**TSNRP ARIG/MWHRIG: Literature on Nitrous Oxide for Labor Analgesia**

Compiled Fall 2016 by CDR Ryan Nations (contact megan.foradori.ctr@usuhs.edu for PDFs of these articles)

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| El-Wahab | *Analgesia and anaesthesia in labour*  2011  Obstetrics, Gynaecology and Reproductive Medicine  21(5):137-141 | Labour is one of the most painful experiences a human encounters. Modern practice encompasses a number of techniques to alleviate this, from complementary therapies to invasive procedures. Pain induces a physiological stress response which has a number of deleterious effects on the body. Pharmacological methods of pain relief are the most popular, namely nitrous oxide, opioids and epidural analgesia. The latter is by far the most effective and is regarded as the gold standard. Importantly, intrapartum opioid use is associated with the risk of neonatal respiratory depression. Nonpharmacological techniques comprise a number of modalities of varied efficacy. Of these, hydrotherapy, acupuncture, continuous labour support and intradermal water blocks show the most promise. None of the methods available constitute the ideal analgesic for labour and the choice should be based on maternal preference, with regular re-evaluation to ensure adequate effect. |
| Jevtovic-Todorovic | *Anaesthetic neurotoxicity and neuroplasty: an expert group report and statement based on the BJA Salzburg Seminar*  **2013**  British Journal of Anaesthesia  111(2): 143-51 | Although previously considered entirely reversible, general anaesthesia is now being viewed as a potentially significant risk to cognitive performance at both extremes of age. A large body of preclinical as well as some retrospective clinical evidence suggest that exposure to general anaesthesia could be detrimental to cognitive development in young subjects, and might also contribute to accelerated cognitive decline in the elderly. A group of experts in anaesthetic neuropharmacology and neurotoxicity convened in Salzburg, Austria for the BJA Salzburg Seminar on Anaesthetic Neurotoxicity and Neuroplasticity. This focused workshop was sponsored by the British Journal of Anaesthesia to review and critically assess currently available evidence from animal and human studies, and to consider the direction of future research. It was concluded that mounting evidence from preclinical studies reveals general anaesthetics to be powerful modulators of neuronal development and function, which could contribute to detrimental behavioural outcomes. However, definitive clinical data remain elusive. Since general anaesthesia often cannot be avoided regardless of patient age, it is important to understand the complex mechanisms and effects involved in anaesthesia-induced neurotoxicity, and to develop strategies for avoiding or limiting potential brain injury through evidence-based approaches. |
| Lee | *Effect of combining anesthetics in neonates on long-term cognitive function*  **2014**  International Journal of Developmental Neuroscience  October; 37: 87–93 | **Background**—With growing evidence that anesthesia exposure in infancy affects cognitive development, it is important to understand how distinct anesthetic agents and combinations can alter long-term memory. Investigations of neuronal death suggest that combining anesthetic agents increases the extent of neuronal injury. However, it is unclear how the use of simultaneously combined anesthetics affects cognitive outcome relative to the use of a single agent.  **Methods**—Postnatal day (P)7 male rats were administered either sevoflurane as a single agent or the combined delivery of sevoflurane with nitrous oxide at 1 Minimum Alveolar Concentration for 4 h. Behavior was assessed in adulthood using the forced alternating T-maze, social recognition, and context-specific object recognition tasks.  **Results**—Animals exposed to either anesthetic were unimpaired in the forced alternating T-maze test and had intact social recognition. Subjects treated with the combined anesthetic displayed a deficit, however, in the object recognition task, while those treated with sevoflurane alone were unaffected.  **Conclusion**—A combined sevoflurane and nitrous oxide anesthetic led to a distinct behavioral outcome compared with sevoflurane alone, suggesting that the simultaneous use of multiple agents may uniquely influence early neural and cognitive development and potentially impacts associative memory. |
| Palanisamy | *Maternal anesthesia and fetal neurodevelopment*  **2012**  International Journal of Obstetric Anesthesia (2012) 21, 152–162 | It is clear from animal studies that commonly used anesthetic agents affect early brain development both histologically and functionally. With human epidemiologic evidence suggesting an association between anesthesia and surgery early in life and late-onset learning disabilities, investigators have focused their attention on the subtle long-term effects of anesthesia exposure. Most obstetric anesthesia studies, however, have focused on either the teratogenic effects of anesthetic agents in the first trimester or on the neonatal status immediately after delivery. Not much attention has been paid to the human second trimester, a period of active fetal brain development typified by neurogenesis and neuronal migration. Of concern though, is that these events are easily perturbed by environmental and pharmacological influences. New research studies have raised significant questions about the fetal impact of maternal anesthesia for non-obstetric and fetal surgery. This review summarizes the major findings in the field of developmental neurotoxicity of anesthetic agents, discusses the susceptibility of the fetal brain to anesthetic effects in a trimester-specific style, and outlines the pitfalls in extrapolating animal research to humans. |

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| Rooks | *Use of Nitrous Oxide in Midwifery Practice–Complementary,*  *Synergistic, and Needed in the United States*  2007  Journal of Midwifery & Women’s Health  52 (3), 186-9 | (Introduction) A 50/50 mixture of nitrous oxide (N2O) and oxygen is a safe, inexpensive, and reasonably effective labor analgesic that is available and widely used and appreciated by women in Canada, the United Kingdom (UK), Scandinavia, Australia, and many other parts of the modern Western world, but is not even known to most women in the United States, where it is offered in only a few hospitals.  I became interested in N2O while directing a symposium on The Nature and Management of Labor Pain. Systematic reviews of evidence regarding both the effectiveness and harms of virtually every method of labor analgesia being used in the United States were presented at the symposium and published as a supplement to the May 2002 issue of the American Journal of Obstetrics and Gynecology. Dr. Mark Rosen’s paper on N2O was based on findings from his systematic review and two decades of personal experience providing N2O to women during labor at Moffitt Hospital at the University of California at San Francisco (UCSF). UCSF has recently adopted new guidelines that authorize midwives, as well as anesthesiologists, to teach and assist women to use N2O in labor. |
| Rooks | *Labor Pain Management*  *Other Than Neuraxial: What Do We Know*  *and Where Do We Go Next?*  **2012**  BIRTH 39(4) Dec 2012  318-322 | Analgesia and coping with labor pain can prevent suffering during childbirth. Nonpharmacologic methods help women manage labor pain. Strong evidence is available for the efficacy of continuous one-to-one support from a woman trained to provide nonmedical care during labor, immersion in warm water during first-stage labor, and sterile water injected intracutaneously or subcutaneously at locations near a woman’ s lumbosacral spine to reduce back-labor pain. Sterile water injections also reduce the incidence of cesarean deliveries. Nitrous oxide labor analgesia is not potent, but helps women relax, gives them a sense of control, and reduces and distracts their perception of pain. It is inexpensive; can be administered and discontinued safely, simply, and quickly; has no adverse effects on the normal physiology and progress of labor; and does not require intensive monitoring or co-interventions. Parenteral opioids provide mild-to-moderate labor pain relief, but cause side effects. Although observational studies have found associations between maternal use of opioids and neonatal complications, little higher level evidence is available except that meperidine is associated with low Apgar scores. Patient-controlled intravenous administration of remifentanil provides better analgesia and satisfaction than other opioids, but can cause severe side effects; continuous monitoring of arterial oxygen saturation, anesthesia supervision, one-to-one nursing, and availability of oxygen are recommended. The demand for inexpensive, simple, safe but effective labor pain management for women will undoubtedly increase in places that lack wide access to it now. |

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| Rosen | *Nitrous oxide for relief of labor pain: A systematic review*  2002  Am J Obstet Gynecol  186(5) | A systematic review was conducted to determine the efficacy and safety of nitrous oxide for labor analgesia. Eleven randomized controlled trials with adequate control groups and outcome assessment by patients during or shortly after the intervention were used to determine efficacy. To determine adverse outcome, descriptions found in 8 controlled trials and in 8 observational studies were included. A nonsystematic review of studies on occupational exposure was also conducted. Nitrous oxide is not a potent labor analgesic, but it is safe for parturient women, their newborns, and health care workers in attendance during its administration. It appears to provide adequately effective analgesia for many women. |
| Sun | *Early childhood general anaesthesia exposure and neurocognitive development*  **2010**  British Journal of Anaesthesia 105 (S1): i61–i68 (2010) | A great deal of concern has recently arisen regarding the safety of anaesthesia in infants and children. There is mounting and convincing preclinical evidence in rodents and non-human primates that anaesthetics in common clinical use are neurotoxic to the developing brain in vitro and cause long-term neurobehavioural abnormalities in vivo. An estimated 6 million children (including 1.5 million infants) undergo surgery and anaesthesia each year in the USA alone, so the clinical relevance of anaesthetic neurotoxicity is an urgent matter of public health. Clinical studies that have been conducted on the long-term neurodevelopmental effects of anaesthetic agents in infants and children are retrospective analyses of existing data. Two large-scale clinical studies are currently underway to further address this issue. The PANDA study is a large-scale, multisite, ambi-directional sibling-matched cohort study in the USA. The aim of this study is to examine the neurodevelopmental effects of exposure to general anaesthesia during inguinal hernia surgery before 36 months of age. Another large-scale study is the GAS study, which will compare the neurodevelopmental outcome between two anaesthetic techniques, general sevoflurane anaesthesia and regional anaesthesia, in infants undergoing inguinal hernia repair. These study results should contribute significant information related to anaesthetic neurotoxicity in children. |