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Developmental Delay in Children Due to Inactivation of Methionine Synthase by Nitrous Oxide During Labour

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ABSTRACT

A previous study by our group has shown a potential link between the use of nitrous oxide for pain relief during labour and the subsequent diagnosis of developmental delay in the children. The current study extends these findings through the urinary metabolic analysis on 13 children who have been diagnosed with autism (developmental delay), and who were born to 11 mothers who used nitrous oxide for pain relief during labour. Elevated levels of the methylB12 deficiency markers, HVA, VMA, QA and pyroglutamic acid, were found supporting the notion that there had been extensive inactivation of the enzyme methionine synthase. There was lack of correlation between either MMA – a marker of Adenosyl B12 deficiency, and glutaric acid, a marker of functional B2 deficiency. The results are consistent with the known ability of nitrous oxide to form NO-Co(III)cobalamin, which subsequently irreversibly inactivates the enzyme methionine synthase. The data is in direct opposition to the contention of many anaesthetists, obstetricians and maternity staff who claim that nitrous oxide is harmless to the mother and baby. The findings are consistent with the hypothesis that the increased usage of nitrous oxide during labour has been a major factor in the 30-fold increase in the rate of autism in the past 30 years. The findings strongly suggest that nitrous oxide should be banned during labor.

***Lay Summary:** The current study supports the contention that the use of nitrous oxide for pain relief during labour has been a major factor in inactivating Methyl B12 through the formation of NO-Co (III)B12, and the presence of the inactive vitamin B12 in the brains of the children has led to the developmental delay.*

Keywords
Autism, Vitamin B12, Nitrous oxide, Labor.

Introduction

Previous studies by our group [1-4] and others [5-11] have shown that both overt vitamin B12 deficiency, and functional vitamin B12 deficiency, can cause developmental delay in children. In the former case, the vitamin B12 deficiency is readily detected by simple measurement of serum vitamin B12 levels, and corrected by administration of vitamin B12. In the later case, serum vitamin B12 may be normal or elevated, and hence alternative markers such as serum MMA, and homocysteine measured, or urinary markers such as HVA, VMA, QA, and 5HIAA must be measured to ascertain the functional and paradoxical B12 deficiency [12]. Analysis using Organic Acids testing of the urine of the latter group of children has shown that the functional vitamin B12 deficiency, appears to be caused by functional vitamin B2 deficiency, due to dietary lack of Iodine, Selenium and/or Molybdenum in the children [13], each of which has independently been shown to cause developmental delay in children and can cause irreversible brain damage to the fetus resulting in severe mental retardation [14-26]. Mechanistically functional vitamin B2 deficiency affects the rate of methylation in the body, due to the requirement for FMN and FAD for the enzyme methionine synthase reductase (MTRR), and FAD for methylene-tetrahydrofolate reductase (MTHFR). This reduced methylation observable in both overt and functional vitamin B12 deficiency, then results in developmental delay due to lack of production of creatine, melatonin, and acetylcholine,

amongst other factors.

There has been a rapid rise in the rate of autism over the past 40 years, with rates increasing from around 0.1% to now over 4%. Such a rate cannot be explained genetically, or environmentally, as parents of the children have not been affected. There, has, though been a rapid rise in the use of nitrous oxide during labour, from around 1% of births to now over 50%. Nitrous oxide has been known to irreversibly inactivate vitamin B12 and the toxicity is known to the medical profession who are warned that "Prolonged occupational exposure may cause health issues for clinicians (e.g. reduced fertility, disrupted vitamin B12 synthesis". This is in direct contrast to the advice given to the mothers, that nitrous oxide is perfectly safe and will not harm their baby.

During the intoxication of vitamin B12 by nitrous oxide, the nitrous preferentially attacks Co(I)B12, present in methionine synthase, and irreversibly forms the toxic NO-Co(III)B12 compound thereby inactivating methionine synthase and effectively stopping methylation. The susceptibility of vitamin B12 is dependent upon the rate of regeneration of MethylCo(III)B12 from Co(I)B12. In this reaction Co(I)B12 + 5MTHF[methionine synthase] ⇔ MethylCo(III)B12 + THF. The reaction is implicitly dependent upon the presence of 5MTHF (5-methyltetrahydrofolate). 5MTHF is generated with the folate cycle as 5,10-methylene-tetrahydrofolate, however it needs the activity of the enzyme MTHFR, a B2/B3 dependent enzyme for this conversion. Hence in functional B2 deficiency, due to lack of Iodine, Selenium, Molybdenum and/or vitamin B2, the function of the enzyme will be reduced and so Co(I)B12 will build up, and be presented as a reactant for nitrous oxide. Potentially Co(I)B12 could be reduced to Co(II)B12, and the enzyme methionine synthase reductase could reform MethylCo(III)B12 by reaction with SAM. MTRR, though is dependent upon B2/B3 and hence in the same deficiency of Iodine, Selenium, Molybdenum and/or vitamin B2, this reaction will also be reduced, and hence the formation of NO-Co(III)B12 will predominate. There is an important distinction between inactivation of methionine synthase due to build up of Co(II)B12 and the formation of NO-Co(III)B12 and that methionine synthase will eventually release the inactive Co(II)B12, which will be secreted into blood, whereas NO-Co(III)B12 bound to methionine synthase will not be released. Further, MethylCo(III)B12 can be regenerated once the Iodine, Selenium, Molybdenum and/or vitamin B2 deficiency is resolved, whereas there will be little to no regeneration of methionine synthase activity in the nitrous oxide affected persons. The current study has looked at the metabolic profiles of 13 nitrous affected children with autism born to 11 mothers who had nitrous oxide during labour.

Methods

Study sample data analysis was carried out under the Australian National Health and Medical Research Council guidelines (NHMRC). Under these guidelines, all data was de-identified and steps were taken to ensure the anonymity and confidentiality of the data. De-identification has consisted of absolute anonymity and confidentiality of the data, such that no specifics such as gender, ethnicity, Country of Origin, etc., is associated with any data point in the study.

As such per the NHMRC guidelines: 1. The research does not carry any risk to the participants 2. The benefits of the research are many and will be of considerable benefit to any past, current or future participants, and as such represent no harm. 3. The participants had been notified at the time of analysis that data presented for analysis might potentially be used in research – but would be totally de-identified (which it has been). 4. Given the total de-identification of the data, there is absolute protection of their privacy 5. Data is only housed in one location and has only been assessed by one person, and as such the confidentiality of the data can be assured. 6. No financial benefits from the data are anticipated, rather the data will be used to help prevent and treat those to whom the data applies. 7. The waiver is not prohibited by State, Federal or International Law. A retrospective analysis was performed upon data submitted to us for analysis from children who had been diagnosed with ASD from countries including USA, United Kingdom, Canada and Australia. No selection was made in the acceptance of data, with no data being rejected. We were not made privy to either the methods of assessment nor of the severity of the Developmental Delay in the Children. Data is presented regardless of sex, or age. Metabolic analysis was performed on Organic Acid Test Data (Great Plains Laboratories, Lenexa, KS, USA), which had been submitted to us for interpretation, by parents of children with autism spectrum disorder. Data from the 5 children with autism was compared to a person who was healthy, and who had no previously identified health condition (NT). Data was tabulated in an Excel spreadsheet, and processed using the standard plotting functions in the program. Individual data is plotted as Scattergrams (Figures 1-3). Correlations for the 3 nitrous oxide children are plotted separately.

Urinary Organic Acids Testing (Oasis diagnostics) was used to compare the Adenosyl B12 (Adenosylcobalamin) deficiency marker, MMA (methylmalonic acid), with 4 methyl B12 deficiency markers HVA (homovanillic acid, VMA (vanillylmalonic acid), QA (quinolinic acid) and pyroglutamic acid.

Results

Organic Acids Testing of developmentally delayed children from mothers who had received nitrous oxide during labour, has shown a preferential deficiency of methyl B12 as shown by elevated HVA, VMA, QA, and pyroglutamate, rather than Adenosyl B12 deficiency, as judged by elevated MMA. The results are commensurate with the known toxic activity of nitrous oxide on the enzyme methionine synthase.

Comparison of MMA levels (a marker of Adenosyl B12 deficiency), with HVA, VMA, QA and Pyroglutamic acid (markers of Methyl B12 deficiency (Figure 1) between 13 nitrous affected children showed little correlation between HVA and MMA, whereas there was a linear correlation between HVA and MMA in neurotypical subjects (Russell-Jones, 2026B).

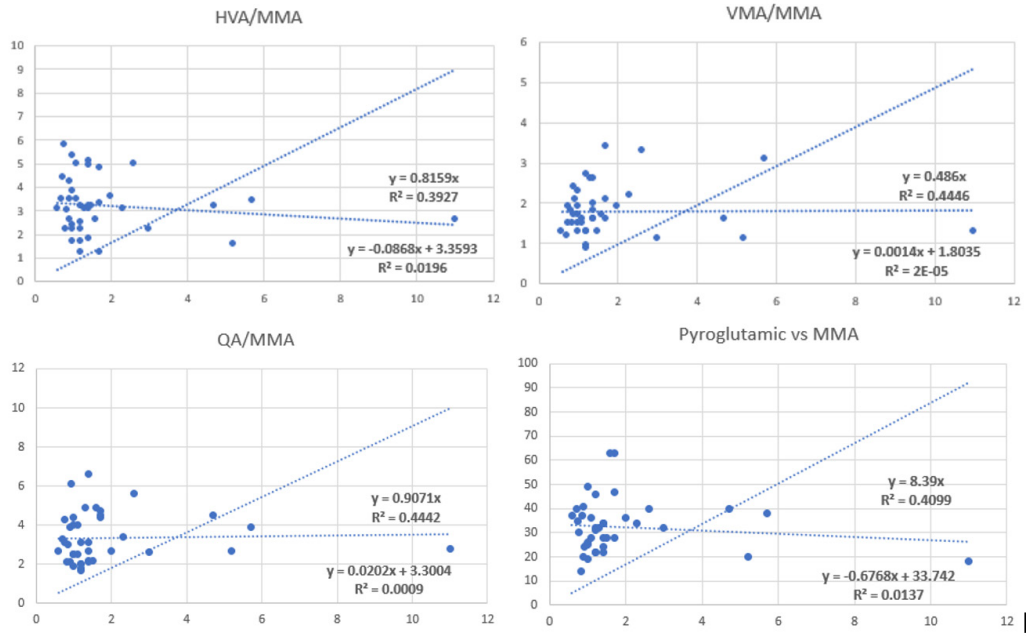

Figure 1: Comparison of metabolic markers of Adenosyl B12 deficiency (MMA horizontal axis), with the methyl B12 deficiency markers HVA, VMA, QA and Pyroglutamic acid (Vertical axes).

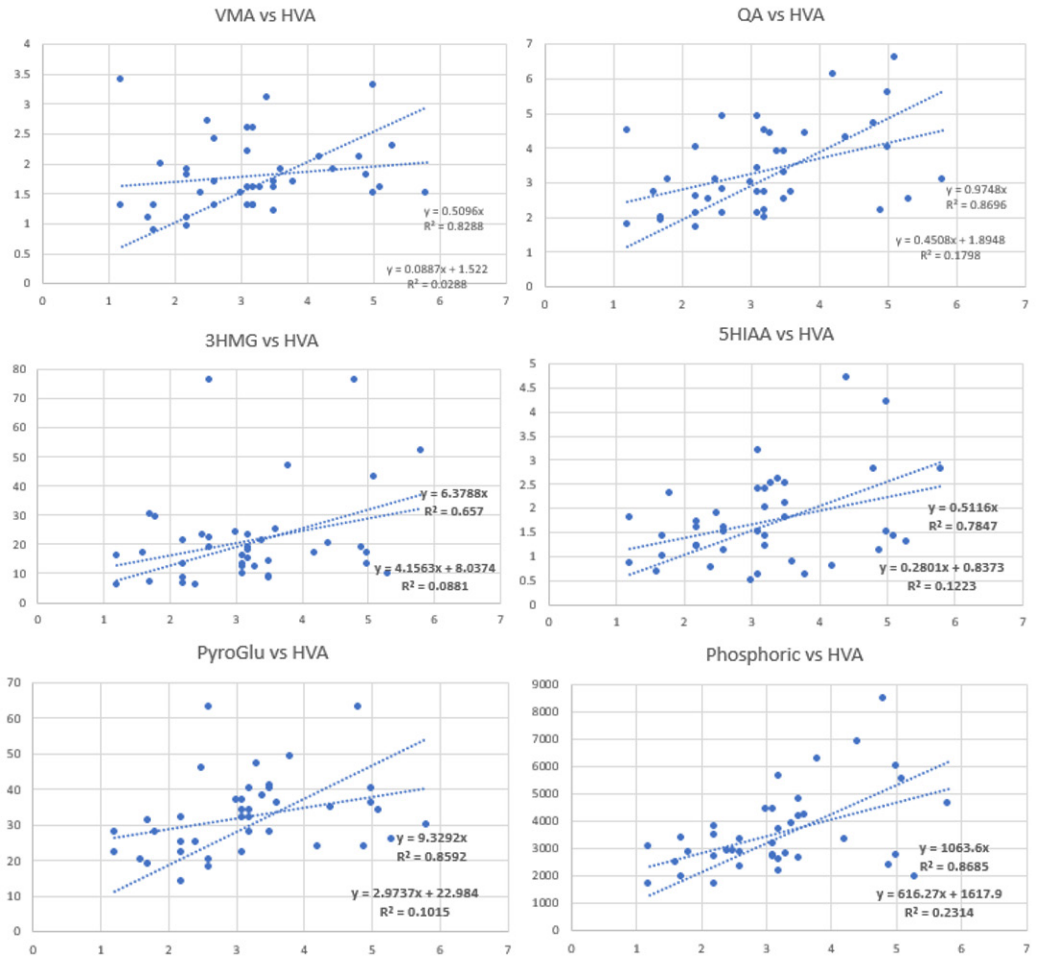

Figure 2: Comparison of multiple measurements of neurotransmitter metabolites associated with methyl B12 deficiency (VMA, QA, 5HIAA, Pyroglutamic Acid, Phosphoric acid), with HVA (horizontal axis), a marker of Methyl B12 deficiency.

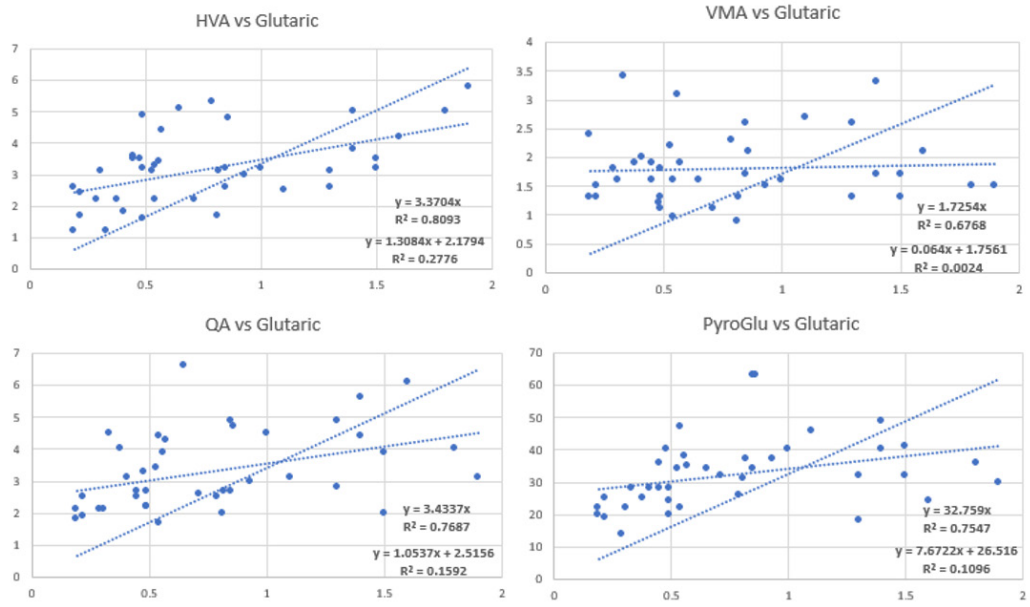

Figure 3: Comparison of multiple measurements of neurotransmitter metabolites associated with methyl B12 deficiency (HVA, VMA, QA, 5HIAA and Pyroglutamic Acid), with Glutaric acid (horizontal axis), a marker of functional B2 deficiency.

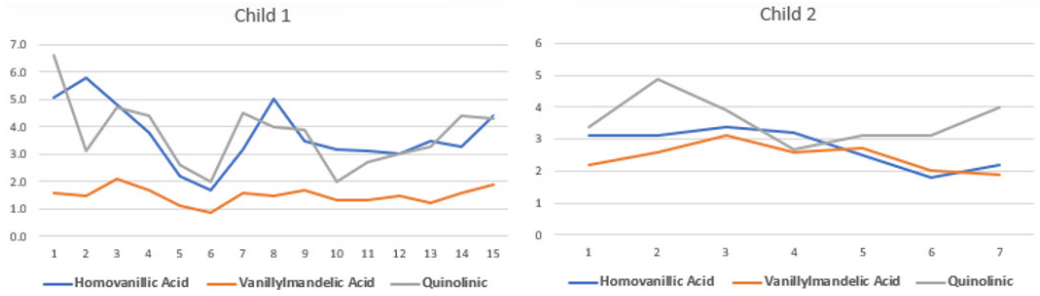

Figure 4: Monitoring of HVA, VMA and QA over time, in two nitrous oxide affected children. Child 1 for 7 years, Child 2 for 4 years.

In contrast to the data comparing HVA to methyl deficiency markers, it was found that in the nitrous affected ASD group there was little to poor correlation to the functional B2 deficiency marker, glutaric aicd (Figure 3). The data would not be commensurative with functional vitamin B2 deficiency causing methyl B12 deficiency.

Successive measurements of HVA, VMA and QA in two children over multiple assessments revealed little change in the methylB12 deficiency of the children.

The data would support the hypothesis that nitrous oxide preferentially and permanently reduces the activity of methionine synthase, rather than reducing the activity of the B2 dependent enzymes methylene tetrahydrofolate reductase and methionine synthase reductase.

Discussion

Many previous studies have shown two main causes of developmental delay in children, overt vitamin B12 deficiency, and functional vitamin B12 deficiency. In the former case, overt deficiency is readily detected by the measurement of serum vitamin B12 levels, and then subsequently corrected by administration of vitamin B12. In the latter case, functional vitamin B12 deficiency is caused by a deficiency in active vitamin B2, due to insufficiency in the diet of Iodine, Selenium and/or Molybdenum [1-4,13]. The functional vitamin B2/B12 deficiency due to Iodine deficiency is the single most preventable cause of developmental delay in children, as such Iodine deficiency in the mother can cause irreversible brain damage to the fetus resulting in severe mental retardation" [14-23]. Some success has been achieved by resolving the Iodine/Selenium/Molybdenum deficiency through the use of appropriate minerals and the application of transdermal Adenosyl/Methyl B12. In the previous study by Russell-Jones [1,2] there was good correlation between functional vitamin B2 deficiency (as measured by elevated glutaric acid) acid with the methyl B12 deficiency markers HVA, VMA, QA, and 3HMG.

More recently, preliminary studies have shown that there is a third, ever increasing cause of developmental delay, and that is the administration of nitrous oxide to the mother during labour [27].

Administration of nitrous oxide to the mother is purely for the analgesic effect on the mother, which is dependent upon nitrous inhalation. The nitrous is then absorbed rapidly through the lungs,

distributed quickly to mother and foetus, and not metabolized. In the mother the nitrous is quickly eliminated by exhalation. In order to maintain, pain-relief the mother repeatedly breaths in more and more nitrous, thus setting up a "window" of effectiveness.

The problem arises though in the foetus. The foetus also quickly receives the nitrous, but it cannot exhale the nitrous, rather, it acts as a depot for the nitrous, which must diffuse back against a concentration gradient in the mother, and then eventually leave the mother via her lungs. The foetus, though, is passive in this, and does not gain any benefit from the "waves" of nitrous it receives, rather the nitrous oxide builds up in fetal tissues, and reaches higher effective/toxic concentrations in the brain, which persists longer after maternal inhalation occurs.

Further, the toxicity of nitrous is dependent upon time and dose, and the irreversible inactivation of methionine synthase, through the generation of toxic NO-Co(III)B12 is cumulative, so that with every breath the mother takes, more and more toxic NO-Co(III) B12 is formed. Hence, whilst the mother eliminates nitrous oxide rapidly by exhalation, the fetus cannot exhale at all. Every molecule of nitrous must diffuse back across the placenta, resulting in slower clearance, higher effective fetal brain concentrations, and prolonged exposure. The fetus, thus becomes an end-point reservoir for a Schedule 6 toxin during the most sensitive phase of its brain development.

The results refute the claims by the medical profession that nitrous oxide is safe for mother and child. There have been no long-term studies to demonstrate this, and in fact several studies, including the current study would go against these claims, which appear to be based on the condition of the newborn at birth. It is not scientifically defensible to infer long term neurodevelopmental safety of fetal nitrous oxide exposure from normal neonatal appearance or short term postnatal observations. Autism, developmental delay, and other neurodevelopmental conditions are behavioural diagnoses made months to years after birth using structured criteria and specialist assessment. They cannot be identified in the first hour, day, or even week of life, and their assessment lies entirely outside the remit and expertise of the anaesthetist or attending medical staff.

One might naively think that whilst there may be extensive inactivation of methionine synthase by the nitrous oxide, administration of active Methyl B12 will eventually displace the toxic NO-Co(III)B12. This though is not the case. Loading of the brain with vitamin B12 occurs predominantly in the womb, and once the child is born transport of B12 into the brain is almost non-existent, hence the B12 that you have in the brain at birth, has to be maintained for life. A time course study on two children indicates that the methyl B12 deficiency persists for years with little change (Figure 4).

The lack of correlation between MMA and the methyl B12 deficiency markers, and the poor correlation between glutaric acid levels (a measure of functional B2 deficiency) is strongly supportive of the concept that the damage to B12 has occurred due to nitrous oxide usage by the mother. The extent of damage would be greater the longer the duration of nitrous used, the volume inhaled during that time (which may be reflective of the pain tolerance level of the mother), the MTHFR, and MTRR status of the child, and the functional B2 sufficiency of the mother, ie Iodine, Selenium, and/or Molybdenum.

In contrast to some other studies, that have reported on the effect of nitrous oxide [28], the children in the current study had normal or elevated levels of serum vitamin B12. The data in some ways represents studies by others on nitrous oxide intoxication by the use of Nangs. Whilst in some, the damage from nitrous intoxication is reversible in many individuals the damage is long lasting and many do not recover from the intoxication [29-33]. Hence progressive nitrous oxide-induced peripheral neuropathy in an adult can result in permanent damage, and logically such damage would not only be worse but also be permanent in a neonate.

The data presented supports our earlier preliminary work on functional methyl B12 deficiency in children diagnosed with autism who are born to mothers who have used nitrous oxide during pregnancy. The current work also supports the concerns of many other workers on the dangers of nitrous oxide use [28-30, 34-43]. This linkage to the use of nitrous oxide with subsequent functional methyl b12 deficiency potentially supports the contention that the dramatic increase in the rate of autism is largely due to the increased use of nitrous oxide during labour, which when combined with a nutritional deficiency in the mother of Iodine, Selenium, Molybdenum and/or vitamin B2, has disastrous consequences to the neonate. This contention is further supported by the lack of association of methyl B12 markers with either Adenosyl B12 deficiency markers or functional vitamin B2 deficiency markers. One would seriously question whether the reduction in pain and the elevation in euphoria over several hours of labour is worth it for a life-time of pain and anguish in raising a child with developmental delay. Of note, nitrous oxide has never been properly evaluated for use in pregnancy. Its current use is a historical artefact, not an evidence based practice. The data presented would indicate that before the use of nitrous oxide in pregnancy is continued, it should undergo standard rigorous analysis. Whilst the results are preliminary, they are readily testable and it would seem prudent to err on side of caution, and at least for the moment it to BAN the use of nitrous oxide during labour.

Summary

Metabolic analysis of 13 children, born to 11 mothers who used nitrous oxide during labour, and who were subsequently diagnosed with developmental delay, revealed elevated markers of both adenosyl and methyl B12 deficiency. Methyl B12 deficiency markers, were however, disproportionally high, supporting the concept that nitrous oxide reacts with Co(I)B12 to form biologically inactive NOCo(III)B12, with resultant inactivation of methionine synthase. All mothers had been told at time of labour that nitrous was safe and would not harm their children. Attempts to reduce the functional methyl B12 deficiency in the brain, as

assessed by the markers HVA and VMA were unsuccessful. The data presented strongly refutes the claims that the use of nitrous oxide during labour is harmless. Rather, the data strongly supports the notion that the use of nitrous oxide during labour can be highly toxic and can lead to a life-time of methyl B12 deficiency in the brain, with subsequent incurable developmental delay. As such the use of nitrous oxide during labour should be totally avoided.

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