Nitrous Oxide and Autism

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Nitrous in Pregnancy

Brodsky JB, Cohen EN. Adverse effects of nitrous oxide. Med Toxicol. 1986 Sep-Oct;1(5):362-74. doi: 10.1007/BF03259849. PMID: 3537624.

Although once considered completely devoid of complications, it is now recognised that the misuse or inappropriate use of nitrous oxide (N2O) often results in adverse side effects. Hypoxia, particularly the entity 'diffusion hypoxia', can occur with the administration of inadequate amounts of oxygen during or immediately after a N2O anaesthetic. N2O will diffuse into air-containing cavities within the body faster than nitrogen diffuses out. This results in a temporary increase in either the pressure and/or volume of the cavity depending upon the distensibility of its walls. The magnitude of the effect is proportional to the blood supply of the cavity, the concentration of N2O inhaled and the length of time the patient is exposed to N2O. Significant morbidity or even death can result from this phenomenon. **A property unique to N2O is its ability to oxidise and inactivate the vitamin B12 components of certain enzymes in both animals and man. One such enzyme, methionine synthetase is essential for normal DNA production. Animal and human studies have demonstrated that the haematological, immune, neurological and reproductive systems are each affected.** These adverse effects of N2O can occur after both acute (surgical) or long term (occupational) exposure to the gas. Because of its effects on the

pressure and volume characteristics of air-containing spaces, N2O should not be used for patients with bowel obstruction, pneumothorax, middle ear and sinus disease, and following cerebral air-contrast studies. Many anaesthesiologists feel that use of N2O should be restricted during the first two trimesters of pregnancy because of its effects on DNA production and the experimental and epidemiological evidence that N2O causes undesirable reproductive outcomes. Since N2O affects white blood cell production and function, it has been recommended that N2O not be administered to immunosuppressed patients or to patients requiring multiple general anaesthetics. **Many anaesthesiologists believe that the potential dangers of N2O are so great that it should no longer be used at all for routine clinical anaesthesia**. However, the continued use of N2O remains a controversial topic since, at present, a suitable substitute gas is not available.

Vallejo MC, Zakowski MI. Pro-Con Debate: Nitrous Oxide for Labor Analgesia. Biomed Res Int. 2019 Aug 20;2019:4618798. doi: 10.1155/2019/4618798. PMID: 31531352; PMCID: PMC6720045.

This Pro-Con debate will provide the practitioner with an evidence-based knowledge approach to assist the clinician in determining whether to employ (Pro) or not to employ (Con) this technique in the obstetrical suite for labor analgesia. Nitrous oxide has been used safely in dentistry and medicine for many centuries. However, accumulating preclinical and clinical evidence increasingly suggests previously unrecognized adverse maternal and fetal effects of nitrous oxide, which warrants reconsideration of its use in pregnant women and a more detailed informed consent. Nitrous oxide is associated with metabolic, oxidative, genotoxic, and transgenerational epigenetic effects in animals and humans that may warrant limiting its usefulness in labor. This debate will discuss and review the clinical uses, advantages, and disadvantages of nitrous oxide on occupational effects of nitrous oxide exposure, neuroapoptosis, FDA warning on inhalational anesthetics and the developing brain, research limitations, occupational exposure safety limits, effects on global warming, and potential for diversion.

Fetal Effects of Maternal Nitrous Oxide

Nitrous oxide is a relatively insoluble inhaled anesthetic that rapidly crosses the placenta. A 1-3 hour exposure inactivates methionine synthase in the mother *and* fetus [102, 103]. Nitrous oxide use by parturients ranging from minutes to 11 hours revealed human placental methionine synthase activity decreased, with a faster decrease in women with lower vitamin B12 levels [104]. Over 20% of women may be deficient in vitamin B12 at term, exacerbating the effects of nitrous oxide exposure [102]. After a 1-hour exposure to 50% nitrous, methionine synthase activity in the fetal rat liver was 18% of baseline [103]. Methionine synthase activity in human liver was 50% after 46 min of exposure to 70% nitrous, and 0% after 200 min of exposure [103]. Recovery of methionine synthase activity may take up to 3-4 days. The fetal effects of maternal nitrous oxide administration may warrant maternal and fetal testing for predisposition to its adverse metabolic effects. The neonatal effects of in utero exposure to nitrous oxide is unknown, however Apgar scores and umbilical blood gases are unchanged, with no known clinical adverse effects [105]. The neonatal effects of decreases methionine synthase activity are unknown at this time.

3.7.1. Epigenetic Effects

Nitrous oxide exposure may also have epigenetic and transgenerational effects. Nitrous oxide and isoflurane exposure in a rat model caused substantial epigenetic modulation downregulated expression of brain-derived neurotrophic factor (BDNF) and c-Fos within 2 h [106]. MK-801, an NMDA antagonist, caused phosphorylation of histone H3 and epigenetic changes within 30 min in rat prefrontal cortex [107]. Ketamine, another NMDA antagonist, also affected epigenetic histone modifications in a rat model [108]. Nitrous oxide may decrease serum vitamin B12 and folate acutely. Prolonged Vitamin B12 and folate shortage was associated epigenetic changes including altered cardiometabolic risk factors in human offspring [109]. Nitrous oxide generates ROS, which are known to cause DNA damage or epigenetic modifications [39].

3.7.2. Potential Consequences of Nitrous Oxide on Human Behavior and Cognition

Multiple studies have shown an association and/or causation of general anesthetics with neuronal apoptosis and learning disabilities in fetal and neonatal rats, nonhuman primates and humans [15, 18, 53, 80, 110, 111]. Basic science evidence shows the ability of general anesthetics, NMDA antagonists and nitrous oxide to produce neuronal and oligodendrocyte apoptosis, metabolic derangements or genotoxicity in mother and fetus. Exposure to anesthesia as an infant may have induced apoptosis of myelin producing oligodendrocytes with a decrease in white matter brain volume on MRI in children age 12-15 years old, P=.016 [112].

As little as 90-120 min of total exposure time to general anesthetics from different episodes was associated with an increased incidence of learning disability and ADHD in young human children (adjusted hazard ratio 1.8, P<.04) [54, 55]. Multiple exposures to general anesthetics in young children was significantly associated with learning disabilities and attention-deficit/hyperactivity disorder, hazard ratio 2.17 (95% CI, 1.32-3.59) with decreases in cognitive ability and academic achievement [55]. We cannot predict which neonates or infants exposed to nitrous oxide during labor will need anesthesia following unexpected NICU admission or surgery in the period of increased susceptibility to neuroapoptosis (third trimester, 3 years), nor do we currently know if there are any potential effects of exposure to intermittent 50% nitrous oxide/50% oxygen during labor.

Claims that there is no evidence against it despite over 200 references saying that it causes B12 inactivation.

Likis FE, Andrews JC, Collins MR, Lewis RM, Seroogy JJ, Starr SA, Walden RR, McPheeters ML. Nitrous oxide for the management of labor pain: a systematic review. Anesth Analg. 2014 Jan;118(1):153-67. doi: 10.1213/ANE.0b013e3182a7f73c. Erratum in: Anesth Analg. 2014 Apr;118(4):885. PMID: 24356165.

Richardson MG, Lopez BM, Baysinger CL. Should Nitrous Oxide Be Used for Laboring Patients? Anesthesiol Clin. 2017 Mar;35(1):125-143. doi: 10.1016/j.anclin.2016.09.011. PMID: 28131115.

Nitrous oxide, long used during labor in Europe, is gaining popularity in the United States. It offers many beneficial attributes, with few drawbacks. Cost, safety, and side effect profiles are favorable. Analgesic effectiveness is highly variable, yet maternal satisfaction is often

high among the women who choose to use it. Despite being less effective in treating labor pain than neuraxial analgesic modalities, nitrous oxide serves the needs and preferences of a subset of laboring parturients. Nitrous oxide should, therefore, be considered for inclusion in the repertoire of modalities used to alleviate pain and facilitate effective coping during labor.

Hellams A, Sprague T, Saldanha C, Archambault M. Nitrous oxide for labor analgesia. JAAPA. 2018 Jan;31(1):41-44. doi: 10.1097/01.JAA.0000527700.00698.8c. PMID: 29278565.

Rooks JP. Safety and risks of nitrous oxide labor analgesia: a review. J Midwifery Womens Health. 2011 Nov-Dec;56(6):557-65. doi: 10.1111/j.1542-2011.2011.00122.x. Epub 2011 Oct 21. PMID: 22060215.

Hoffman S, Sidebottom A, Wrede J, Kreiger R, Watkins A, Taghon J. Association of Self-Administered Nitrous Oxide for Labor Analgesia With Maternal and Neonatal Process and Outcome Measures. J Obstet Gynecol Neonatal Nurs. 2021 Mar;50(2):154-166. doi: 10.1016/j.jogn.2020.11.002. Epub 2021 Jan 23. PMID: 33493464.

Nodine PM, Collins MR, Wood CL, Anderson JL, Orlando BS, McNair BK, Mayer DC, Stein DJ. Nitrous Oxide Use During Labor: Satisfaction, Adverse Effects, and Predictors of Conversion to Neuraxial Analgesia. J Midwifery Womens Health. 2020 May;65(3):335-341. doi: 10.1111/jmwh.13124. Epub 2020 May 26. PMID: 32452155.

“N_2 O is a useful, safe option for labor analgesia in the United States.”

Pinyan T, Curlee K, Keever M, Baldwin KM. A Nurse-Directed Model for Nitrous Oxide Use During Labor. MCN Am J Matern Child Nurs. 2017 May/Jun;42(3):160-165. doi: 10.1097/NMC.0000000000000336. PMID: 28448331.

“ Initiation and management of nitrous oxide by registered nurses is a safe and cost-effective option for labor pain.”

Effect on the foetus

Bodin L, Axelsson G, Ahlborg G Jr. The association of shift work and nitrous oxide exposure in pregnancy with birth weight and gestational age. Epidemiology. 1999 Jul;10(4):429-36. doi: 10.1097/00001648-199907000-00012. PMID: 10401879.

We examined the relation between shift work and occupational nitrous oxide exposure in the second trimester of pregnancy and birth weight and gestational age at delivery among the members of the Swedish Midwives Association. Eighty-four per cent of members who were registered in 1989 responded to a postal questionnaire concerning occupational exposures, including work schedule and the use of nitrous oxide, in relation to each of their pregnancies. We obtained information on births from the Swedish Medical Birth Register. We used models with allowance for dependence between births for the same woman and found that night work was associated with preterm birth (<37 weeks) [odds ratio (OR) = 5.6; 95% confidence limits (CL) = 1.9, 16.4] and to a lesser extent with low birth weight [OR = 1.9 (95% CL = 0.6, 5.8)]. Three-shift work schedule (day, evening, and night rotation) showed a possible association with preterm birth [OR = 2.3 (95% CL = 0.7, 7.3)]. **Exposure to nitrous oxide use was associated with reduced birth weight (-77 gm; 95% CL = -129, -24) and an increase in the odds of infants being small for gestational age (< or = 10th percentile of weight for gestational week) (OR = 1.8; 95% CL = 1.1, 2.8).**