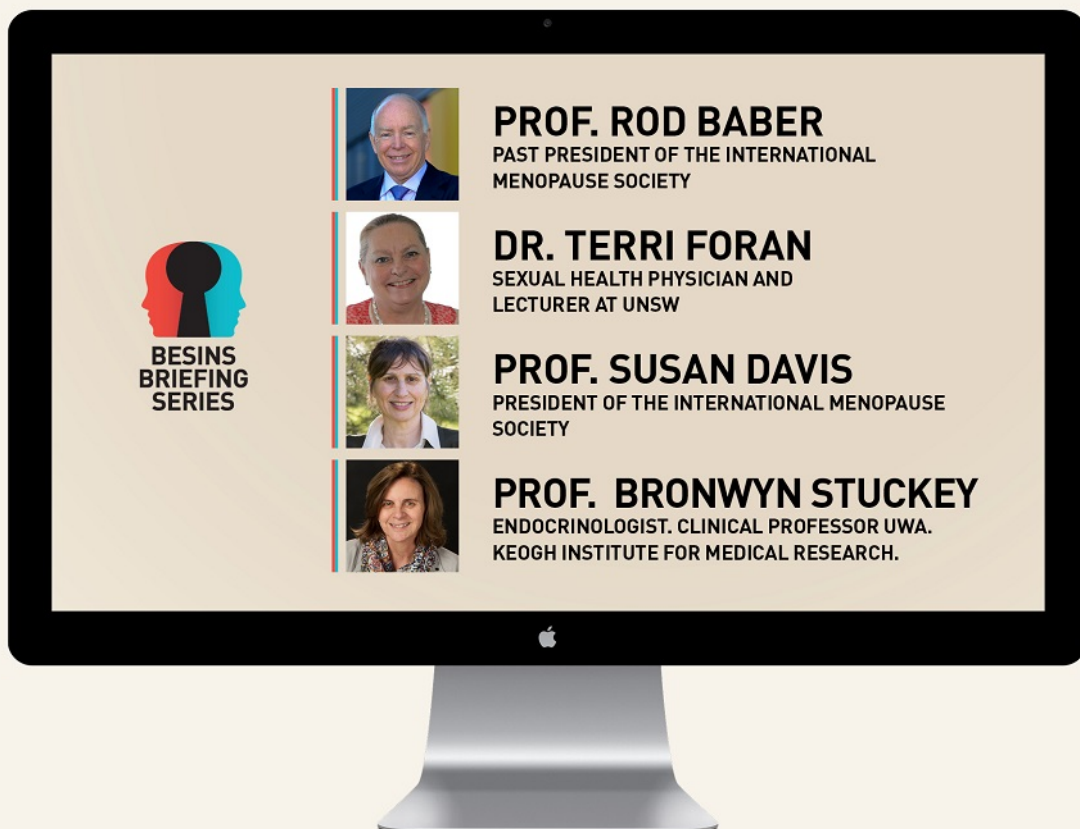


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## SHORT COMMUNICATION

# The impact of withholding nitrous oxide in labour during the COVID-19 pandemic on maternal and neonatal outcomes

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Nitrous oxide is commonly used in Australia for labour analgesia. Its use in labour is potentially associated with aerosol generation. During the first wave of the COVID-19 pandemic of 2020, nitrous oxide was suspended on many birthing units to reduce the risk of transmission. We aimed to determine the impact of withholding nitrous oxide for labour analgesia, during the COVID-19 pandemic, on epidural rates, opioid analgesia use, and maternal and neonatal outcomes. Withholding nitrous oxide for labour analgesia did not alter epidural rates but did significantly increase opioid analgesia use. Caesarean section rates, post-partum blood loss and neonatal APGAR scores did not change.

**KEYWORDS**

adverse birth outcomes, analgesia, Covid-19, epidural, greenhouse gases, nitrous oxide

**INTRODUCTION**

COVID-19 infections in pregnant women increase the risk for maternal and fetal morbidity and mortality.<sup>1,2</sup> Initial data showed that COVID-19 infection in pregnancy was associated with an 11% rate of admission to the intensive care unit, 26% pre-term birth rate and a 2% neonatal mortality rate.<sup>1</sup> A meta-analysis by Allotey et al. reported a transmission rate of 1.8% in babies born to mothers with SARS-Cov-2 infection.<sup>3</sup> Pregnant women may be more likely to have asymptomatic COVID-19 than the general population.<sup>4,5</sup> Therefore, labouring pregnant women with COVID-19 infection increase the risk of virus transmission to healthcare workers, other

staff, patients, and visitors.<sup>1,6</sup> Protective strategies that reduce infection transmission should be considered.<sup>6</sup>

Nitrous oxide (N<sub>2</sub>O) is commonly used for labour analgesia. N<sub>2</sub>O provides analgesia, amnesia and anxiolysis, allowing women to better tolerate discomfort during labour.<sup>7,8</sup> Administered via a demand valve, the parturient is encouraged to inhale through a mouthpiece at the onset of uterine contractions. N<sub>2</sub>O delivery is patient-controlled, well-tolerated with a rapid onset, rapid offset and no residual effects on the neonate.<sup>7</sup>

The use of N<sub>2</sub>O for labour analgesia in Australia commenced in the 1960s. N<sub>2</sub>O is available on all birthing units in the United Kingdom (UK), and is a commonly used labour analgesia

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method in Canada, Finland and Australia.<sup>7,9</sup> In the United States, less than 1% of birthing units have N<sub>2</sub>O; used by only 2% of labouring women and epidural rates are higher.<sup>8</sup> Rates of N<sub>2</sub>O and epidural use in the UK are similar to that of Australia. In 2018, 78% of Australian women used at least one form of analgesia in labour. The most common analgesic agent was N<sub>2</sub>O (53%), followed by neuraxial (epidural) analgesia (40%) and opioids (14%).<sup>10</sup>

There remains a paucity of data on whether the second stage of labour is an aerosol generating behaviour and the provision of N<sub>2</sub>O an aerosol generating procedure (AGP)<sup>1,11,12</sup> Discomfort during labour can result in pain, hyperventilation, shouting, coughing, vomiting, and when in use breathing around the N<sub>2</sub>O mouthpiece. The second stage of labour necessitates close healthcare worker contact with the patient for up to four hours, as well as exposure to aerosolisation from stool, urine and other perineal fluids. Groups around the world have included labour and caesarean section as possible AGP requiring appropriate personal protective equipment use.<sup>6</sup> The impact of COVID-19 on obstetric patients has included birthing units globally withdrawing N<sub>2</sub>O for labour analgesia due to the AGP and potential for virus transmission. In early 2020, the majority of obstetrics and gynaecology associations in the United States advised against the use of N<sub>2</sub>O.<sup>13</sup> In Australia, the Society for Obstetric Anaesthesia and Perinatology and Royal Australian College of Obstetricians and Gynaecologists advised against providing N<sub>2</sub>O analgesia to pregnant, labouring or post-partum patients with suspected, probable or confirmed COVID-19.<sup>14,15</sup>

Given the evidence in the literature, the COVID-19 pandemic provided a 'natural experiment' and opportunity to re-evaluate the role and need for N<sub>2</sub>O, with the aim to determine the impact of withdrawing N<sub>2</sub>O on labour analgesia use and maternal and neonatal outcomes.

## MATERIALS AND METHODS

This retrospective observational study was approved by the Central Adelaide Ethics Committee (Reference: 14995). Patient case notes were retrospectively reviewed for all women labouring at an Australian metropolitan hospital between March 9 and April 29, 2020. The N<sub>2</sub>O withheld group included 122 patients who delivered in the 19-day study period from March 29 to April 16, when N<sub>2</sub>O was unavailable. The N<sub>2</sub>O available group included 121 patients who delivered in the 19-day period from March 9 to 28. Women who delivered prior to, or within 30 min of arriving; as well as those with an intrauterine fetal death and incomplete clinical records were excluded. Demographic variables (age, marital status, ethnicity, American Society of Anesthesiologists physical status classification and body mass index (BMI)), obstetric variables (gravida, parity, antenatal complications, gestational age at delivery, presence of a support person, labour was spontaneous or induced, reason for induction of labour), labour measures

(analgesia use, delivery mode, complications) and maternal and neonatal outcomes were recorded.

## Outcome measures

Outcome measures included analgesia used (none, N<sub>2</sub>O (when available), opioids, or epidural, delivery mode (normal vaginal delivery vs vacuum extraction, forceps or emergency caesarean section), total labour duration, labour complications (as defined per discharge summary), estimated blood loss, post-partum haemorrhage (PPH) and neonatal APGAR scores.

## Statistical analysis

Descriptive statistics included counts and percentages for categorical variables and median (interquartile range) for continuous variables. Statistical models included logistic regression for binary outcomes, linear regression (log-transformed for skewness where appropriate) for continuous outcomes and proportional odds models for ordinal outcomes. Estimates and 95% confidence intervals were produced for N<sub>2</sub>O available vs withheld. Models were adjusted for risk factors, including age, ethnicity, obesity, primiparity, at term pregnancy, presence of a support person and induction of labour. A *P*-value of less than 0.05 was considered statistically significant. R statistical software version 4.1.0 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

## RESULTS

There were 122 women in the N<sub>2</sub>O withheld group, and 121 in the N<sub>2</sub>O available group. Maternal demographics were similar between the two groups (Table 1), although gestational age and primiparity were slightly higher in the N<sub>2</sub>O withheld group.

There was no significant difference in epidural use when N<sub>2</sub>O was available compared with when it was withheld during labour (adjusted odds ratio (OR) = 0.76, 95% CI = 0.42, 1.38, *P* = 0.368) (Table 2). There were no combined spinal epidurals in our cohort. When N<sub>2</sub>O was available, opioids (adjusted OR = 0.34, 95% CI = 0.18, 0.63, *P* < 0.001) or any analgesia other than N<sub>2</sub>O (adjusted OR = 0.37, 95% CI = 0.2, 0.69, *P* = 0.002) was significantly lower. No significant difference was observed when N<sub>2</sub>O was withheld in labour duration, delivery mode, estimated blood loss, PPH and neonatal APGAR scores.

## DISCUSSION

Despite the long history of N<sub>2</sub>O for labour analgesia, at present, there are no data on the impact of sudden disruptions of availability. The mandated withdrawal of N<sub>2</sub>O as part of a protective COVID-19 response allowed a 'natural' experiment into the effects

**TABLE 1** Demographic data for nitrous oxide (N<sub>2</sub>O) withheld and N<sub>2</sub>O available groups (descriptive statistics are *n* (%), unless otherwise specified)

	N <sub>2</sub> O available ( <i>n</i> = 121)	N <sub>2</sub> O withheld ( <i>n</i> = 122)	P-value
Age, median (interquartile range (IQR))	28.00 (25.00, 31.00)	28.00 (24.25, 32.00)	0.91
Body mass index, median (IQR)	27.00 (23.00, 32.80)	25.80 (22.75, 30.92)	0.43
Obesity	42 (34.7)	34 (27.9)	0.31
Married	112 (92.6)	112 (91.8)	1
Caucasian	90 (74.4)	86 (70.5)	0.59
Gravida, median (IQR)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.26
Parity, median (IQR)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.18
Primiparous	44 (36.4)	58 (47.5)	0.10
Gestational age, weeks, median (IQR)	39.1 (38.1, 40.1)	39.4 (39.0, 40.3)	0.04
At term birth			0.64
Pre-term	8 (6.6)	5 (4.1)	
Post-term	10 (8.3)	12 (9.8)	
At term	103 (85.1)	105 (86.1)	
Nil antenatal complications	34 (28.1)	30 (24.6)	0.64
Support person	105 (86.8)	100 (82.0)	0.39
Induction of labour	54 (44.6)	53 (43.4)	0.96
American Society of Anesthesiologists score			0.69
1	53 (43.8)	55 (45.1)	
2	52 (43.0)	47 (38.5)	
3	16 (13.2)	20 (16.4)	
Delivery method			0.80
Normal vaginal delivery	89 (73.6)	90 (73.8)	
Forceps	7 (5.8)	4 (3.3)	
Ventouse	7 (5.8)	8 (6.6)	
Caesarean section (CS)	18 (14.9)	20 (16.4)	
Emergency CS urgency category <sup>16</sup>	18 (14.87)	19 (15.6)	0.41
1, urgent	5 (27.8)	4 (21.1)	
2, within 60 min	12 (66.7)	10 (52.6)	
3	1 (5.6)	4 (21.1)	
4	0 (0.0)	1 (5.2)	
N <sub>2</sub> O use	74 (61.2)		
Birth weight, g, mean (SD)	3413 (485)	3489 (498)	0.24

on labour outcomes which would be difficult to conduct under normal circumstances. Our study demonstrated that withholding N<sub>2</sub>O for labour analgesia did not have a significant impact on epidural rates; however, systemic opioid use significantly increased. Maternal and neonatal outcomes were not negatively affected.

A 2016 comparative study looked at epidural rates before and after N<sub>2</sub>O introduction at a single centre.<sup>16</sup> Epidural rates prior to and after N<sub>2</sub>O introduction were 77% and 74% respectively. In 2017, a study examined factors influencing conversion from N<sub>2</sub>O to neuraxial analgesia in labour; 63.2% of women converted to neuraxial analgesia; factors associated with conversion were labour induction and labour augmentation.<sup>17</sup> Finally, a 2017 study assessed conversion rates from N<sub>2</sub>O to other analgesia techniques and parturient satisfaction with N<sub>2</sub>O use.<sup>18</sup> Findings

included 68.9% of patients switching from N<sub>2</sub>O to another technique (with 92% switching to epidural), a mean patient satisfaction score of 7.4 out of 10, and no adverse effects of N<sub>2</sub>O on neonatal APGAR scores.

Taking our results and the findings by Richardson *et al.* into consideration, the usefulness of and the need for the availability of N<sub>2</sub>O in labour wards could be questioned, particularly given the current debate around greenhouse gas emissions from health-care sectors, which, in Australia account for 7% of the nation's footprint.<sup>19</sup> N<sub>2</sub>O dominated the greenhouse emissions from anaesthetic gases in 2017 in England's National Health Service and contributes up to 3% of global N<sub>2</sub>O emissions.<sup>20,21</sup> In a recently released professional document, the Australian and New Zealand College of Anaesthetists advocated for a reduced utilisation of

**TABLE 2** Birth outcomes

Outcome	Nitrous oxide available (n = 121)	Nitrous oxide withheld (n = 122)	Adjusted estimate (95% CI)	P, adjusted
Any analgesia use <sup>†</sup>	89 (74%)	75 (62%)	1.70 (0.92, 3.14)	0.09
Analgesia use other than nitrous oxide <sup>†</sup>	54 (45%)	75 (62%)	0.37 (0.2, 0.69)	0.002
Opioid use <sup>†</sup>	23 (19%)	46 (38%)	0.34 (0.18, 0.63)	<0.001
Epidural use <sup>†</sup>	46 (38%)	53 (43%)	0.76 (0.42, 1.38)	0.37
Labour complications <sup>†</sup>	71 (59%)	85 (70%)	0.77 (0.42, 1.39)	0.38
Post-partum haemorrhage <sup>†</sup>	22 (18%)	21 (17%)	1.17 (0.58, 2.37)	0.66
Natural vaginal delivery <sup>†</sup>	89 (74%)	90 (74%)	0.66 (0.32, 1.36)	0.26
Estimated blood loss, <sup>‡</sup> mL, median (interquartile range (IQR))	350 (250, 538)	350 (250, 500)	1.00 (0.85, 1.17)	0.97
Labour duration, <sup>‡</sup> hours, median (IQR)	3.8 (2.4, 6.3)	4.9 (2.7, 7.2)	1.00 (0.83, 1.19)	0.98
APGAR score at 5 min, <sup>¶</sup> median (IQR)	9.00 (8.00, 9.00)	9.00 (8.00, 9.00)	0.73 (0.38, 1.38)	0.33
APGAR score at 10 min, <sup>¶</sup> median (IQR)	9.00 (9.00, 9.00)	9.00 (9.00, 9.00)	1.36 (0.41, 4.49)	0.62

<sup>†</sup>Odds ratio for the outcome (Yes vs No) for nitrous oxide available/withheld.

<sup>‡</sup>Ratio for a one-unit increase in the outcome for nitrous oxide available/withheld.

<sup>¶</sup>Proportional odds ratio for a higher APGAR score for nitrous oxide available/withheld.

N<sub>2</sub>O as part of an approach to enhance environmental sustainability in anaesthesia.<sup>22</sup> Therefore, this aspect adds significant weight to discussions about future strategies and underpins the responsibility of clinicians, nursing staff and midwives to mitigate risks and provide a sustainable environment and health.<sup>23,24</sup> In any debate on replacing N<sub>2</sub>O with low carbon alternatives, safety outcomes should be balanced against maternal satisfaction; however, these data were not available in our study.

### Strengths

The strength of this study is that it observed the natural phenomenon when a therapeutic option was not available in a labour ward with an established N<sub>2</sub>O regime. Selection bias was eliminated as all eligible women birthing during the study period were included. The large range of demographic, pregnancy, labour and neonatal outcome data collected allowed for assessment of multiple outcomes and statistical adjustment of important potential confounders, such as induction of labour and parity. The sample size was large enough to detect a difference in opioid use.

### Limitations

This study was a single centre assessment; however, demographic data, labour analgesia, delivery mode rates in our population were similar between the two groups and when compared to the Australian national data. In 2018, 65% of Australian women had a vaginal delivery, of which 12.7% had instrumental births. There were 35.3% who had caesarean section. However, induction of labour (IOL) rates for this study population were approximately 10% higher than the 2018 Australian IOL rate of 34.2%.<sup>10</sup> The study size may not have been large enough to detect a difference in outcomes other than opioid use. The total doses of epidural drugs

and opioids were not recorded, but could have provided further information. Maternal and staff satisfaction were not assessed, due to the retrospective nature of this audit.

### CONCLUSION

Although opioid use significantly increased when N<sub>2</sub>O during labour was withheld, there was no increase in epidural use and no significant differences in delivery mode, labour, maternal or neonatal outcomes were observed. Should N<sub>2</sub>O be withheld from clinical practice, this action appears to be safe for labouring women with regard to the maternal and neonatal outcomes assessed in this study.

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### REFERENCES

1. Wapm Working Group on COVID. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. *Ultrasound Obstet Gynecol* 2021; **57**(2): 232–241.
2. Gurol-Urganci I, Jardine JE, Carroll F *et al*. Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: National cohort study. *Am J Obstet Gynecol* 2021; **225**(5): 522.e1–e11.
3. Allotey J, Chatterjee S, Kew T *et al*. SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: Living systematic review and meta-analysis. *BMJ* 2022; **376**: e067696.
4. Breslin N, Baptiste C, Miller R *et al*. Coronavirus disease 2019 in pregnancy: Early lessons. *Am J Obstet Gynecol MFM* 2020; **2**(2): 100111.

5. Gao W, Lv J, Pang Y, Li LM. Role of asymptomatic and pre-symptomatic infections in covid-19 pandemic. *BMJ* 2021; **375**: n2342.
6. Palatnik A, McIntosh JJ. Protecting labor and delivery personnel from COVID-19 during the second stage of labor. *Am J Perinatol* 2020; **37**(8): 854–856.
7. Collins MR, Starr SA, Bishop JT, Baysinger CL. Nitrous oxide for labor analgesia: Expanding analgesic options for women in the United States. *Rev Obstet Gynecol* 2012; **5**(3–4): e126–e131.
8. Lew V, McKay E, Maze M. Past, present, and future of nitrous oxide. *Br Med Bull* 2018; **125**(1): 103–119.
9. Nodine PM, Collins MR, Wood CL *et al.* Nitrous oxide use during labor: Satisfaction, adverse effects, and predictors of conversion to neuraxial analgesia. *J Midwifery Womens Health* 2020; **65**(3): 335–341.
10. Australian Institute of Health and Welfare. Australia's mothers and babies 2018 Available from: <https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-and-babies-2018-in-brief/summary>. Accessed 4/12/2021.
11. Greenhalgh T, Jimenez JL, Prather KA *et al.* Ten scientific reasons in support of airborne transmission of SARS-CoV-2. *Lancet* 2021; **397**(10285): 1603–1605.
12. Bauer ME, Bernstein K, Dinges E *et al.* Obstetric anesthesia during the COVID-19 pandemic. *Anesth Analg* 2020; **131**(1): 7–15.
13. Dashraath P, Wong JLJ, Lim MXK *et al.* Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol* 2020; **222**(6): 521–531.
14. The Society for Obstetric Anaesthesia and Perinatology. COVID-19: The SMFM/SOAP guidelines for labor and delivery. 2020 Available from: <https://www.obgproject.com/2020/03/29/covid-19-the-smfm-soap-guidelines-for-labor-and-delivery/>. Accessed 2/12/2021.
15. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. COVID-19: Protection of midwives and doctors in the birth unit Available from: <https://ranzcog.edu.au/news/covid-19-protection-of-midwives-and-doctors-in-th>. Accessed 2/12/2021.
16. Bobb LE, Farber MK, McGovern C, Camann W. Does nitrous oxide labor analgesia influence the pattern of neuraxial analgesia usage? An impact study at an academic medical center. *J Clin Anesth* 2016; **35**: 54–57.
17. Sutton CD, Butwick AJ, Riley ET, Carvalho B. Nitrous oxide for labor analgesia: Utilization and predictors of conversion to neuraxial analgesia. *J Clin Anesth* 2017; **40**: 40–45.
18. Richardson MG, Lopez BM, Baysinger CL *et al.* Nitrous oxide during labor: Maternal satisfaction does not depend exclusively on analgesic effectiveness. *Anesth Analg* 2017; **124**(2): 548–553.
19. Malik A, Lenzen M, McAlister S, McGain F. The carbon footprint of Australian health care. *Lancet Planetary Health* 2018; **2**(1): e27–e35.
20. Seglenieks R, Wong A, Pearson F, McGain F. Discrepancy between procurement and clinical use of nitrous oxide: waste not, want not. *Br J Anaesth* 2022; **128**(1): e32–e34.
21. Ishizawa Y. Special article: General anesthetic gases and the global environment. *Anesth Analg* 2011; **112**(1): 213–217.
22. McGain F, Ma SC, Burrell RH *et al.* Why be sustainable? The Australian and New Zealand College of Anaesthetists professional document PS64: Statement on environmental sustainability in Anaesthesia and pain medicine practice and its accompanying background paper. *Anaesth Intensive Care* 2019; **47**(5): 413–422.
23. Talley NJ. A sustainable future in health: Ensuring as health professionals our own house is in order and leading by example. *Med J Aust* 2020; **212**(8): 344.
24. Gynter A, Pearson F, McGain F. *Nitrous oxide use on the labour ward: Efficacy and environmental impact*. Melbourne, Australia: Aust N Zeal College Anaesthetists, 2021; 193–202.