



# POSITION STATEMENT

## Nitrous Oxide for Labor Analgesia

It is the position of the American College of Nurse-Midwives that women should have access to a variety of measures to assist them in coping with the challenges of labor. Among these should be nitrous oxide, which is commonly used in many other countries.

The experience of labor pain differs among women, and the response to pain is highly individual. (1) Women should have access to a variety of approaches to promote comfort and reduce pain throughout labor. But women in the United States have fewer labor pain-relief options than women in many other advanced countries. (2)

A blend of inhaled nitrous oxide (N<sub>2</sub>O) 50 percent and oxygen (O<sub>2</sub>) 50 percent is used as a major method of labor analgesia in many countries with high standards for safe and effective health care, such as Australia, Canada, Finland, Sweden, and the United Kingdom (UK) (3; 4, p. S111). However, this has been a very rare option in the United States in recent years. (3)

For labor analgesia, epidural administration of local anesthetic agents and systemic (intravenous or intramuscular) administration of opioids (narcotics) are the two most frequently employed pharmacologic methods in the United States (5). Nitrous oxide is a less potent analgesic than epidural or other neuraxial anesthesia, but may be more effective than systemic opioids, (4, p. S121), with the exception of intravenously administered, short-acting, very potent synthetic opioids, such as remifentanyl (6). Nitrous oxide works by increasing the release of endogenous opioid polypeptide compounds (endorphins), corticotropins and dopamine that are produced in the mother's brain (8, p. 714). The analgesic efficacy of inhaling a relatively low concentration of nitrous oxide is limited; a few women report little or no benefit at all. Yet it is effective enough for the majority of women who try it, and most who have used it say that they were satisfied. (7)

Some unique attributes of nitrous oxide are as follows:

1. Despite widespread and extensive use of nitrous oxide analgesia for labor analgesia in many countries since the early 1900s, (7) no studies or published observations have identified significant adverse effects on the neonate. There is no increased requirement for neonatal resuscitation, and newborn alertness and responsiveness during the important early period of maternal-infant bonding and early effective breastfeeding are unaffected. (4, p. S122) It is safe for a woman to use nitrous oxide throughout the entire second stage of labor.. (4, 7)

2. Nitrous oxide analgesia can be administered quickly, easily and safely and has a very rapid onset of action.
3. Nitrous oxide analgesia can be discontinued as quickly and easily as it is started. The effects begin to dissipate immediately after the woman stops breathing nitrous oxide and are completely gone within five minutes.
4. Nitrous oxide analgesia has no adverse effects on the progress of labor; the spontaneous vaginal birth rate is unaffected. Administration of nitrous oxide is not associated with increased risk of maternal or fetal complications and does not require more intensive or invasive monitoring.
5. After a brief period of explanation and supervision, nitrous oxide is self-administered through a mask that the woman holds to her own face. Self-administration allows the woman to determine when and how much nitrous oxide she uses.
6. If a woman doesn't like or tires of using nitrous oxide, she can stop using it and begin using another method without residual effects from the nitrous oxide.

### **Two concerns about Nitrous Oxide Analgesia for labor in the United States.**

One long-standing concern about nitrous oxide analgesia for labor pertains to the reproductive risk to female health workers, including midwives and labor nurses who work closely with patients using nitrous oxide analgesia. (8) A more recent concern is abnormal apoptotic cell "suicide" in brain cells of baby rodents exposed to very high and long (especially relative to the period of rapid brain development in a rodent) exposures to nitrous oxide and a wide class of other neuro-active drugs, including virtually all general anesthetics. (9) The time of susceptibility is the period of neuro-synaptogenesis, which includes the first week of life in baby rats and the last three months of gestation and first three years of post-natal life in immature humans. Because of the seriousness of these concerns, some of the most important findings and conclusions from the important 2008 review by Sanders et al. (9) are summarized here. These two concerns result from completely different pathogenic pathways.

Inactivation of methionine synthase causes few cases of illness but underlies the concern about occupational risk from repeated exposures to nitrous oxide: Most of the few health problems that have been attributed to nitrous oxide, including occupational health risks, are due to inactivation of an enzyme that is necessary for normal cell function and cannot be produced in the absence of vitamin B12. (9, p. 711) Decreased methionine synthase can result in both genetic and protein aberrations that result in very few cases of disease but may result in reproductive failure due to repetitious (usually employment-based) exposures to N<sub>2</sub>O. Persons with hereditary vitamin B12 deficiency disorder, pernicious anemia, Crohn's disease, ileal disease or chronic malnutrition due to alcoholism are at increased risk. Persons with an inherited B12 deficiency know it and take B12 replacement pills. In addition, pregnant women

who adhere to a strict completely vegan diet are at risk, as are many elderly persons, up to 20% of whom are deficient in vitamin B. (9, p. 713)

The only other groups at high risk for acute pathology from exposure to nitrous oxide are long-term recreational N<sub>2</sub>O drug abusers (9, p. 714) and surgical patients who receive high doses of N<sub>2</sub>O *anesthesia*—not analgesia—for 6 hours or more. Exposure to anesthetic concentrations continuously for more than 3-6-hours may cause biochemical changes, but clinical effects have not been shown in healthy people without reduced vitamin B12/folate stores when exposed for less than 12 continuous hours. Given the frequent use of high concentrations of N<sub>2</sub>O during surgery and the scarcity of disease caused by methionine synthase deficiency, it is not a very big problem. (9, p. 714) In any case, the problem can be solved by treating high-risk individuals with vitamins.

Occupational risks are related to subfecundability and increased incidence of spontaneous abortions, presumably caused by inactivation of methionine synthase due to N<sub>2</sub>O. (9, p. 717) Dose—the concentration inhaled and the duration of exposure—is always important. Another consideration with occupational risk is cumulative body burden, which is increased by repetitive exposures and reduced by *restitution*. Cellular-level damage can begin during a midwife's or labor nurse's shift in a poorly ventilated hospital where N<sub>2</sub>O is used without scavenging, but the damage-producing process stops—or pauses—when the midwife leaves the hospital's contaminated environment. (Scavenging equipment uses suction to eliminate contaminated exhalations of patients using nitrous oxide from the immediate environment, e.g. labor room or operating room.) While away from the hospital, the body begins to repair any cellular-level damage. Our survival depends on the ability of our body to heal. Healing the damage that has not yet reached a point of actual pathology is restitution. However, if someone returns to work in a nitrous oxide polluted environment before restitution is complete, the damage-producing process can accumulate and restitution will become incomplete. Over time, the damage may produce noticeable effects in the form of subfecundability or an increased incidence of spontaneous abortions.

Subfecundability in the form of maternal absorption of malformed conceptions has been found in animal studies of the reproductive effects of exposure to nitrous oxide. However, the studies used very prolonged exposures to very high doses of N<sub>2</sub>O, limiting applicability to the clinical setting. (9, p. 717) More months on average to conceive was found in a study of dental assistants working in settings that did not use scavenging of exhaled N<sub>2</sub>O. It was estimated that the ambient air in which they worked was contaminated by greater than 1,000 parts per million (ppm) of N<sub>2</sub>O. Nitrous oxide-induced fertility problems occur in rats at 1,000 ppm but not at 500 ppm or lower. (9, p. 717) Rats are known to be particularly sensitive to damage from N<sub>2</sub>O. (9, p. 712)

Current United States standards for Management of Waste Anesthetic Gases call for limiting occupational exposure to N<sub>2</sub>O to not more than an 8-hour time-weighted average (TWA) concentration of 25 ppm. (9, p. 16) The UK, Finland, Germany, and Sweden set 100 ppm as their upper limits. The US's 25 ppm standard was set arbitrarily during the 1970s, without benefit of

actual data. Nevertheless, the American Society of Anesthesiologists (ASA), the National Institute of Occupational Safety and Health (NIOSH) and the US Occupational Safety and Health Administration (OSHA) all believe that this standard has been effective in protecting American health workers. Concerns about reproductive toxicity from occupational exposure to nitrous oxide at levels below the 25-ppm standard are not supported by the available data, which, however, do not include findings from prospective studies.

Apoptotic loss of neurons in the brains of baby rodents creates concern about exposure of fetuses and young children. The other major concern about use of nitrous oxide for labor analgesia relates to apoptotic neuronal death or, as shown in some studies, seemingly severe but *reversible* neuronal damage in the brains of baby rodents, mainly rats, exposed to very high concentrations of N<sub>2</sub>O. Some studies used hyperbaric chambers to force more N<sub>2</sub>O into the baby rats' blood than would be possible at normal atmospheric pressures. Studies using 5-day old rhesus monkeys suggest that the rat studies "may be of less clinical importance than initially feared." (9, p. 715) The greatest concerns expressed about findings from the baby rodent studies have come from pediatricians and anesthesiologists worried about the large numbers of newborns and other very young children who require long surgeries, often to repair congenital heart and other major structural defects. Although there are other anesthetics, use of nitrous oxide facilitates more rapid induction and emergence from anesthesia in children (as well as adults). Sanders et al. found no evidence of apoptosis in neonatal rat brains from exposure to N<sub>2</sub>O concentrations less than 75%.

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While nitrous oxide is not without side effects and will not be agreeable to or effective for every laboring woman, it is an inexpensive, simple, reasonably safe and effective analgesic. It is important that midwives know about nitrous oxide analgesia and be able to offer it to women during labor.

In accordance with ethical, evidence-based practice, the American College of Nurse-Midwives (ACNM):

- Recognizes that women need access to a range of options for pain relief in labor;
- Recognizes that the reasonable efficacy and safety of nitrous oxide as an analgesic for labor has been the subject of research that has supported its use as a widely accepted component of quality maternity care in other medically sophisticated countries;
- Recognizes the unique and beneficial qualities of nitrous oxide analgesia during labor;
- Recognizes that certified nurse-midwives and certified midwives can be trained to administer and oversee safe use of nitrous oxide analgesia during labor;
- Supports the education and training of certified nurse midwives and certified midwives in safe administration of nitrous oxide;
- Supports the education of women about the use of nitrous oxide as an option for pain relief in labor;

- Urges continued research and evaluation of the use of nitrous oxide analgesia in all obstetrical/anesthesia departments to facilitate the inclusion of nitrous oxide as an option for laboring women throughout the United States.

### References:

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### Additional Resource:

McGowan Jr FX, Davis PJ. Anesthetic-related neurotoxicity in the developing infant: Of mice, rats, monkeys and, possibly, humans. *Anesthesia & Analgesia* 2008;106(6):1599-1602.

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