O-sensitive badges (dosimeters). If the dosimeters indicate that they are getting more exposure than allowed, the work environment must be changed.

DISCUSSION AND RECOMMENDATIONS

Recommendations for New Research

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. Concerns about hyperhomocysteinemia associated with use of high concentrations of N₂O during anesthesia for surgery caused some anesthesiologists to oppose introducing N₂O/O₂ labor analgesia at some hospitals in the United States. The effects of N₂O on homocysteine levels in plasma result from doses that are much higher than those used during labor and are largely temporary when they occur. Offering N₂O/O₂ labor analgesia does not require a large investment in new equipment and training. Perhaps university hospitals that offer it should conduct prospective studies to measure women's blood-plasma homocysteine levels before beginning use of N₂O/O₂ during labor and before hospital discharge and to measure the level of N₂O in their neonates' umbilical cord blood at birth.

Research is being conducted to increase our understanding of apoptotic damage to the brain of a fetus or young child caused by general anesthesia.³⁴ Because the relationship between dose and harm from exposure to N₂O is clear, this concern has an extremely tenuous pertinence to the safety of N₂O/O₂ labor analgesia. However, professionals with experience and knowledge about N₂O/O₂ labor analgesia should be at the table when research needed to protect immature human brains from exposure to drugs suspected of increasing the risk of neuro-apoptosis during synaptogenesis is being discussed.

Research is needed 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. Research also is needed to determine how many breaths a woman using N₂O/O₂ labor analgesia intermittently needs to exhale into the scavenging equipment at the end of each contraction.

The finding of a dose-dependent association between intrapartum exposure to N₂O and amphetamine addiction as an adult is concerning, even though many of the mothers of the amphetamine addicts in the study that found that association were using 100% N₂O.⁴⁰ There is continuing, but still inadequate, concern about possible effects of exposing immature humans to all kinds of neuroactive drugs during the perinatal period, including opioids administered by any route and anesthetics administered by epidural.⁶⁵ Current neonatal neurobehavioral scale assessments (much less Apgar scores) are inadequate to assess the long-term safety of drugs used during the perinatal period.

Clinical Implications

In addition to women who have had recent ear surgery, women who have any condition that puts them at increased risk of vitamin B₁₂ deficiency should not use N₂O during labor until it has been determined that their vitamin B₁₂ levels are within a normal range, which should occur during pregnancy. Intrapartum care professionals in all countries should take an active role in assuring that the applicable N₂O OELs are met. Those in the work environment could take leading roles in developing innovative ways to protect care providers.

Needs for Greater Access to Labor Analgesia and to Greater Choice

Many women lack access to a reasonably effective method of labor analgesia when they need it.^{9,16,18,19} Sixty-one percent of women who had singleton vaginal births in the 27 US states that collect birth certificate data on labor analgesia had neuraxial analgesia in 2008.⁶⁶ Some women do not need or want an epidural; some want or need an epidural but cannot access one when they need help because of where they live, the hospital they use for labor, or the day-of-the-week, time-of-day, or competing needs for the services of anesthesia professionals. There are growing shortages of both anesthesiologists⁶⁷ and nurse anesthetists,⁶⁸ especially in rural areas.⁶⁸ Approximately 18% of all US births occur in rural areas.⁶⁹ As Finnish anesthesia professors wrote in a 2011 review of labor analgesia, "Although millions of parturients profit from neuraxial analgesia for labor, there are far more of those who do not have this choice for one reason or another. They need alternative ways to relieve labor pain."¹⁶

Nitrous oxide can help address the uneven access to labor analgesia in the United States. A major benefit is the simplicity of its use.¹² A sterile field and anesthesia professional are not needed. Nitrous oxide labor analgesia is safe and has no negative effects on the physiology of labor. To greatly expand access to labor analgesia in the United States, nurses as well as

midwives should be taught to offer and monitor use of N₂O/O₂ analgesia for women in labor (M. Rosen, MD, Department of Anesthesiology, University of California at San Francisco; personal communication, May 2011).

CONCLUSIONS

Nitrous oxide has many benefits for ameliorating the pain and anxiety of labor, including quick action and quick exit from the body.^{1,18} Nitrous oxide labor analgesia does not cause complications or adverse outcomes for the mother, fetus, or neonate. Because it does not reduce the release of endogenous oxytocin by the mother's pituitary gland, it does not affect uterine contractility or cause an increase in the use of synthetic oxytocin (Pitocin), the drug that is most often associated with preventable adverse perinatal outcomes in the United States.⁷⁰ Intravenously administered synthetic oxytocin cannot replicate the effectiveness and safety of the mother's hormonal management of labor.

Because N₂O/O₂ labor analgesia does not have adverse effects that could threaten the safety of the mother or fetus, laboring women who use it do not need routine intravenous access, continuous electronic fetal monitoring, or other procedures that are intrusive and restrict the mother's freedom of movement during labor. Nitrous oxide labor analgesia is safe for the mother, fetus, and neonate and can be made safe for caregivers.

AUTHOR

Judith Rooks, CNM, MPH, MS, FACNM, is a midwife and epidemiologist with many years' service as an educator and researcher in women's reproductive health. A past president of the American College of Nurse-Midwives, she has researched labor pain and analgesia since directing the 2001 Nature and Management of Labor Pain Symposium sponsored by the Maternity Center Association (now known as Childbirth Connection) and has worked toward expanding access to nitrous oxide for labor analgesia in the United States.

CONFLICT OF INTEREST

The author has no conflicts of interest to disclose.

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