

APPENDIX A. Exact Search Strings and Results

Table 1: Preliminary PubMed search strategies

	Preliminary search terms	Preliminary search results
#1	"Nitrous Oxide"[Mesh] OR "nitrous oxide"[tw] OR "N2O"[tw] OR "laughing gas"[tw] OR "Entonox "[Substance Name] OR Entonox[tw] OR Equanox[tw] OR Kalinox[tw] OR Medimix[tw] OR "Dinitrogen Monoxide"[tw] OR Kalinox[tw] OR Medimix[tw] OR "Dinitrogen Monoxide"[tw]	19,052
#2	"Labor Pain"[Mesh] OR "Labor, Obstetric"[Mesh] OR labor[tw] OR "parturition"[MeSH Terms] OR "pregnancy"[MeSH Terms] OR "pregnancy"[tw] OR "Analgesia, Obstetrical"[mh] OR "obstetric"[tw] OR birth[tw] OR childbirth[tw] OR labour[tw] OR intrapartum[tw] OR delivery, obstetric[mh]	867,187
#3	#1 AND #2 AND eng[la] AND humans[mh]	646
#4	#3 AND letter[pt]	27
#5	#3 AND comment[pt]	14
#6	#3 AND case reports[pt]	50
#7	#3 AND review[pt]	72
#8	#3 AND news[pt]	2
#9	#3 AND editorial[pt]	5
#10	#3 AND historical article[pt]	6
#11	#3 AND meta-analysis[pt]	1
#12	#3 NOT (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)	495*

Table 2: EMBASE search strategies

Preliminary search terms		Preliminary search results
#1	nitrous oxide.mp. or nitrous oxide/ or entonox.mp. or nitrous oxide plus oxygen/ or n20.mp. or laughing gas.mp. or equanox.mp. or kalinox.mp. or medimix.mp. or dinitrogen monoxide.mp.	30,451
#2	pregnancy/ or pregnancy.mp. or CHILDBIRTH/ or childbirth.mp. or labor pain.mp. or labor pain/ or obstetric analgesia.mp. or obstetric analgesia/ or delivery/ or delivery.mp. or INTRAPARTUM CARE/ or intrapartum.mp. or LABOR/ or labor.mp.	537,234
#3	#1 AND #2	1,789
#4	Limit #3 to (human and english language)	1,178
#5	Limit #4 to (editorial or letter or "review")	319
#6	#4 NOT #5	859*

Table 3: CINAHL search strategies

Preliminary search terms		Preliminary search results
#1	(MH "Nitrous Oxide") OR "nitrous oxide" OR "N2O" OR "laughing gas" OR Entonox OR Equanox OR Kalinox OR Medimix OR "Dinitrogen Monoxide"	925
#2	(MH "Pregnancy") OR (MH "Childbirth") OR (MH "Labor") OR (MH "Labor Pain") OR "labor pain" OR pregnancy OR childbirth OR birth OR labour OR intrapartum OR (MH "Analgesia, Obstetrical") OR (MH "Delivery")	100,226
#3	#1 AND #2	90
#4	#3 AND PT (Commentary OR Editorial OR Letter OR Review)	21
#5	#3 NOT #4	69

APPENDIX B. Sample Data Abstraction Forms

Nitrous Oxide for the Management of Labor Pain CER Abstract Review Form

First Author, Year: _____

EndNote Ref ID #: _____

Abstractor Initials: ___ ___

Retain for:

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude reviews, editorials, commentaries, letters to editor, etc.)	Yes	No	Cannot Determine
2. Study size ≥ 20 pregnant women in labor (record N if study size < 20: ____) OR addresses harms or occupational exposures	Yes	No	Cannot Determine
3. Relevant to CER topic If "No", select at least one of the following reasons: a. ____ Other pain management b. ____ Termination of pregnancy c. ____ Retained placenta and perineal repairs d. ____ Other _____	Yes	No	Cannot Determine
4. Study published in English	Yes	No	Cannot Determine

____ BACKGROUND/DISCUSSION

____ REVIEW OF REFERENCES

____ OTHER _____

COMMENTS:

Nitrous Oxide for the Management of Labor Pain Full-text Review Form

First Author, Year: _____

EndNote Ref ID #: _____

Abstractor Initials: _____

Primary Inclusion/Exclusion Criteria		
5. Original research (exclude reviews, editorials, commentaries, letters to editor, etc.) If yes, record the following: Comparison group: Randomized (NA if no comparison group): <input type="checkbox"/> Yes <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> No <input type="checkbox"/> Not reported <input type="checkbox"/> Not reported/NA	Yes	No
6. Study size \geq 20 pregnant women in labor (record N if study size < 20: _____) OR addresses harms or occupational exposure during labor	Yes	No
7. Relevant to CER topic If "No", select at least one of the following reasons: a. ___ Other pain management b. ___ Termination of pregnancy c. ___ Retained placenta and perineal repairs d. ___ Other _____	Yes	No
8. Study published in English	Yes	No
9. Does study answer any of the following key questions? (circle applicable questions)	Yes	No
<p>KQ1. What is the effectiveness of nitrous oxide when compared to other methods for the management of labor pain among women intending a vaginal birth?</p> <p>KQ2. What is the comparative effectiveness of nitrous oxide on women's satisfaction with their birth experience and pain management?</p> <p>KQ3. What is the comparative effectiveness of nitrous oxide on the route of birth?</p> <p>KQ4. What is the nature and frequency of adverse effects associated with the use of nitrous oxide for the management of labor pain, including but not limited to:</p> <ul style="list-style-type: none"> • Maternal adverse effects, such as nausea and vomiting, dizziness, unconsciousness, and postpartum complications. • Fetal/neonatal adverse effects, such as low Apgar scores and abnormal fetal cord blood gases. • Childhood adverse effects, such as drug dependency and developmental complications. • Adverse effects on health care providers and other individuals present for labor. <p>KQ5. What are the health system factors influencing the use of nitrous oxide for the management of labor pain, including but not limited to provider preferences, availability, setting, and resource utilization?</p>		
10. If you answered YES to all questions, please review references and note relevant citation numbers below:		

Retain for: ___ **BACKGROUND/DISCUSSION** ___ **REVIEW OF REFERENCES** ___ **OTHER** _____

COMMENTS:

APPENDIX C. Evidence Tables

Tables are sorted by last name of first author.

Table 1. List of Acronyms/Abbreviations/Symbols

±	plus or minus
≤	less than or equal to
≥	greater than or equal to
%	percent
ACGIH	American Conference of Governmental Industrial Hygienists
AE	adverse events
AHRQ	Agency for Healthcare Research Quality
ANSI	American National Standard Institute
BUN	blood urea nitrogen
CGA	Compressed Gas Association
CI	confidence interval(s)
CINAHL	Cumulative Index to Nursing and Allied Health Literature
cm	centimeter
DHHS	Department of Health and Human Services
etc.	et cetera
EPA	U.S. Environmental Protection Agency
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
fl	fluid liter
g	gram(s)
g/dl	gram per dekaliter
g/ml	grams per milliliter
Hb	hemoglobin
IM	Intramuscular
JCAHO	Joint Commission on Accreditation of Healthcare Organization
Kg	kilogram
KQ	key question
mcM/L	micrometer per liter
mcmol/L	micromolar
mEq/L	milliequivalents per liter
Mg	milligram
mg/dl	milligrams per decilitre
min	minute(s)
ml	milliliter
mm	millimeter
mmHg	millimeters of mercury
mOsm/kg	milliosmoles per kilogram of water
mU/min	milliunits per minute
n, N	number
NACS	Neonatal Psychological Assessment

NFPA	National Fire Protection Association
NIOSH	National Institute for Occupational Health and Safety
NOQAS	Newcastle-Ottawa Quality Assessment Scale
NR	not recorded
NS	not significant
N ₂ O	nitrous oxide
OSHA	Occupational Safety and Health Administration
O ₂	oxygen
P, p	p value
pH	power of hydrogen
PICOTS	Population(s), Intervention(s), Outcome(s), Timing, Setting
PCO ₂	partial pressure of carbon dioxide
PO ₂	oxygen partial pressure
ppm	parts per million
pt	patient
RCT	randomized control trial
REL	recommended exposure limit
ROB	Cochrane Risk of Bias
RR	relative risk
SD	standard deviation
SE	standard error
SGA	small for gestational age
TENS	transcutaneous electric nerve stimulation
TEP	technical expert panel
TLV	threshold limit value
torr	non-SI unit of pressure
TSCA	Toxic Substances Control Act
UCSF	University of California, San Francisco
U.S.	United States
USP	United States Pharmacopeia
VAS	visual analogue scale
vs., v	versus
w/	with
wk(s)	week(s)
yr(s)	year(s)
µg/l	micrograms per liter

Evidence Table: Nitrous Oxide for Management of Labor Pain

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Abboud et al., 1995</p> <p>Country: US</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Healthy parturients undergoing normal vaginal delivery <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Clinically significant history of gastrointestinal, hepatic, renal, endocrine or respiratory disease, convulsive or neurological disorders • Fetal distress or any history of chronic alcohol or drug use 	<p>Groups: G1: N₂O in 30-60% O₂, mixed and administered by an anesthesiologist and initiated during the second stage of labor G2: Desflurane 1-4.5% and O₂, mixed and administered by an anesthesiologist and initiated during the second stage of labor</p> <p>N at enrollment: G1: 40 G2: 40</p> <p>N at follow-up: (24 hours) G1: 40 G2: 40</p> <p>Age, mean yrs ± SD: G1: 25.7 ± 5.7 G2: 26.3 ± 5.7</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): G1: 27 (67.5) G2: 28 (70.0)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain, %: (5 point scale from 0-4) Satisfactory (3 or 4):¹ Maternal report: G1: 63 G2: 63 Anesthesiologist report: G1: 63 G2: 58 Obstetrician report: G1: 55 G2: 50</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal: Birth amnesia: G1: 0 G2: 9 (22.5) G1/G2: <i>P</i> < 0.05 Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 35 (87.5) G2: 31 (77.5) Assisted:² G1: 5 (12.5) G2: 9 (22.5) Cesarean: G1: 0 G2: 0</p>	<p>Satisfaction with pain management, %: Participant would accept same treatment again: G1: 90 G2: 93</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: Blood loss, ml, mean: G1: 335 G2: 364</p> <p>Neonatal status, n (%): Apgar score < 7: 1 minute: G1: 3 (8) G2: 5 (13) 5 minutes: G1: 0 G2: 0 NACS < 35: 2 hours: G1: 7 (18) G2: 4 (10) 24 hours: G1: 3 (8) G2: 0</p> <p>Adverse effects: NR</p>

Comments:

¹ Physician scale ranges from 0 (no demonstrable analgesia) to 4 (no observable signs of pain); patient scale ranges from 0 (none or worse) to 4 (absolutely no pain).

² Includes forceps and vacuum

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Abboud et al., 1989</p> <p>Country: US</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women undergoing normal vaginal delivery <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: N₂O 30-60% in O₂ administered continuously by an anesthesiologist until moment of birth G2: Isoflurane 0.2-0.7% in O₂ administered continuously by an anesthesiologist until moment of birth</p> <p>N at enrollment: G1: 30 G2: 30</p> <p>N at follow-up: G1: 30 G2: 30</p> <p>Age: NR¹</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: G1: NR G2: 20 mg ketamine (for difficult forceps delivery)</p> <p>Pain management, %: No local anesthetic for delivery: G1: 53 G2: 47</p> <p>Local infiltration: G1: 3 G2: 0</p> <p>Pudendal nerve block: G1: 27 G2: 20</p> <p>Epidural: G1: 7 G2: 7</p> <p>Epidural and pudendal: G1: 10 G2: 26</p> <p>Duration of prepartum analgesia, minutes, mean ± SD: G1: 14.7 ± 2.2 G2: 13 ± 2.4</p>	<p>Pain, %: (scale from 0 to 4)² Satisfactory (3 or 4): Mother: G1: 87 G2: 83</p> <p>Anesthesiologist: G1: 97 G2: 90</p> <p>Obstetrician: G1: 83 G2: 87</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, %:³ Vaginal: G1: > 83 G2: > 83</p> <p>Assisted: G1: < 17 G2: < 17</p> <p>Cesarean: G1: 0 G2: 0</p>	<p>Satisfaction with pain management, %: Shortly after delivery, answered "yes" to "would you have the same agent again?": G1: 93 G2: 93</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: Blood loss estimated ml, mean ± SD: G1: 350 ± 22 G2: 320 ± 24</p> <p>Hemoglobin, g/100 ml, mean ± SD: Antepartum: G1: 12.7 ± 0.2 G2: 13.2 ± 0.2 12-24 hours postpartum: G1: 11.0 ± 0.3 G2: 11.6 ± 0.2</p> <p>Hematocrit, mean % ± SD: Antepartum: G1: 38.2 ± 0.6 G2: 39.3 ± 0.7 12-24 hours postpartum: G1: 33.1 ± 0.8 G2: 35.1 ± 0.7</p> <p>Serum fluoride level < 5.6 mcmol/L, n (%): Before anesthesia, G1: 30 (100) G2: 30 (100) 12-24 hours postpartum: G1: 30 (100) G2: 30 (100)</p> <p>Urine fluoride level, mcmol/L, mean ± SD: Before anesthesia: G1: 38.9 ± 5.8 G2: 41.4 ± 4.6 12-24 hours postpartum: G1: 23.62 ± 2.2</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Abboud et al., 1989 (continued)				<p>G2: 36.5 ± 3.1 G1/G2: <i>P</i> < 0.05</p> <p>Neonatal status: Apgar score, 1 minute, %: 0-4: G1: 0 G2: 0 5-7: G1: 7 G2: 7 8-10: G1: 93 G2: 93</p> <p>Apgar score, 5 minutes, %: 0-4: G1: 0 G2: 0 5-7: G1: 0 G2: 0 8-10: G1: 100 G2: 100</p> <p>pH, mean ± SD: Umbilical vein: G1: 7.33 ± 0.01 G2: 7.34 ± 0.01 Umbilical artery: G1: 7.27 ± 0.01 G2: 7.28 ± 0.01</p> <p>PCO₂ mmHg, mean ± SD: Umbilical vein: G1: 42.4 ± 1.2 G2: 41 ± 1.3 Umbilical artery: G1: 51.5 ± 1.5 G2: 50 ± 1.9</p> <p>Base excess mEq/L, mean ± SD: Umbilical vein: G1: -2.8 ± 0.4 G2: -3 ± 0.3 Umbilical artery: G1: -2.2 ± 0.5 G2: -3 ± 0.5</p> <p>PO₂ mmHg, mean ± SD: Umbilical vein: G1: 32.1 ± 1.4 G2: 33 ± 1.4</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Abboud et al., 1989 (continued)				<p>Umbilical artery: G1: 20.1 ± 1.1 G2: 20 ± 0.9</p> <p>O₂ saturation, mean % ± SD: Umbilical vein: G1: 55.7 ± 2.4 G2: 58 ± 2.9 Umbilical artery: G1: 26.1 ± 2.2 G2: 26 ± 2.4</p> <p>Urine fluoride levels from first voided urine < 5.6 mcmol/L, n (%): G1: 30 (100) G2: 30 (100)</p> <p>Adverse effects: Maternal: Partial amnesia, n: G1: 0 G2: 1⁴</p> <p>Neonatal: NR Childhood: NR Occupational: NR</p>

Comments:

¹ Authors state maternal age was slightly higher in G1.

² Physician scale ranges from 0 (no demonstrable analgesia) to 4 (no observable signs of pain); patient scale ranges from 0 (none or worse) to 4 (absolutely no pain).

³ Authors report that more than 83% of parturients in both groups had spontaneous vaginal deliveries; the rest were delivered by forceps.

⁴ Parturient had difficult forceps delivery and 20 mg of ketamine.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Author: Abboud et al., 1981 Country: US Participant source: NR Setting: Hospital Enrollment period: NR Design: RCT ***** Inclusion criteria: • Normal vaginal delivery Exclusion criteria: • See inclusion criteria	Groups: G1: N ₂ O, 30% to 60% and O ₂ administered by anesthesiologist G2: Enflurane, 0.25% to 1.25% and O ₂ N at enrollment: G1: 50 G2: 55 N at follow-up: G1: 50 G2: 55 Age, mean yrs (SE): G1: 25.1 (0.9) G2: 23.4 (0.7)	Provider preferences: NR Provider specialty, %: Obstetrician: Total: 100 Cost of intervention: NR Other pain management methods available: Single- or multiple-dose meperidine intramuscular (IM), single-dose alpha-prodine subcutaneous (SC), local infiltration; pudendal block Pain management, %: Narcotic analgesia: < 1 hour before delivery: G1: 10 G2: 7 1-2 hours before delivery: G1: 12 G2: 14.5 > 2 hours before delivery: G1: 22 G2: 14.5 None: G1: 56 G2: 64 Single-dose meperidine IM: G1: 10 G2: 4 Multiple-dose meperidine IM: G1: 10 G2: 6 Single-dose alphaprodine SC: G1: 24 G2: 27 Local anesthesia: None: G1: 56	Pain: (5 point scale 0-4) ¹ Satisfactory (3 or 4), shortly after delivery, %: Mother: G1: 76 G2: 89 Anesthesiologist: G1: 70 G2: 80 Obstetrician: G1: 58 G2: 84 G1/G2: <i>P</i> < 0.05 Labor progress: NR Fetal status: NR Timeliness: NR Labor co-interventions: NR Adverse effects: Maternal: Estimated blood loss, ml, mean (SE): G1: 327 (13) G2: 321 (15) Neonatal: NR Occupational: NR Route of birth, %: Vaginal spontaneous: G1: 82 G2: 82 Assisted: Outlet forceps: G1: 10 G2: 14 Mid-forceps: G1: 2 G2: 2 Vacuum: G1: 6 G2: 2 Cesarean: Not applicable	Satisfaction with pain management: (asked shortly after delivery) “Would you have the same agent again?”, %: Yes: G1: 86 G2: 96 No: G1: 12 G2: 2 Maybe: G1: 2 G2: 2 Satisfaction with birth experience: NR Maternal status: Hemoglobin, g/100 ml, mean (SE): Antepartum: G1: 12.8 (0.2) G2: 12.9 (0.2) 12-24 hrs postpartum: G1: 12.0 (0.2) G2: 11.5 (0.2) Hematocrit, mean % (SE): Antepartum: G1: 38.0 (0.6) G2: 38.2 (0.5) 12-24 hrs postpartum: G1: 35.4 (0.6) G2: 34.4 (0.6) Blood sodium, meq/L, mean (SE): Before anesthesia: G1: 137 (0.3) G2: 137 (0.3) 12-24 hrs postpartum: G1: 138 (0.2) G2: 138 (0.3) Blood potassium, meq/L, mean (SE): Before anesthesia: G1: 4.0 (0.04) G2: 3.9 (0.04) 12-24 hrs postpartum: G1: 4.0 (0.1) G2: 4.0 (0.1) Blood chloride, meq/L,

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Abboud et al., 1981 (continued)		<p>G2: 51</p> <p>Local infiltration: G1: 14 G2: 16</p> <p>Pudendal block: G1: 30 G2: 33</p> <p>Duration of prepartum analgesia, minutes, mean (SE): G1: 13.5 (1.5) G2: 14.7 (1.2)</p>		<p>mean (SE):</p> <p>Before anesthesia: G1: 103 (0.3) G2: 103 (0.3)</p> <p>12-24 hrs postpartum: G1: 102 (0.2) G2: 103 (0.3)</p> <p>Blood bicarbonate, meq/L, mean (SE):</p> <p>Before anesthesia: G1: 17.7 (0.3) G2: 18.6 (0.3) G1/G2: $P < 0.05$</p> <p>12-24 hrs postpartum: G1: 22.7 (0.3) G2: 22.4 (0.3)</p> <p>Blood BUN, mg/100 ml, mean (SE):</p> <p>Before anesthesia: G1: 8.1 (0.4) G2: 8.2 (0.3)</p> <p>12-24 hrs postpartum: G1: 8.1 (0.3) G2: 7.9 (0.3)</p> <p>Blood creatinine, mg/100 ml, mean (SE):</p> <p>Before anesthesia: G1: 0.7 (0.02) G2: 0.7 (0.01)</p> <p>12-24 hrs postpartum: G1: 0.7 (0.01) G2: 0.7 (0.02)</p> <p>Blood uric acid, mg/100 ml, mean (SE):</p> <p>Before anesthesia: G1: 5.1 (0.1) G2: 5.3 (0.1)</p> <p>12-24 hrs postpartum: G1: 5.3 (0.2) G2: 5.4 (0.1)</p> <p>Blood osmolality, mOsm/kg, mean (SE):</p> <p>Before anesthesia: G1: 281 (0.8) G2: 280 (0.6)</p> <p>12-24 hrs postpartum: G1: 284 (0.6) G2: 282 (0.6)</p> <p>Serum fluoride, mcM/L, mean (SE):</p> <p>Before anesthesia: G1: 1.6 (0.1) G2: 1.4 (0.1)</p> <p>12-24 hrs postpartum:</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Abboud et al., 1981 (continued)				<p>G1: 1.5 (0.1) G2: 1.6 (0.1)</p> <p>Urine sodium, meq/L, mean (SE): Before anesthesia: G1: 142 (8.5) G2: 130 (6.8) 12-24 hrs postpartum: G1: 93.7 (7.7) G2: 88.2 (5.3)</p> <p>Blood potassium, meq/L, mean (SE): Before anesthesia: G1: 76.4 (6.5) G2: 83.7 (7.5) 12-24 hrs postpartum: G1: 39.3 (2.9) G2: 39.0 (3.4)</p> <p>Urine osmolality, mOsm/kg, mean (SE): Before anesthesia: G1: 599 (36.0) G2: 615 (32.7) 12-24 hrs postpartum: G1: 468 (28.8) G2: 480 (28.3)</p> <p>Urine fluoride, mcM/L, mean (SE): Before anesthesia: G1: 18.3 (2.2) G2: 20.0 (2.1) 12-24 hrs postpartum: G1: 15.9 (3.4) G2: 34.4 (4.0) G1/G2: <i>P</i> < 0.05</p> <p>Neonatal status: Birth weight, g, mean (SE): G1: 3,304 (61) G2: 3,461 (57)</p> <p>Apgar score, 1 minute, %: 0-4: G1: 0 G2: 2 5-7: G1: 6 G2: 6 8-10: G1: 94 G2: 92</p> <p>Apgar score, 5 minutes, %:</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Abboud et al., 1981 (continued)				<p>0-4: G1: 0 G2: 0</p> <p>5-7: G1: 6 G2: 6</p> <p>8-10: G1: 94 G2: 92</p> <p>Blood gases pH, mean (SE): Umbilical vein: G1: 7.34 (0.01) G2: 7.34 (0.01) Umbilical artery: G1: 7.27 (0.01) G2: 7.26 (0.01)</p> <p>Blood gases PCO₂, torr, mean (SE): Umbilical vein: G1: 35.6 (0.9) G2: 35.5 (0.7) Umbilical artery: G1: 42.5 (1.6) G2: 44.5 (1.1)</p> <p>Blood gases PO₂, torr, mean (SE): Umbilical vein: G1: 28.1 (0.9) G2: 30.5 (1.0) Umbilical artery: G1: 16.9 (0.7) G2: 17.9 (0.7)</p> <p>Blood gases base excess, meq/L, mean (SE): Umbilical vein: G1: -5.6 (0.4) G2: -6.3 (0.3) Umbilical artery: G1: -7.0 (0.6) G2: -6.3 (0.5)</p> <p>Blood gases calculated O₂ saturation, mean %: Umbilical vein: G1: 63.5 G2: 69 Umbilical artery: G1: 28 G2: 31</p> <p>Urine sodium, meq/L, mean (SE): G1: 17.9 (2.1)</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Abboud et al., 1981 (continued)				<p>G2: 17.9 (2.0)</p> <p>Blood potassium, meq/L, mean (SE): G1: 23.3 (1.6) G2: 22.7 (1.7)</p> <p>Urine osmolality, mOsm/kg, mean (SE): G1: 167 (16.6) G2: 164 (19.9)</p> <p>Serum fluoride levels, umbilical cord, mcM/L, mean (SE): G1: 1.8 (0.1) G2: 2.4 (0.2) G1/G2: $P < 0.05$</p> <p>Urine fluoride levels first voided urine, mcM/L, mean (SE): G1: 3.5 (0.3) G2: 4.0 (0.5)</p> <p>Adverse effects: Maternal: Complete amnesia for delivery, %: G1: 10 G2: 7</p> <p>Neonatal: NR Childhood: NR Occupational: NR</p>

Comments:

¹ Physician scale ranges from 0 (no demonstrable analgesia) to 4 (no observable signs of pain); patient scale ranges from 0 (none or worse) to 4 (absolutely no pain).

Evidence Table: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Ahlborg et al., 1996</p> <p>Country: Sweden</p> <p>Participant source: Community</p> <p>Setting: NR</p> <p>Enrollment period: 01/1989 to 12/1989</p> <p>Design: Trend</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women born in 1940 or after • Found in membership files of the Swedish Midwives Association in 1989 • Most recent pregnancy only <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Termination prior to 1983 	<p>Groups: G1: Midwives exposed to N₂O during deliveries Ga: > 30 N₂O deliveries per month Gb: 21-30 N₂O deliveries per month Gc: 11-20 N₂O deliveries per month. Gd: 1-10 N₂O deliveries per month Ge: 0 N₂O deliveries per month</p> <p>N at enrollment: (questionnaires returned) G1a: 41 G1b: 43 G1c: 136 G1d: 160 G1e: 346</p> <p>N at follow-up: G1a: 41 G1b: 43 G1c: 136 G1d: 160 G1e: 346</p> <p>Age, yrs: ≤ 29: Total: 196 30-34: Total: 386 ≥ 35: Total: 169</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR Childhood: NR Occupational: Became pregnant in first cycle, %: G1a: 14.6 G1b-d: 37.3 G1e: 42.8 Number of cycles to conception, women pregnant within 13 cycles, mean: G1a: 4.6 G1b: 3.1 G1c: 3.0 G1d: 2.8 G1e: 3.1 > 13 cycles to pregnancy, %: G1a: 29 G1b: 7 G1c: 8 G1d: 6 G1e: 10 Fecundability ratio, crude: G1a: 0.51 G1b: 1.10 G1c: 0.98 G1d: 1.10 G1e: 1.0 Fecundability ratio, adjusted (95% CI): G1a: 0.63 (0.43-0.94) G1b: 1.19 (0.89-1.59) G1c: 1.05 (0.86-1.28) G1d: 1.18 (0.98-1.41) G1e: 1.0</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Arfeen et al., 1994</p> <p>Country: Scotland</p> <p>Participant source: NR</p> <p>Setting: NR</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Healthy mothers • Normal medical and obstetric history • In first stage of labor • Cervical dilation > 2 cm <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: Entonox. Breathed during contractions. G2: Epidural analgesia. Maintained with infusion of 20 ml/hr of 0.1% plain bupivacaine, bolus injections of 0.25% bupivacaine if needed.</p> <p>N at enrollment: (1st stage of labor) G1: 20 G2: 20</p> <p>N at follow-up: (completed study) G1: 19 G2: 18</p> <p>Age, median yrs (range): G1: 26.0 (20-36) G2: 27.5 (21-45)</p> <p>Race/ethnicity: NR</p> <p>Parity, median (range): G1: 1 (0-3) G2: 0 (0-4) G1/G2: $P = 0.02^1$</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain, n: G1: NR G2: 0</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: At least 1 desaturation, n (%): G1: 8 (42) G2: 6 (33) G1/G2: $P = NS$ Total number of desaturations, n (% of time): G1: 74 (2.37) G2: 31 (1.08) G1/G2: $P = 0.002^2$ Hypoxic episodes, n: G1: 29 G2: 21 Duration of hypoxic episodes, seconds, mean: G1: 30.6 G2: 17.7 G1/G2: $P = 0.002^1$ Hypoxic episodes, median severity, % (range): G1: 88 (84-89) G2: 89 (86-89) G1/G2: $P = 0.03^1$</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: Median SpO₂ (range): G1: 96.0 (84-100) G2: 95.0 (86-99) G1/G2: $P = NS$</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Comments:

¹ Mann-Whitney test.

² Chi-squared test.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Arora et al., 1992</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> •Normal labor with regular painful uterine contractions •Required inhalational analgesia <p>Exclusion criteria:</p> <ul style="list-style-type: none"> •See inclusion criteria 	<p>Groups: G1: Participants received Entonox or Entonox-isoflurane for five contractions, room air for one contraction, then the other agent for five contractions G1a: Received Entonox first G1b: Received Entonox-isoflurane first</p> <p>N at enrollment: (In labor) G1: 41</p> <p>N at follow-up: G1: 39 G1a: 19 G1b: 20</p> <p>Age, mean yrs: G1: 28.7</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): G1: 16 (41.0)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Oxytocin, diamorphine, epidural</p> <p>Pain management, n (%): Oxytocin: G1:13 (33.3) Diamorphine: G1:19 (48.7) Epidural: G1:2 (5.1)</p>	<p>Pain, mean ± SD (median): Linear visual analog scale G1a: 5.8 ± 1.5 (5.0) G1b: 7.0 ± 1.5 (7.0) G1a/G1b: <i>P</i> = 0.001</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal, n (%): Dizziness: G1: 5 (12.8) G1a: 1 (5.2) G1b: 4 (20.0) Unpleasant or nauseating odor: G1a: NR G1b: 6 (30.0) Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 25 (64.1) Assisted: G1: 9 (23.1) Cesarean: G1: 5 (12.8)</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects, n (%): Maternal: NR Neonatal: Apgar-minus-color score < 8: G1: 20 (51.3) Childhood: NR Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Arthurs et al., 1979</p> <p>Country: United Kingdom</p> <p>Participant source: NR</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women in labor who chose to use nitrous oxide <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: N₂O mix 50/50 administered intermittently by mask plus continuous N₂O mix 50/50 via nasal cannula G2: N₂O 50/50 administered intermittently by mask</p> <p>N at enrollment: G1: 24 G2: 25</p> <p>N at follow-up: G1: 22 G2: 22</p> <p>Age : NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n: G1: 13 G2: 10</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Pethidine, epidural</p> <p>Pain management, n (%): Pethidine: G1: 19 (79) G2: 22 (88)</p> <p>Epidural: G1: 3 (NR) G2: 4 (NR)</p>	<p>Pain: (0% to 100%)¹ Linear analogue score, mean increase ± SD: After 2 contractions: G1: 0.3 ± 16.2 G2: 11.5 ± 14.6 After 4 contractions: G1: 5.7 ± 17.0 G2: 17.9 ± 12.1</p> <p>Pain relief, after 4 contractions, n (%): Pain had increased: G1: 21 (84) G2: 4 (17) No change: G1: 4 (16) G2: 7 (29) Pain had decreased: G1: 0 G2: 13 (54) G1/G2: <i>P</i> < 0.0005</p> <p>Pain relief, midwife report: Complete: G1: 7 (29) G2: 1 (4) Considerable: G1: 15 (63) G2: 15 (60) Slight: G1: 2 (8) G2: 9 (36) G1/G2: <i>P</i> = 0.02</p> <p>None: G1: 0 G2: 0</p> <p>Labor progress: Duration of labor, hours:minutes, mean (SE): G1: 7:54 (0:48) G2: 8:42 (1:07)</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status, n (%): Too drowsy, midwife report: G1: 2 (8) G2: 2 (8) Restless, midwife report: G1: 2 (8) G2: 8 (32) Non-cooperative, midwife report: G1: 0 G2: 1 (4)</p> <p>Neonatal status: Apgar score, mean ± SD: 1 minute: G1: 7.8 ± 1.9 G2: 7.7 ± 1.9 5 minutes: G1: 9.6 ± 0.7 G2: 9.3 ± 1.1</p> <p>Adverse effects: Maternal: Hazy memory of labor: G1: 13 (54) G2: 7 (28)</p> <p>Memory of delivery: Hazy: G1: 2 (8) G2: 4 (16) None: G1: 1 (4) G2: 0</p> <p>Neonatal: NR Childhood: NR Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Arthurs et al., 1979 (continued)			<p>Adverse effects, n (%):Maternal:</p> <p>Nausea during labor: G1: 8 (33) G2: 9 (36)</p> <p>Vomiting during labor: G1: 6 (25) G2: 11 (44)</p> <p>Dreams: G1: 6 (25) G2: 7(28)</p> <p>Paraesthesia: G1: 8 (33) G2: 10 (40)</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth:</p> <p>Vaginal: NR</p> <p>Assisted: NR</p> <p>Cesarean: G1: 1 G2: 1</p>	

Comments:

¹ 0% = no pain, 100% = max pain

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Axelsson et al., 1996</p> <p>Country: Sweden</p> <p>Participant source: Community</p> <p>Setting: NR</p> <p>Enrollment period: 01/1989 to 12/1989</p> <p>Design: Cross-sectional</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Female members of Swedish midwives association Born 1940 or later Worked more than half the time during first trimester Information on background variables was complete <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Ongoing pregnancy at time of questionnaire Pregnancies before 1980 Ectopic pregnancies Women with five or more spontaneous abortions 	<p>Groups: G1: Midwives exposed to N₂O during deliveries G1a: Midwives using N₂O for > 50% of deliveries G1b: Midwives using N₂O for ≤ 50% of deliveries G2: Midwives not using N₂O</p> <p>N at enrollment: NR</p> <p>N at follow-up, n (%): G1a: 705 G1b: 538 G2: 1,262</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal: NR Neonatal: NR Occupational: Spontaneous abortions: G1a: 111/705 (15.7) G1b: 71/538 (13.2) G2: 168/1,262 (13.3) Spontaneous abortions, women who worked as a midwife during the first trimester:¹ G1a: 98/624 (15.7) G1b: 65/495 (13.1) G2: 89/598 (14.8)</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR Childhood: NR Occupational: Spontaneous abortion, nitrous oxide exposure odds ratio, crude: G1a: 1.22 G1b: 0.99 G2: 1.0 Spontaneous abortion, nitrous oxide exposure odds ratio, adjusted (95% CI): G1a: 1.17 (0.84-1.62) G1b: 0.95 (0.66-1.35) G2: 1.0 Spontaneous abortions, women who worked as a midwife during the first trimester, n:¹ All: G1a: 98 G1b: 65 G2: 89 Early: G1a: 77 G1b: 50 G2: 73 Late: G1a: 21 G1b: 15 G2: 19 Spontaneous abortion, nitrous oxide exposure odds ratio, women who worked as a midwife during the first</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Axelsson et al., 1996 (continued)				<p>trimester, crude:* All: G1a: 1.07 G1b: 0.86 G2: 1.0 Early: G1a: 1.02 G1b: 0.81 G2: 1.0 Late: G1a: 1.27 G1b: 1.11 G2: 1.0</p> <p>Spontaneous abortion, nitrous oxide exposure odds ratio, women who worked as a midwife during the first trimester, adjusted (95% CI):¹ All: G1a: 0.95 (0.62-1.47) G1b: 0.75 (0.48-1.19) G2: 1.0 Early: G1a: 0.94 (0.58-1.53) G1b: 0.70 (0.42-1.17) G2: 1.0 Late: G1a: 1.05 (0.44-2.52) G1b: 1.02 (0.41-2.53) G2: 1.0</p>

Comments:

¹ About a third of the pregnancies occurred when the woman had an occupation other than midwife (e.g., nurse).

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Beppu, 1968</p> <p>Country: Japan</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Fit volunteers in normal labor • Uncomplicated pregnancies and onset of labor between the 38th and 42nd weeks <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: N₂O (50-80%) and O₂, delivery method NR G1a: Vaginal delivery G1b: Caesarean delivery</p> <p>N at enrollment: G1: 26 G1a: 20 G1b: 6</p> <p>N at follow-up: G1: 26 G1a: 20 G1b: 6</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: G1a: NR G1b: 0.5 mg atropine, 50 mg meperidine for premedication of anesthesia; halothane</p> <p>Pain management: Inhalation time, minutes, mean (range): G1a: 28 (4-108) G1b: 24 (18-36)</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n (%): Vaginal: G1: 20 (76.9) Assisted: NR Cesarean: G1: 6 (23.1)</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: Nitrous oxide concentration, mg/dl, mean ± SD: Cubital artery: G1a: 23.82 ± 14.55 G1b: 26.25 ± 13.40 Cubital vein: G1a: 16.85 ± 10.60 G1b: 25.76 ± 10.70</p> <p>Neonatal status: Nitrous oxide concentration, mg/dl, mean ± SD: Intravillous space: G1a: NR G1b: 24.50 ± 8.90 Umbilical artery: G1a: 7.51 ± 3.67 G1b: 18.43 ± 3.46 Umbilical vein: G1a: 11.02 ± 7.25 G1b: 18.50 ± 6.00</p> <p>Apgar score, mean (range): G1a: 8.8 (6-9) G1b: 8.8 (6-9)</p> <p>Adverse effects: Maternal: NR</p> <p>Neonatal, n: Asphyxia: G1a: 0 G1a: 0</p> <p>Sleepy baby: G1a: 2 G1a: 0</p> <p>Childhood: NR Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Author: Beppu, 1968 Country: Japan Participant source: Community Setting: Hospital Enrollment period: NR Design: Prospective cohort ***** Inclusion criteria: NR Exclusion criteria: NR	Groups: G1: Infant of mother who received N ₂ O mix (% and delivery method NR) G2: Infant of mother who received trichloroethylene G3: Infant of mother who received halothane N at enrollment: G1: 148 G2: 210 G3: 283 N at follow-up: G1: 148 G2: 210 G3: 283 Age: NR Race/ethnicity: NR Parous: NR	Provider preferences: NR Provider specialty: NR Cost of intervention: NR Other pain management methods available: NR Pain management: NR	Pain: NR Labor progress: NR Fetal status: NR Timeliness: NR Labor co-interventions: NR Adverse effects: NR Route of birth: NR	Satisfaction with pain management: NR Satisfaction with birth experience: NR Maternal status: NR Neonatal status, n (%): Asphyxia, Cazean's classification: None: G1: 141 (95.27) G2: 199 (94.76) G3: 267 (95.06) First degree: G1: 5 (3.38) G2: 8 (3.81) G3: 10 (3.53) Second degree: G1: 2 (1.35) G2: 3 (1.43) G3: 4 (1.41) Asphyxia, Flagg's classification: None: G1: 139 (93.91) G2: 196 (93.34) G3: 267 (94.36) First degree: G1: 6 (4.05) G2: 10 (4.76) G3: 10 (3.53) Second degree: G1: 2 (1.35) G2: 2 (0.95) G3: 4 (1.41) Third degree: G1: 1 (0.69) G2: 2 (0.95) G3: 2 (0.70) Asphyxia, Lund's classification: None: G1: 138 (93.24) G2: 196 (93.34) G3: 265 (93.64) Slight: G1: 7 (4.72) G2: 10 (4.76) G3: 12 (4.24) Moderate:

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Beppu, 1968 (continued)				G1: 2 (1.35) G2: 2 (0.95) G3: 3 (1.06) Severe: G1: 1 (0.69) G2: 2 (0.95) G3: 3 (1.06) Asphyxia, Silverman's classification: 0 point: G1: 128 (86.50) G2: 190 (90.49) G3: 269 (91.53) 1 point: G1: 12 (8.10) G2: 14 (6.66) G3: 17 (6.00) 2 points: G1: 6 (4.05) G2: 4 (1.90) G3: 4 (1.41) ≥ 3 points: G1: 2 (1.35) G2: 2 (0.95) G3: 3 (1.06) Adverse effects: NR

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Bergsjø and Lindbaek, 1971</p> <p>Country: Norway</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Crossover RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women with established labor with obvious pain • Delivery was expected to be normal <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Women with a history of liver and kidney disease • Anticipated difficult delivery 	<p>Groups: G1: N₂O 50% /O₂ 50% (Entonox) inhaled through face mask working by demand flow used first G2: Methoxyflurane used first Ga: N₂O chosen as preferred drug Gb: Methoxyflurane chosen as preferred drug Gc: Undecided on drug preference</p> <p>All patients tried both N₂O and methoxyflurane, the order decided at random; patients then selected the preferred agent to use during labor.</p> <p>N at enrollment: G1: 26 G2: 37</p> <p>N at follow-up: G1: 26 G1a: 14 G1b: 12 G1c: 0 G2: 37 G2a: 26 G2b: 10 G2c: 1</p> <p>Age, n (%): < 20: G1: 0 G2: 4 (10.8) 20-29: G1: 16 (61.5) G2: 27 (73.0) ≥ 30: G1: 10 (38.5) G2: 6 (16.2)</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primigravidae: G1: 16 (61.5) G2: 23 (62.2) Multiparae: G1: 10 (38.5)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Diazepam 10 mg intramuscularly (IM) or pethidine 100 mg IM</p> <p>Pain management, n: Diazepam < 30 min after trial start: Ga: 1 Gb: 1 Gc: NR Diazepam ≥ 30 min after trial start: Ga: 1 Gb: 4 Gc: NR Pethidine < 30 min after trial start: Ga: 8 Gb: 0 Gc: NR Pethidine ≥ 30 min after trial start: Ga: 6 Gb: 3 Gc: NR Diazepam and/or pethidine < 30 min after trial start: Ga: 9 Gb: 1 Gc: NR Diazepam and/or pethidine ≥ 30 min after trial start: Ga: 7 Gb: 6 Gc: NR No additional drugs: Ga: 17 Gb: 12 Gc: NR</p>	<p>Pain: NR</p> <p>Labor progress: Dilation of cervix at start of trial, n (%): 1-2 cm: G1: 7 (26.9) G2: 9 (24.3) 3 cm: G1: 7 (26.9) G2: 10 (27.1) 4 cm: G1: 6 (23.1) G2: 10 (27.1) 5 cm: G1: 2 (7.7) G2: 3 (8.0) ≥ 6 cm: G1: 4 (15.4) G2: 4 (10.8) Not stated: G1: 0 G2: 1 (2.7) Duration of labor, n: ≤ 6 hours: Ga: 19 Gb: 5 > 6 hours: Ga: 21 Gb: 17</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: Satisfaction with preferred drug, n: Excellent: Ga: 3 Gb: 0 Gc: 0 Good: Ga: 33 Gb: 21 Gc: 1 Moderate: Ga: 4 Gb: 1 Gc: 0 Poor: Ga: 0 Gb: 0 Gc: 0</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Apgar score, patients who continued with preferred drug, n: ≤ 4: Ga: 0 Gb: 0 5: Ga: 1 Gb: 1 6: Ga: 0 Gb: 0 7: Ga: 2 Gb: 3 8: Ga: 5 Gb: 2 9: Ga: 21 Gb: 12 10: Ga: 4 Gb: 2</p> <p>Adverse effects, n:¹ Maternal, patient report:</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Bergsjø and Lindbaek, 1971 (continued)	G2: 14 (37.8)			<p>Nausea, by cause: N₂O: Total: 4 Methoxyflurane: Total: 2</p> <p>Dizziness and similar sensations, by cause: N₂O: Total: 11 Methoxyflurane: Total: 11</p> <p>Dry mouth, mask unpleasant, by cause: N₂O: Total: 6 Methoxyflurane: Total: 0</p> <p>Bad smell or taste, by cause: N₂O: Total: 0 Methoxyflurane: Total: 9</p> <p>Numbness, by cause: N₂O: Total: 1 Methoxyflurane: Total: 0</p> <p>No reported side effect, by cause: N₂O: Total: 42 Methoxyflurane: Total: 44</p> <p>Maternal, objective/observed: Drowsiness, by cause: N₂O: Total: 7 Methoxyflurane: Total: 8</p> <p>Euphoria, by cause: N₂O: Total: 4 Methoxyflurane: Total: 0</p> <p>Hiccups, by cause: N₂O: Total: 1 Methoxyflurane: Total: 0</p> <p>Vomiting, by cause:</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Bergsjø and Lindbaek, 1971 (continued)				N ₂ O: Total: 3 Methoxyflurane: Total: 1 Neonatal: NR Childhood: NR Occupational: NR

Comments:

¹ Adverse effect numbers may exceed total number as some patients reported more than one side effect.

Evidence Table: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Bodin et al., 1999</p> <p>Country: Swedeb</p> <p>Participant source: Community</p> <p>Setting: Other</p> <p>Enrollment period: 01/1989 to 12/1989</p> <p>Design: Cross-sectional *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Members of Swedish Midwives Association Born in 1940 or later In second trimester between 1980 and 1987 that ended as single birth in the Swedish Medical Birth Register Working more than half time (greater than 20 hours per week) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> See inclusion criteria 	<p>Groups: G1: N₂O used at assisted deliveries G1a: N₂O used in ≥ 50% of all deliveries G1b: N₂O used in < 50% of all deliveries G2: Did not work with N₂O</p> <p>N at enrollment: Total: 1,781¹</p> <p>N at follow-up: G1a: 454 G1b: 357 G2: 931</p> <p>Age, yrs: ≤ 29: Total: 960 30-34: Total: 642 ≥ 35: Total: 179</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): 1: Total: 694 (38.9) 2: Total: 679 (38.1) 3: Total: 320 (17.9) 4: Total: 72 (4.0) ≥ 5: Total: 16 (0.8)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR</p> <p>Preterm birth rate, %: G1a: 4.2 G1b: 4.2 G2: 4.2</p> <p>Occupational: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Birth weight, grams, mean ± SD: G1a: 3,516 ± 534 G1b: 3,524 ± 527 G2: 3,588 ± 519</p> <p>Birth weight in term births, adjusted difference (95% CI): G1/G2: -77 (-112,-8)</p> <p>Birth weight, linear regression effect differences, adjusted (95% CI): G1/G2: -102 (-183,-22)</p> <p>Low birth weight (LBW) rate, %: G1a: 3.5 G1b: 3.1 G2: 1.9</p> <p>Low birth weight odds ratio, adjusted (95% CI): G1: 1.5 (0.7,3.3) G2: 1.0</p> <p>Low birth weight, logistic regression effect difference, adjusted (95% CI): G1: 3.4 (0.9,13.4)</p> <p>Gestational age at delivery, weeks, mean ± SD: G1a: 39.7 ± 1.9 G1b: 39.6 ± 1.8 G2: 39.7 ± 1.9</p> <p>Gestational age in term births, adjusted difference (95% CI): G1/G2: 0.02 (-0.20, 0.23)</p>

Evidence Table: Nitrous Oxide for the Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Bodin et al., 1999 (continued)				<p>Gestational age, linear regression effect difference, adjusted (95% CI): G1: 0.30 (-0.03,0.63)</p> <p>Small for gestational age (SGA) rate, %: G1a: 13.4 G1b: 11.5 G2: 9.7</p> <p>SGA odds ratio, adjusted (95% CI): G1: 1.8 (1.1,2.8) G2: 1.0</p> <p>Logistic regression effect differences of SGA, adjusted (95% CI): G1: 3.0 (1.2,7.2)</p> <p>Adverse effects: NR</p>

Comments:

¹ 1,781 pregnancies linked to 1,302 women.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Carstoniu et al., 1994</p> <p>Country: Canada</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Crossover RCTs *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Admitted in labor and delivery suite at Toronto Hospital <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Age < 18 yrs Maternal cardiorespiratory disease Evidence of fetal distress or abnormal heart rate pattern Any condition affecting accuracy of pulse oximetry Use of opioid or analgesia 	<p>Groups: G1: NC (cross-over) G2: CN (cross-over) Ga: 50% N₂O in O₂ (N) Gb: Compressed air (C)</p> <p>N at enrollment: (admission to labor and delivery) Total: 29</p> <p>N at follow-up: G1: 14 G2: 12</p> <p>Age, mean yrs ± SD: G1: 31.1 ± 5.8 G2: 28.4 ± 5.0</p> <p>Race/ethnicity: NR</p> <p>Parous, n: Primipara: G1: 7 G2: 7</p> <p>Multipara: G1: 7 G2: 5</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: VAS score, baseline, mean ± SD: Contraction 1: G1: 5.6 ± 2.1 G2: 4.9 ± 2.5 Contraction 2: G1: 5.2 ± 2.2 G2: 5.8 ± 2.7</p> <p>VAS score, trial, mean: Contraction 1: Ga: 5.1 Gb: 4.9 Contraction 2: Ga: 5.2 Gb: 5.2 Contraction 3: Ga: 5.7 Gb: 6.1 Contraction 4: Ga: 5.2 Gb: 5.6 Contraction 5: Ga: 5.6 Gb: 5.7 Ga/Gb: <i>P</i> = NS</p> <p>SpO₂, baseline, mean % ± SD: Contraction 1: G1: 97 ± 2.0 G2: 97 ± 2.0 Contraction 2: G1: 97 ± 2.0 G2: 96 ± 2.0</p> <p>SpO₂, trial, mean %: Contraction 1: Ga: 97 Gb: 97 Contraction 2: Ga: 97 Gb: 96 Contraction 3: Ga: 97 Gb: 96 Contraction 4: Ga: 97 Gb: 96 Contraction 5: Ga: 97 Gb: 96 Ga/Gb: <i>P</i> < 0.05</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Carstoniu et al., 1994 (continued)			Labor progress: Cervical dilation, cm, mean \pm SD: G1: 3 \pm 1.4 G2: 3 \pm 1.3 Duration of labor, hours, mean \pm SD: G1: 7.9 \pm 3.8 G2: 7.6 \pm 4.9 Fetal status: NR Timeliness: NR Labor co-interventions: NR Adverse effects: NR Route of birth: NR	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Chia et al., 1990</p> <p>Country: Singapore</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: 2 RCTs</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Patients admitted in the morning to labor suite in early labor or for induction of labor • Consented to use TENS or Entonox for pain relief <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Expressed desire for epidural analgesia • Admitted in advanced labor • Previously given other forms of analgesia • For groups G3 and G4, delivered without requesting further anesthesia 	<p>Groups:</p> <p>G1: Entonox (50% N₂O in O₂) as first method pain relief in patients in early labor, instructed by midwife on breathing technique on admission to labor ward.</p> <p>G2: Transcutaneous electric nerve stimulation (TENS). Patient controlled flow of current using control box after demonstration of equipment.</p> <p>G3: Entonox (50% N₂O in O₂) in nulliparous patients scheduled for surgical induction. Patients switched to TENS when Entonox was not sufficient for pain relief. Same administration method as above for G1.</p> <p>G4: TENS at a first method in patients scheduled for surgical induction. Patients switched to Entonox when TENS was not sufficient for pain relief. Same methods as listed above for G2.</p> <p>N at enrollment: (admitted in early labor or for surgical induction)</p> <p>G1: 53 G2: 48 G3: 10 G4: 10</p> <p>N at follow-up:</p> <p>G1: 53 G2: 48 G3: 9¹ G4: 10</p> <p>Age, mean yrs ± SD:</p> <p>G1: 28.3 ± 4.3 G2: 28.4 ± 4.2 G3: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available:</p> <p>G1+G2: Pethidine alone, pethidine combined with TENS or Entonox, or epidural</p> <p>G3: TENS (at first switch), if inadequate then combined Entonox and either TENS or 75 mg IM pethidine</p> <p>G4: Entonox (at first switch), if inadequate then combined TENS and either Entonox or 75 mg IM pethidine</p> <p>Pain management, additional methods, n (%):</p> <p>No additional relief: G1: 9 (17) G2: 9 (18.8) G3: NR G4: NR</p> <p>Pethidine: G1: 38 (71.7) G2: 28 (58.3) G3: NR G4: NR</p> <p>Other modalities: G1: 6 (11.3) G2: 11 (22.9) G3: NR G4: NR</p>	<p>Pain, n (%): (patient described intensity on 1-10 scale the day after delivery)</p> <p>1-5: G1: 2 (3.2) G2: 4 (8.3)</p> <p>6-10: G1: 51 (96.2) G2: 44 (91.7)</p> <p>Description of pain, time of request for pain relief in early labor: Mild: G3: 3 (30) G4: 7 (78) G3/G4: <i>P</i> = NS Moderate: G3: 4 (40) G4: 0 G3/G4: <i>P</i> = NS Severe: G3: 3 (30) G4: 2 (22) G3/G4: <i>P</i> = NS</p> <p>Type of relief from first method of pain relief: Nil: G3: 5 (50) G4: 1 (11) G3/G4: <i>P</i> = NS Partial: G3: 5 (50) G4: 8 (89) G3/G4: <i>P</i> = NS Complete: G3: 3 (30) G4: 0 G3/G4: <i>P</i> = NS</p> <p>After switching to second method: Mild: G3: 0 G4: 0 G3/G4: <i>P</i> = NS Moderate: G3: 5 (56) G4: 4 (40) G3/G4: <i>P</i> = NS Severe: G3: 4 (44) G4: 5 (50)</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Chia et al., 1990 (continued)	G4: NR Race/ethnicity: NR Parous, n (%): Nulliparous: G1: 33 (62.3) G2: 26 (54.2) G3: 9 (100) G4: 10 (100)		G3/G4: <i>P</i> = NS Type of relief with second method, n: Same as before: G3: 4 G4: 1 G3/G4: <i>P</i> = NS Worse than before: G3: 6 G4: 2 G3/G4: <i>P</i> = NS Partial: G3: 4 G4: 6 G3/G4: <i>P</i> = NS Complete: G3: 0 G4: 0 G3/G4: <i>P</i> = NS Labor progress, n (%): Observed length of first stage of labor: ≤ 8 hours: G1: 30 (56.6) G2: 35 (72.9) G1/G2: <i>P</i> = NS > 8 hours: G1: 23 (43.4) G2: 13 (27.1) G1/G2: <i>P</i> = NS Length of labor, hours:minutes, mean: G1b: 6:16 G2b: 4:48 G1/G2: <i>P</i> = NS Fetal status: NR Timeliness: NR Labor co-interventions, n (%): Augmented or induced: G1: 16 (30.2) G2: 23 (47.9) G3: 9 (100) G4: 10 (100) Adverse effects: NR Route of birth: NR	

Comments:

¹ One patient in G3 did not switch to TENS.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Clark et al., 1967</p> <p>Country: US</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Nonrandomized trial *****</p> <p>Inclusion criteria: NR</p> <p>Exclusion criteria: NR</p>	<p>Groups: G1: Methoxyflurane analgesia with the inhaler and anesthesia with N₂O and methoxyflurane G2: Anesthesia with N₂O and methoxyflurane G3: Methoxyflurane analgesia with the inhaler or some type of regional block</p> <p>N at enrollment: G1: 42 G2: 11 G3: 41</p> <p>N at follow-up: (infant blood gas and pH obtained) G1: 17 G2: 0 G3: 4</p> <p>Age, mean yrs: G1: 24.5 G2: 18.6 G3: 26.4</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%*): G1: 9 (21.4) G2: 5 (45.4) G3: 6 (14.6)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: G1: Meperidine G2: Meperidine, oxytocin (after delivery) G3: Meperidine, conduction anesthesia (epidural)</p> <p>Pain management, n (%): Meperidine: G1: 7 (16.6*) G2: 1 (9.0*) G3: 5 (12.1*)</p> <p>Oxytocin (after delivery): G2: 11 (100)</p> <p>Conduction anesthesia (epidural): G3: 11 (26.8)</p>	<p>Pain, %:¹ Excellent: G1: 20 G2: NR G3: 14 Good: G1: 37 G2: NR G3: 46 Fair: G1: 32 G2: NR G3: 24 Poor: G1: 11 G2: NR G3: 16</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status:-- Apgar score < 7, 1 minute, n: G1: 14/42 G2: 4/11² G3: 2/42</p> <p>Umbilical artery pH, mean (range): G1: 7.27 (7.17-7.38) G2: NR G3: 7.29 (7.25-7.33)</p> <p>Umbilical artery pO₂, mean (range): G1: 29.0 (13.40-52.6) G2: NR G3: 26.40 (21.7-31.2)</p> <p>Umbilical artery pCO₂, mean (range): G1: 56.7 (34.0-90.0) G2: NR G3: 43.33 (40-50)</p> <p>Umbilical artery Neg BE, mean (range): G1: -3.07 (-11.0,0.80) G2: NR G3: -6.06 (-9.8,-2.1)</p> <p>Femoral vein pH, 1 hour, mean (range): G1: 7.31 (7.19-7.39) G2: NR G3: 7.27 (7.23-7.34)</p> <p>Femoral vein pO₂, 1 hour, mean (range): G1: 42.8 (22.9-80.7) G2: NR G3: 41.87 (32.8-60.2)</p> <p>Femoral vein pCO₂, 1 hour, mean (range): G1: 42.5 (26.0-58) G2: NR G3: 53.87 (45-75)</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Clark et al., 1967 (continued)				<p>Femoral Vein Neg BE, 1 hour, mean (range): G1: -5.2 (-11.4,-2.0) G2: NR G3: -3.82 (-9.0,-0.10)</p> <p>Adverse effects, n (%): Maternal: Nausea and vomiting: G1: 6 (14.2)³ G2: 0 G3: 2 (4.8)</p> <p>Neonatal: Stillborn: G1: 0 G2: 0 G3: 1 (2.4)</p> <p>Pneumonitis: Total: 3</p> <p>Apneic spells: Total: 1</p> <p>Ocular discharge: Total: 1</p> <p>Respiratory distress syndrome: Total: 1</p> <p>Diarrhea: Total: 1</p> <p>Childhood: NR</p> <p>Occupational: NR</p>

Comments:

* Calculated by reviewer.

¹ Pain Relief Scale: Excellent – patient lay quietly during contractions in a tranquil state; Good – appreciable relief of pain, but still some discomfort; Fair – some, but not satisfactory relief of pain; Poor – little or no relief of pain.

² All breech

³ Six in this group had nausea and/or vomiting during or after the analgesia and anesthesia. In addition, two additional participants vomited during labor, before the inhaler was started.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Constantine et al., 1989</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Pregnant women using Entonox either alone or in combination with pethidine during labor <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: Entonox (50% O₂, 50% N₂O) Ga: Mask alone Gb: Mask with humidifier Gc: Mouthpiece alone Gd: Mouthpiece with humidifier</p> <p>N at enrollment: G1: 149 G1a: 49 G1b: 36 G1c: 37 G1d: 27</p> <p>N at follow-up: G1: 149 G1a: 49 G1b: 36 G1c: 37 G1d: 27</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, %: Required further analgesia: G1: 52</p> <p>Length of nitrous use, hours, mean ± SD: G1a-b: 3.3 ± 2.5 G1c-d: 3.3 ± 2.1</p>	<p>Pain, n (%): Rated good: G1: 80 (53) G1a-b: 43 (50.5) G1c-d: 37 (57.8) Rated moderate: G1: 42 (28) G1a-b: 25 (29.4) G1c-d: 17 (26.5) Rated poor: G1: 20 (14) G1a-b: 11 (12.9) G1c-d: 9 (14.1) Rated useless: G1: 7 (5) G1a-b: 6 (7.0) G1c-d: 1 (1.5)</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal: Nausea: G1: 55 (37) G1a: 22 (45) G1b: 9 (25) G1c: 13 (36) G1d: 11 (41)</p> <p>Dry nose: G1: 23 (15) G1a: 11 (31) G1b: 5 (18) G1c: 6 (17) G1d: 1 (4)</p> <p>Dry mouth: G1: 116 (78) G1a: 37 (75) G1b: 26 (72) G1c: 31 (86) G1d: 22 (81)</p> <p>Light headed: G1: 87 (58) G1a: 16 (33) G1b: 20 (56)</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Constantine et al., 1989 (continued)			G1c: 28 (76) G1d: 23 (85) G1c/G1a: $P < 0.05$ G1c-d/G1a-b: $P < 0.01$ Tingling: G1: 37 (25) G1a: 15 (31) G1b: 5 (18) G1c: 11 (31) G1d: 6 (22) Neonatal: NR Occupational: NR Route of birth: NR	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Deckardt et al., 1987</p> <p>Country: (West) Germany</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort</p> <ul style="list-style-type: none"> Patients assigned to pain managements according to their own request <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Healthy pregnant women Singleton pregnancy Received training in prepared childbirth <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Patients with premature rupture of membranes 	<p>Groups:¹</p> <p>G1: N₂O with O₂ 1:1 breathed at irregular intervals and meperidine</p> <p>G2: 50-100 mg intra-muscularly 2-4 hours before delivery</p> <p>G3: Patients received lumbar peridural anesthesia (9-12 ml bupivacaine 0.25%)</p> <p>G4: No analgesic drugs</p> <p>G1: Control/women at term but not in labor</p> <p>G2: Primiparas</p> <p>G3: Multiparas</p> <p>N at enrollment: (admitted to study as soon as true labor had begun and progressive dilation to 3-4 cm was ascertained)</p> <p>G1: 25</p> <p>G1a: 16</p> <p>G1b: 9</p> <p>G2: 15</p> <p>G2a: 15</p> <p>G2b: 0</p> <p>G3: 6</p> <p>G3a: 0</p> <p>G3b: 6</p> <p>G4: 9</p> <p>N at follow-up:</p> <p>G1: 25</p> <p>G1a: 16</p> <p>G1b: 9</p> <p>G2: 15</p> <p>G2a: 15</p> <p>G2b: 0</p> <p>G3: 6</p> <p>G3a: 0</p> <p>G3b: 6</p> <p>G4: 9</p> <p>Age, mean yrs ± SD:</p> <p>G1a: 24.3 ± 4.40</p> <p>G1b: NR</p> <p>G2a: 27.4 ± 4.85</p> <p>G3: NR</p> <p>Gb: 27.6 ± 3.62</p> <p>G4: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available:</p> <p>G1: Lumbar peridural anesthesia</p> <p>G2: N₂O and meperidine</p> <p>G3: Lumbar peridural anesthesia, N₂O, and meperidine</p> <p>Pain management: NR</p>	<p>Pain, mean ± SD (range): (VAS 0-10):</p> <p>G1a: 7.1 ± 1.2 (5-9)</p> <p>G2a: 3.5 ± 2.0 (1-8)</p> <p>Gb: 4.9 ± 1.7 (NR)</p> <p>G1a/G2a: <i>P</i> < 0.001</p> <p>Labor progress: Labor duration, hours, mean ± SD:</p> <p>G1a: 3.3 ± 1.7</p> <p>G2a: 4.5 ± 1.5</p> <p>Gb: NR</p> <p>G1a/G2a: <i>P</i> < 0.05</p> <p>Uterine contraction rate during labor, mean ± SD:</p> <p>G1a: 21.8 ± 4.13</p> <p>G2a: 20.2 ± 4.27</p> <p>Gb: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions, n (%): Oxytocin stimulation (infusion rate 1-3.6 mU/min):</p> <p>G1a: 11 (68.7)</p> <p>G2b: 11 (73.3)</p> <p>Gb: NR</p> <p>Adverse effects: NR</p> <p>Arterial oxygen saturation, % mean ± SD (range):</p> <p>G1a: 88.8 ± 3.9 (74-100)</p> <p>G2a: 94.3 ± 1.3 (85-100)</p> <p>Gb: 93.9 ± 2.0 (NR)</p> <p>G4: 96 (NR)</p> <p>Route of birth, n (%): Vaginal spontaneous:</p> <p>Total: 40</p> <p>Assisted forceps:</p> <p>Total: 5</p> <p>Cesarean:</p> <p>Total: 1</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Umbilical artery pH, mean ± SD:</p> <p>G1a: 7.21 ± 0.10</p> <p>G2a: 7.29 ± 0.06</p> <p>Gb: 7.31 ± 0.05</p> <p>G1a/G2a: <i>P</i> = 0.01</p> <p>Umbilical artery base excess, mean ± SD:</p> <p>G1a: -9.5 ± 4.5</p> <p>G2a: -6.4 ± 2.2</p> <p>Gb: -5.1 ± 3.5</p> <p>Apgar score, 1 minute, mean ± SD:</p> <p>G1a: 8.1 ± 0.9</p> <p>G2a: 8.5 ± 0.7</p> <p>Gb: NR</p> <p>Apgar score, 5 minutes, mean ± SD:</p> <p>G1a: 9.7 ± 0.5</p> <p>G2a: 10.0 ± 0</p> <p>Gb: NR</p> <p>Apgar score, 10 minutes, mean ± SD:</p> <p>G1a: 10.0 ± 0</p> <p>G2a: 10.0 ± 0</p> <p>Gb: NR</p> <p>Birth weight, g, mean ± SD:</p> <p>G1a: 3,424 ± 395</p> <p>G2a: 3,256 ± 726</p> <p>Gb: 3,358 ± 361</p> <p>Gestational age, weeks, mean ± SD:</p> <p>G1a: 39.7 ± 0.68</p> <p>G2a: 39.3 ± 1.23</p> <p>Gb: 239.7 ± 0.70</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Deckardt et al., 1987 (continued)	Race/ethnicity: NR Parous, n (%): G1: 9 (36) G2: 0 G3: 6 (100) G4: NR			

Comments:

¹ Results are reported for groups G1a, G2a and Gb, but not separately for groups G1b and G3b.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Einarsson et al., 1996</p> <p>Country: Sweden</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women undergoing vaginal delivery <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Maternal cardiorespiratory disease • Pre-eclampsia • Evidence of fetal distress • Used opioids • Used regional analgesia 	<p>Groups: G1: 70% N₂O in O₂¹ G2: 50% N₂O in O₂¹</p> <p>N at enrollment: G1: 12 G2: 12</p> <p>N at follow-up: G1: 12 G2: 12</p> <p>Age, median yrs (range): G1: 28 (19-41) G2: 29 (21-37)</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primiparous: G1: 6 (50) G2: 8 (66.7)</p> <p>Multiparous: G1: 6 (50) G2: 4 (33.3)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: Cervical dilation at time of study, cm, median (range): G1: 4.5 (3.0-8.0) G2: 5.0 (4.0-7.0)</p> <p>Fetal status, n (%): Decline in fetal heart rate: G1: 0 G2: 1 (8.3)*</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>End-tidal CO₂, median %: Before N₂O inhalation: G1: 3.7 G2: 3.5 At end of N₂O inhalation: G1: 3.6 G2: 3.6 30 seconds after N₂O: G1: 3.6 G2: 3.5 60 seconds after N₂O: G1: 3.8 G2: 3.5 120 seconds after N₂O: G1: 3.8 G2: 3.8</p> <p>End-tidal O₂, median %: Before N₂O inhalation: G1: 16.0 G2: 16.2 At end of N₂O inhalation: G1: 25.4 G2: 43.7 30 seconds after N₂O: G1: 17.5 G2: 18.4 G1/G2: <i>P</i> < 0.05</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Einarsson et al., 1996 (continued)			<p>60 seconds after N₂O: G1: 16.3 G2: 16.9 G1/G2: <i>P</i> = NS</p> <p>120 seconds after N₂O: G1: 15.4 G2: 15.4 G1/G2: <i>P</i> = NS</p> <p>Oxygen saturation, median %: Before N₂O inhalation: G1: 96.3 G2: 97.0 At end of N₂O inhalation: G1: 98.0 G2: 98.8 G1/BL: <i>P</i> < 0.01 G1/BL: <i>P</i> < 0.01 G1/G2: <i>P</i> = NS</p> <p>30 seconds after N₂O: G1: 97.5 G2: 98.0 G1/BL: <i>P</i> < 0.01 G1/BL: <i>P</i> < 0.01 G1/G2: <i>P</i> = NS</p> <p>60 seconds after N₂O: G1: 97.0 G2: 97.0</p> <p>120 seconds after N₂O: G1: 97.0 G2: 97.0</p> <p>Expiratory ventilation volume, L/min, median: Before N₂O inhalation: G1: 13.7 G2: 11.1 At end of N₂O inhalation: G1: 13.9 G2: 11.3</p> <p>30 seconds after N₂O: G1: 12.2 G2: 11.0</p> <p>60 seconds after N₂O: G1: 10.8 G2: 9.9</p> <p>120 seconds after N₂O: G1: 8.7 G2: 9.8</p>	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Einarsson et al., 1996 (continued)			Nitrous inhalation time per contraction, seconds, median: G1: 33 G2: 58 G1/G2: $P = 0.01$ Uterine contraction time, seconds, median: G1: 87 G2: 90 Adverse effects, n (%): Maternal: Hypoxemia: G1: 1 (8.3) G2: 1 (8.3) Neonatal: NR Occupational: NR Route of birth, n (%): Vaginal: G1: 12 (100) G2: 12 (100) Assisted: NR Cesarean: Not applicable	

Comments:

¹ For all participants, administered via a non-rebreathing system with a demand valve; parturients breathed through mouthpiece while using a nose clip and switched on or off as desired.

* Calculated by reviewer

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Harrison et al., 1987</p> <p>Country: Ireland</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 06/1983 to 12/1983</p> <p>Design: Prospective cohort</p> <ul style="list-style-type: none"> Patients selected at random <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Primigravid Initial choice of analgesia was transcutaneous electrical nerve stimulation, Entonox, pethidine and promazine, or lumbar epidural Admitted to main labor ward <p>Exclusion criteria:</p> <ul style="list-style-type: none"> See inclusion criteria 	<p>Groups: G1: Entonox: 50% N₂O, 50% O₂ self-administered, usually towards the end of first stage of labor and during second stage G2: Transcutaneous electrical nerve stimulation (TENS) G3: Pethidine and promazine 50 mg each combined when deemed necessary by mutual consent G4: Lumbar epidural</p> <p>N at enrollment: G1: 20 G2: 50 G3: 50 G4: 50</p> <p>N at follow-up: G1: 20 G2: 50 G3: 50 G4: 50</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n: Total: 0</p>	<p>Provider preferences: NR</p> <p>Provider specialty, %: Midwives and medical personnel: 100</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: G1: TENS, pethidine and promazine, epidural G2: Entonox, pethidine and promazine, epidural G3: Entonox, TENS, epidural G4: Entonox, TENS, pethidine and promazine</p> <p>Pain management, n (%): Initial choice alone: G1: 19 (95) G2: 9 (18) G3: 10 (20) G4: 50 (100)</p> <p>Initial choice + epidural: G1: NA G2: 15 (30) G3: 25 (50) G4: 0</p> <p>Initial choice + pethidine and promazine: G1: 1 (5) G2: 8 (16) G3: NA G4: 0</p> <p>Initial choice + epidural: G1: 0 G2: 8 (16) G3: 15 (30) G4: NA</p> <p>Initial choice + pethidine and</p>	<p>Pain, n (%): (5 point scale 0-4)¹ Degree of pain relief: Nil (pain score 4): G1: 2 (10) G2: 2 (4) G3: 23 (46) G4: 0</p> <p>Partial (score 1-3): G1: 18 (90) G2: 48 (96) G3: 27 (54) G4: 6 (12)</p> <p>Complete (score 0): G1: 0 G2: 0 G3: 0 G4: 44 (88)</p> <p>Degree of pain relief, midwife report: Nil: G1: 0 G2: 1 (2) G3: 16 (32) G4: 0</p> <p>Poor: G1: 4 (20) G2: 1 (2) G3: 10 (20) G4: 0</p> <p>Fair: G1: 9 (45) G2: 14 (28) G3: 21 (42) G4: 1 (2)</p> <p>Good: G1: 7 (35) G2: 34 (68) G3: 3 (6) G4: 8 (16)</p> <p>Excellent: G1: 0 G2: 0 G3: 0 G4: 41 (82)</p> <p>Labor progress: Hours in labor, mean ± SD: Initial choice alone: G1: 5.2 ± 1.7 (n=19) G2: 6.3 ± 2.4 (n=9) G3: 6.2 ± 1.4 (n=10) G4: 7.7 ± 2.4 (n=50)</p>	<p>Satisfaction with pain management, n (%): Positive comments, 1 hour after delivery: G1: 18 (90) G2: 46 (92) G3: 26 (52) G4: 50 (100)</p> <p>Efficacy was yes, 24 hours after delivery: G1: 16 (80) G2: 46 (92) G3: 24 (48) G4: 49 (98)</p> <p>Adequacy was yes, 24 hours after delivery: G1: 12 (60) G2: 40 (80) G3: 9 (18) G4: 49 (98)</p> <p>Satisfaction with birth experience, n (%): (1-24 hours after delivery) Would request same analgesia again: Yes: G1: 16 (80) G2: 30 (60) G3: 19 (38) G4: 44 (88)</p> <p>Qualified yes: G1: 0 G2: 7 (14) G3: 0 G4: 0</p> <p>No: G1: 3 (15) G2: 10 (20) G3: 24 (48) G4: 1 (2)</p> <p>Don't know: G1: 1 (5) G2: 3 (6) G3: 7 (14) G4: 5 (10)</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Harrison et al., 1987 (continued)		promazine + Entonox: G1: NA G2: 7 (14) G3: NA G4: 0 Initial choice + pethidine and promazine + epidural: G1: 0 G2: 3 (6) G3: NA G4: NA	Including other analgesia: G1: 5.4 ± 1.7 (n=1) G2: 8.2 ± 3.0 (n=41) G3: 7.7 ± 2.8 (n=40) G4: NA Fetal status: NR Timeliness: NR Labor co-interventions: NR Adverse effects: NR Route of birth, n (%): Vaginal (normal): G1: 12 (60) G2: 32 (64) G3: 32 (64) G4: 13 (26) Assisted (forceps and vacuum): G1: 7 (35) G2: 14 (28) G3: 18 (36) G4: 31 (62) Cesarean: G1: 0 G2: 4 (8) G3: 0 G4: 3 (6) Breech: G1: 1 (5) G2: 0 G3: 0 G4: 3 (6)	Adverse effects: NR

Comments:

¹ 0 (no pain) to 4 (very severe pain)

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Harrison and Cullen, 1986</p> <p>Country: Ireland</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: 08/1983 to 12/1983</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Born at selected hospital between August and December 1983 • Mothers had taken part in study evaluating different forms of analgesia in labor • Birth weight between 2.65 kg and 4.66 kg • ≥ 36 weeks gestation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: Babies whose mothers received one or more forms of analgesia during labor Ga: N₂O 50% and O₂ 50% (Entonox) self administered as required by patient Gb: Pethidine/promazine Gc: Epidural Gd: Transcutaneous electrical nerve stimulation (TENS) Ge: TENS placebo Gf: General anesthesia</p> <p>N at enrollment: (3-5 days post-delivery) G1: 110 G1a: 46 G1b: 46 G1c: 48 G1d: 27 G1e: 31 G1f: 4</p> <p>N at follow-up: G1: 110</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR¹</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, n: Initial analgesic choice: Entonox: G1: 7 Pethidine/promazine: G1: 45 Epidural: G1: 26 TENS: G1: 15 TENS placebo: G1: 17 General anesthesia: G1: 0</p>	<p>Pain: NR</p> <p>Labor progress: Duration of labor, hours, mean (range): G1: 6 (2-12)</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n: Vaginal: G1: 65 Assisted: G1: 38² Cesarean: G1: 7</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Birth weight, kg, mean (range): G1: 3.488 (2.65-4.66) Gestational age, weeks, mean (range): G1: 40.2 (36-43) Neonatal Psychological Assessment Profile raw scores, mean:³ Habituation to light: G1a: 2.92 G1b: 2.95 G1c: 3.15 G1d: 3.41 G1e: 3.11 G1f: 3.50 Habituation to sound: G1a: 3.29 G1b: 2.86 G1c: 3.03 G1d: 2.64 G1e: 3.35 G1f: 3.75 Auditory inanimate orientation: G1a: 2.53 G1b: 2.43 G1c: 2.15 G1d: 2.37 G1e: 2.48 G1f: 2.00 Visual inanimate orientation: G1a: 1.65 G1b: 1.58 G1c: 1.68 G1d: 1.56 G1e: 1.59 G1f: 1.00 Auditory animate orientation: G1a: 2.57 G1b: 2.62</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Harrison and Cullen, 1986 (continued)				<p>G1c: 2.23 G1d: 2.35 G1e: 2.44 G1f: 1.00 Visual animate orientation: G1a: 2.45 G1b: 2.34 G1c: 2.22 G1d: 2.29 G1e: 2.45 G1f: 2.00 Auditory and visual animate orientation: G1a: 2.80 G1b: 2.61 G1c: 2.66 G1d: 2.61 G1e: 2.83 G1f: 2.00 Alertness: G1a: 2.37 G1b: 2.13 G1c: 2.08 G1d: 2.00 G1e: 2.29 G1f: 1.00 Peak of excitement: G1a: 3.23 G1b: 3.44 G1c: 3.17 G1d: 3.11 G1e: 3.12 G1f: 1.50 Irritability: G1a: 2.21 G1b: 2.37 G1c: 2.23 G1d: 2.33 G1e: 2.51 G1f: 1.50 Consolability: G1a: 2.84 G1b: 2.97 G1C: 2.91 G1D: 2.77 G1E: 3.38 G1F: 1.75 Cuddliness: G1a: 2.60 G1b: 2.40 G1c: 2.47 G1d: 2.44 G1e: 2.50 G1f: 2.50 Self-quieting activity: G1a: 2.00</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Harrison and Cullen, 1986 (continued)				<p>G1b: 1.40 G1c: 2.20 G1d: 2.00 G1e: 1.50 G1f: 1.00</p> <p>Suckling time, %: 1 minute: G1a: 67.58 G1b: 62.00 G1c: 64.45 G1d: 66.13 G1e: 64.92 G1f: NR</p> <p>5 minutes: G1a: 70.63 G1b: 65.83 G1c: 77.46 G1d: 68.25 G1e: 77.14 G1f: NR</p> <p>Adverse effects: NR</p>

Comments:

¹ The authors state mothers were either primigravid or women of the second parity.

² 34 forceps, 3 vacuum, 1 assisted breech

³ Babies were assessed with the Neonatal Psychological Assessment Profile, which combines sections from the Neonatal Behavioural Assessment Scale, items from the Neurological Assessment of pre-term and full-term infants, and two measures of suckling behaviors. The scale ranges from 1-5.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Henderson et al., 2003</p> <p>Country: United Kingdom</p> <p>Participant source: Academic multiple sites</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort</p> <p>*****</p> <p>Inclusion criteria: NR</p> <p>Exclusion criteria: NR</p>	<p>Groups: G1: Midwives exposed to N₂O mix as delivery attendants. Midwives wore passive sampling tube for the first four hours (first half) of their shift, placed on lapel "within the breathing zone." They also completed questionnaires and provided urine samples.</p> <p>N at enrollment: G1: 46¹</p> <p>N at follow-up: G1: 50 shifts of data¹</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty, n (%): Midwives: G1: 46 (100)</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: All were exposed to N₂O, concentration not noted.</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n: Maternal: NR Neonatal: NR</p> <p>Occupational: Time-weighted average of nitrous exposure, n: 10 times the occupational exposure limits: G1: 5/46 5 times the occupational exposure limits: G1: 5/46 2 times the occupational exposure limits: G1: 13/46 Below the occupational exposure limits: G1: 13/46</p> <p>Interindividual environmental concentrations, ppm, mean ± SD (range): G1: 313 ± 358 (2.4-1300)</p> <p>No nitrous oxide present in urine after 4 hours: G1: 3</p> <p>Non-zero values of nitrous oxide in baseline urine prior to starting shift: G1: 22</p> <p>Non-zero baseline urinary concentrations of nitrous oxide, µg/l, mean ± SD (range):</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR Childhood: NR Occupational: See labor and immediate outcomes.</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Henderson et al., 2002 (continued)			G1: 44 ± 51 (3-174) (n=22) Urinary nitrous oxide concentrations in excess of 27 µg/l (biological exposure limit in Italy) before starting their shift: G1: 12 Urinary nitrous oxide concentrations, second sample, µg/l, mean ± SD (range): G1: 114 ± 191 (0-1103) Route of birth: NR	

Comments:

¹ All shifts where midwives were monitored (shifts were 4 hours in length); some participants were monitored more than once. In hospital 1, 15 midwife shifts were monitored, 2 of which were on the same midwife. In hospital 2, 35 midwife shifts were monitored, with 20 monitored only on one shift, and 4 monitored on 2 shifts, 1 on 3 shifts, and 1 on 4 shifts. Text variously describes 46 midwives and 46 shifts, although some midwives were monitored more than once.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Henry et al., 2004</p> <p>Country: Australia</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 10/2002 to 01/2003</p> <p>Design: Cross-sectional *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women in labor <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Age < 17 years • Non-English speaking • Women undergoing elective or urgent cesarean where no labor occurred • Women with stillbirth/neonatal deaths, major congenital anomaly/major neonatal morbidity • Homebirths • Active psychiatric illness at time of labor 	<p>Groups:¹ G1: N₂O G2: Pethidine G3: Epidural anesthesia G4: Local anesthesia (infiltration of the perineum) G5: "Natural" methods which included massage, hot pack, bath/shower, or any other non-pharmacologic method G6: No N₂O</p> <p>N at enrollment: (survey given in the first 24 hours postpartum, completed within 1st postpartum week) Total: 496</p> <p>N at follow-up, n (%): (included surveys) G1: 268 (54) G2: 132 (27) G3: 217 (44) G4: 190 (38) G5: 367 (74) G6: 228 (46) Total: 496</p> <p>Age, mean yrs (range): Total: 32 (18-44)</p> <p>Race/ethnicity: NR</p> <p>Parous, %: Nulliparous: Total: 56</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, n (%): N₂O: Total: 268 (54) Pethidine: Total: 132 (27) Epidural anesthesia: Total: 217 (44) Local anesthesia: Total: 190 (38) "Natural" methods: Total: 367 (74) "Natural" methods only: Total: 46 (9.3)</p> <p>Number of pain management methods used, %: At least one: Total: 93 Two methods: Total: 24 Three methods: Total: 33</p> <p>Pain management, normal vaginal deliveries, %: N₂O: Total: 49 Pethidine: Total: 22 Epidural anesthesia: Total: 26 Local anesthesia: Total: NR "Natural methods": Total: 72 Any pharmacologic: Total: 75</p>	<p>Pain: NR²</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Effect of place of "booking in" vs. place of delivery, %: Booked and gave birth in delivery suite or operating theatre (n = 398): G1: 59 G2: 29 G3: 49 G4: NR G5: 70</p> <p>Booked into birth center, but gave birth in delivery suite or operating theatre (n=44): G1: 43 G2: 27 G3: 46 G4: NR G5: 93</p> <p>Booked and gave birth in birth center (n=51): G1: 20 G2: 5 G3: 0 G4: NR G5: 86</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: (survey given in the first 24 hours postpartum, to be completed within 1st postpartum week) Very satisfied, %: G1: 35 G6: 57 G1/G6: <i>P</i> < 0.01</p> <p>Pain management method, probably or definitely would use again, %: G1: 65 G2: 49 G3: 82 G4: NR G5: 79</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Henry et al., 2004 (continued)		Pain management, “other” deliveries, %: N ₂ O: Total: 66 Pethidine: Total: 40 Epidural anesthesia: Total: 92 Local anesthesia: Total: NR “Natural” methods: Total: 80 Any pharmacologic: Total: 99		

Comments:

¹ Groups are not exclusive.

² Utility of pain management methods only displayed graphically. Epidural analgesia recieved the highest utility scores, with 194/217 (89) rating it 'very useful' in relieving their pain.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Holdcroft and Morgan, 1974</p> <p>Country: United Kingdom</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 7 month period</p> <p>Design: Cross-sectional</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • See exclusion criteria <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Those receiving epidurals • Having a cesarean • Non-English speaking 	<p>Groups: G1: Entonox alone (50% mixture of N₂O and O₂) G2: Entonox and pethidine G3: Pethidine alone G4: No analgesia</p> <p>N at enrollment: (interviewed) G1: 130 G2: 466 G3: 67 G4: 42</p> <p>N at follow-up: (24-48 hours after delivery) G1: 130 G2: 466 G3: 67 G4: 42</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain, n (%): (scale developed by investigators)</p> <p>Pain relief from Entonox: None: G1: 39 (30.0) G2: 157 (33.7)</p> <p>Slight analgesia: G1: 23 (17.7) G2: 80 (17.2)</p> <p>Satisfactory analgesia: G1: 60 (46.2) G2: 212 (45.5)</p> <p>Complete analgesia: G1: 5 (3.8) G2: 8 (1.7)</p> <p>Amnesia: G1: 1 (0.8) G2: 5 (1.1)</p> <p>No pain to relieve: G1: 2 (1.5) G2: 4 (0.9)</p> <p>Pain relief from Entonox by duration of labor, primagravid: Less than 4 hours: None: G1+G2: 9 (30) Slight: G1+G2: 4 (13.3) Satisfactory: G1+G2: 14 (46.6) Complete: G1+G2: 0 Amnesia: G1+G2: 1 (3.3) No pain to relieve: G1+G2: 2 (6.7)</p> <p>4 to 12 hours: None: G1+G2: 72 (38.9) Slight: G1+G2: 29 (15.7) Satisfactory: G1+G2: 75 (40.5) Complete: G1+G2: 4 (2.2) Amnesia: G1+G2: 2 (1.1) No pain to relieve: G1+G2: 3 (1.6)</p> <p>More than 12 hours: None:</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Holdcroft and Morgan, 1974 (continued)			<p>G1+G2: 32 (38.6)</p> <p>Slight: G1+G2: 15 (18.1)</p> <p>Satisfactory: G1+G2: 35 (42.2)</p> <p>Complete: G1+G2: 0</p> <p>Amnesia: G1+G2: 1 (1.2)</p> <p>No pain to relieve: G1+G2: 0</p> <p>Pain relief from Entonox by duration of labor, multipara:</p> <p>Less than 4 hours: None: G1+G2: 27 (30.3)</p> <p>Slight: G1+G2: 13 (14.6)</p> <p>Satisfactory: G1+G2: 45 (50.6)</p> <p>Complete: G1+G2: 3 (3.4)</p> <p>Amnesia: G1+G2: 0</p> <p>No pain to relieve: G1+G2: 1 (1.1)</p> <p>4 to 12 hours: None: G1+G2: 51 (29.1)</p> <p>Slight: G1+G2: 33 (18.8)</p> <p>Satisfactory: G1+G2: 84 (48.0)</p> <p>Complete: G1+G2: 5 (2.9)</p> <p>Amnesia: G1+G2: 2 (1.1)</p> <p>No pain to relieve: G1+G2: 0</p> <p>More than 12 hours: None: G1+G2: 5 (14.7)</p> <p>Slight: G1+G2: 9 (26.5)</p> <p>Satisfactory: G1+G2: 19 (55.9)</p> <p>Complete: G1+G2: 1 (2.9)</p> <p>Amnesia: G1+G2: 0</p> <p>No pain to relieve: G1+G2: 0</p> <p>Pain relief from pethidine:</p>	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Holdcroft and Morgan, 1974 (continued)			<p>No analgesia: G2: 224 (48.1) G3: 32 (47.7)</p> <p>Slight analgesia: G2: 163 (35.0) G3: 15 (22.4)</p> <p>Satisfactory analgesia: G2: 65 (13.9) G3: 15 (22.4)</p> <p>Complete analgesia: G2: 5 (1.1) G3: 0</p> <p>Amnesia: G2: 5 (1.1) G3: 4 (6.0)</p> <p>No pain to relieve: G2: 4 (0.9) G3: 1 (1.5)</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n: Maternal: Vomiting: Total: 22¹</p> <p>Altered consciousness: Total: 27</p> <p>Loss of control: Total: 7</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth: NR</p>	

Comments:

¹ Ascribed to pethidine in 10 patients.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Jacobson et al., 1990</p> <p>Country: Sweden</p> <p>Participant source: Community</p> <p>Setting: Review of data for addicts from county jail, forensic medicine institute, and hospital</p> <p>Enrollment period: Addicts born from 1945 to 1966</p> <p>Design: Case control</p> <p>*****</p>	<p>Groups:¹</p> <p>G1a: Opiate addicts whose mothers received N₂O during labor</p> <p>G1b: Non-addict siblings of addicts, whose mothers may also have received N₂O during labor</p> <p>G2a²: Addicts whose mothers may have received opiates and/or barbiturates during labor</p> <p>G2b²: Non-addict siblings of addicts, whose mothers may have received opiates and/or barbiturates during labor.</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR</p> <p>Childhood: Duration of N₂O exposure of mothers during labor, hours, n (%):</p> <ul style="list-style-type: none"> ≤ 0.25 hours: G1a: 22 (15.2) G1b: 44 (25.3) > 0.25 to ≤ 1 hour: G1a: 30 (20.7) G1b: 46 (26.4) > 1.0 to < 2.5 hours: G1a: 32 (22.1) G1b: 32 (18.4) ≥ 2.5 to < 4.5 hours: G1a: 30 (20.7) G1b: 30 (17.2) ≥ 4.5 hours: G1a: 31 (21.4) G1b: 22 (12.6) <p>Opiate addiction in offspring, relative risk for N₂O exposure of > 1 to < 2.5 hours (95% CI):</p> <p>Matched: G1a/G1b: 1.6 (0.95, 2.6)</p> <p>Unmatched: G1a/G1b: 1.7 (1.2, 2.3)</p> <p>Time between last administration of opiates and/or barbiturates and delivery, hours, n (%):</p> <ul style="list-style-type: none"> ≤ 0.5 hours:

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Jacobson et al., 1990 (continued)				<p>G2a: 1 (0.5) G2b: 2 (0.9)</p> <p>> 0.5 to ≤ 1.5 hours: G2a: 6 (3) G2b: 2 (0.9)</p> <p>> 1.5 to ≤ 4.5 hours: G2a: 23 (11.5) G2b: 16 (7)</p> <p>> 4.5 to ≤ 10 hours: G2a: 13 (6.5) G2b: 6 (2.6)</p> <p>> 10 hours: G2a: 18 (9) G2b: 16 (7)</p> <p>No administration, n (%): G2a: 150 (75) G2b: 194 (84.3)</p> <p>Opiate addiction in offspring, relative risk for single dose of opiates, (95% CI): Matched: G2a/G2b: 1.6 (0.75, 3.6) Unmatched: G2a/G2b: 1.8 (0.94, 3.5)</p> <p>Opiate addiction in offspring, relative risk for single dose of barbituates, (95% CI): Matched: G2a/G2b: 1.7 (0.97, 3.0) Unmatched: G2a/G2b: 1.6 (0.97, 2.6)</p> <p>Occupational: NR</p>

Comments:

¹ Those subjects in G2 not in G1 were missing data for administration of nitrous oxide.

² Opiate doses were 0.01-0.02g morphine or 0.05-0.1 g pethidine hydrochloride, barbiturates doses as 0.05-2g phenobarbitone (and some other barbiturates not described)

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Jacobson et al., 1988</p> <p>Country: Sweden</p> <p>Participant source: Community</p> <p>Setting: Other (custody center for arrests)</p> <p>Enrollment period: 11/1986 to 09/1987</p> <p>Design: Case control</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Adult amphetamine addicts born between 1945 and 1966 • Born in any of the seven largest hospitals in Stockholm • Brought up at home by biological mother <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: Addicts whose mothers were given N₂O during delivery (mix and administration NR) G2: Non-addicted siblings as controls</p> <p>N at enrollment: G1: 200 G2: 195</p> <p>N at follow-up: NR</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, %: Duration of nitrous oxide analgesia: ≥ 4.5 hours: G1: 18.4 G2: 7.1 ≥ 2.5 to < 4.5 hours: G1: 21.3 G2: 20.8 > 1 to < 2.5 hours: G1: 19.9 G2: 16.9 > 0.25 to ≤ 1 hour: G1: 23.4 G2: 27.3 ≤ 0.25 hour: G1: 17.0 G2: 27.9</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n: Vaginal: NR Assisted: NR Cesarean: G1: 0 G2: 0</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR Childhood: Amphetamine addiction in offspring, relative risk for N₂O exposure ≥ 4.5 hours (95% CI): Males: G1/G2: 8.2 (1.2, 55.2) Females: G1/G2: 3.6 (0.96,15.8) Amphetamine addiction in offspring, relative risk for N₂O exposure: ≥ 4.5 hours: G1/G2: 5.6¹ ≥ 2.5 to < 4.5 hours: G1/G2: NR¹ > 1 to < 2.5 hours: G1/G2: NR¹ > 0.25 to ≤ 1 hour: G1/G2: NR¹ ≤ 0.25 hour: G1/G2: 1.0 Occupational: NR</p>

Comments:

¹ Data only displayed graphically. Observed relative risks for all exposure levels fall within the 95% confidence intervals of estimated risks determined from logistic regression analysis.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Jones et al., 1969</p> <p>Country: United Kingdom</p> <p>Participant source: NR</p> <p>Setting: Hospital</p> <p>Enrollment period: 05/1962 to 11/1967</p> <p>Design: RCT *****</p> <p>Inclusion criteria: • Normal delivery</p> <p>Exclusion criteria: • Those who had received instruction in psychoprophylaxis or hypnosis</p>	<p>Groups: G1: N₂O in O₂ (calibrated in 5% steps from 20% to 100% O₂ and checked at continuous flows up to 40 liters/ minute) G2: Methoxyflurane in O₂ enriched air (40% O₂ with a flow of about 30 liters/minute)</p> <p>Both administered by observer</p> <p>N at enrollment: G1: 24 G2: 24</p> <p>Age, mean yrs ± SD: G1: 25.0 ± 5.0 G2: 24.4 ± 5.9</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%*): G1: 13 (54) G2: 13 (54)</p>	<p>Provider preferences: NR</p> <p>Provider specialty, %: Midwife: Total: 100</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Pethidine given within 4 hours of inhalation</p> <p>Pain management, n (%*): Pethidine: G1: 11 (45.8) G2: 14 (58.3)</p> <p>Duration of inhalation, minutes, mean ± SD: G1: 83 ± 66.3 G2: 82.5 ± 72.8</p>	<p>Pain: Anesthetist's assessment of analgesia, mean % of time satisfactory ± SD: All factors: G1: 70.9 ± 17.6 G2: 73.8 ± 26.3 All factors, pethidine within 4 hours of inhalation: G1: 72.9 ± 19.0 G2: 67.5 ± 29.6 All factors, no pethidine: G1: 69.3 ± 16.0 G2: 82.6 ± 18.8 Reactions to contractions: G1: 77.2 ± 14.7 G2: 81.4 ± 22.3 Level of consciousness: G1: 94.5 ± 7.2 G2: 94.0 ± 8.7 Restlessness: G1: 97.2 ± 6.4 G2: 92.1 ± 14.7</p> <p>Anesthetist's assessment of analgesia, all factors, mean % of time satisfactory, n (%): 0-59: G1: 2 (8) G2: 3 (13) 60-69: G1: 4 (17) G2: 3 (13) 70-79: G1: 8 (33) G2: 2 (8) 80-89: G1: 5 (21) G2: 4 (16) 90-100: G1: 5 (21) G2: 12 (50) G1/G2: <i>P</i> < 0.05</p> <p>Anesthetist's assessment of analgesia, all factors, mean % of time satisfactory: First stage: G1: 71.2</p>	<p>Satisfaction with pain management, n (%): Midwife report: Complete pain relief: G1: 2 (9) G2: 9 (38) G1/G2: <i>P</i> < 0.05 Complete or considerable pain relief: G1: 15 (65) G2: 20 (83)</p> <p>Maternal report, immediately after delivery: Complete pain relief: G1: 4 (18) G2: 7 (29) Considerable pain relief: G1: 15 (68) G2: 12 (50) Slight pain relief: G1: 3 (14) G2: 4 (17) No pain relief: G1: 0 G2: 1 (4) Pain relief complete or considerable, 48 hours post delivery: G1: 19 (83) G2: 22 (92)</p> <p>Satisfaction with birth experience, n (%): Better than previous labour, multiparae: G1: 6 (46) G2: 8 (62)</p> <p>Neonatal status: Apgar score, 1 minute: G1: NR G2: NR G1/G2: <i>P</i> = NS</p> <p>Adverse effects: Maternal: Too drowsy, midwife report, n (%*): G1: 3 (12.5) G2: 3 (12.5)</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Jones et al., 1969 (continued)			<p>G2: 73.8 Second stage: G1: 73.8 G2: 71.2 Third stage: G1: 67.5 G2: 62.0 30 minutes before delivery: G1: 66.7 G2: 73.1</p> <p>Labor progress: Duration of second stage labor, minutes, mean \pm SD: G1: 32.0 \pm 23.4 G2: 36.7 \pm 25.3</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n (%): Vaginal: G1: 19 (79) G2: 19 (79)</p> <p>Assisted: G1: 5 (21) G2: 5 (21)</p> <p>Cesarean: G1: 0 G2: 0</p>	<p>Blood loss, midwife estimate, ml, mean (range): G1: 160 (25-500) G2: 176 (30-500)</p> <p>Vomiting, n (%): During labor (assessed immediately after delivery): G1: 4 (17) G2: 0</p> <p>At some point during labor or in succeeding 24 hours (assessed 36-48 hours after delivery): G1: 6 (25) G2: 4 (17)</p> <p>Nausea, n (%): During labor (assessed immediately after delivery): G1: 8 (35) G2: 2 (8)</p> <p>At some point during labor or in succeeding 24 hours (assessed 36-48 hours after delivery): G1: 13 (54) G2: 5 (21) G1/G2: $P < 0.05$</p> <p>Memory of labor and delivery (assessed 36-48 hours after delivery): G1: NR G2: NR G1/G2: $P = NS$</p> <p>Neonatal, n: Fetal distress: G1: 1 G2: 0</p> <p>Neonatal deaths: Total: 2</p> <p>Childhood: NR</p> <p>Occupational: NR</p>

Comments:

* Calculated by reviewer.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Jones et al., 1969</p> <p>Country: United Kingdom</p> <p>Participant source: NR</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Normal delivery <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Received instruction in psychoprophylaxis or hypnosis 	<p>Groups: G1: N₂O in O₂ (50%/50%) G2: Methoxyflurane (0.35%) in air</p> <p>Both self-administered intermittently.</p> <p>N at enrollment: G1: 25 G2: 25</p> <p>N at follow-up: NR</p> <p>Age, mean yrs ± SD: G1: 26.5 ± 7.2 G2: 24.1 ± 5.1</p> <p>Race/ethnicity: NR</p> <p>Primiparous, n (%): G1: 9 (36) G2: 11 (44)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Other analgesic (pethidine) or sedative drugs were given by the midwife on her usual indications.</p> <p>Pain management n (%*): Pethidine: G1: 17 (68) G2: 16 (64)</p> <p>Mean duration of inhalation, minutes, mean ± SD: G1: 66.1 ± 39.2 G2: 90.1 ± 67.5 G1/G2: <i>P</i> = NS</p>	<p>Pain, n: Anesthetist's assessment of analgesia, mean % of time satisfactory ± SD: All factors: G1: 61.5 ± 29.9 G2: 78.1 ± 20.1 G1/G2: <i>P</i> < 0.05 All factors, pethidine within 4 hours of inhalation: G1: 61.3 ± 30.8 G2: 85.4 ± 12.8 G1/G2: <i>P</i> < 0.01 All factors, no pethidine: G1: 60.5 ± 32.7 G2: 65.1 ± 24.6 G1/G2: <i>P</i> = NS Reactions to contractions: G1: 62.3 ± 30 G2: 79.3 ± 20 G1/G2: <i>P</i> < 0.05 Level of consciousness: G1: 98.9 ± 2.2 G2: 98.7 ± 3.7 Restlessness: G1: 98.5 ± 4.2 G2: 99.4 ± 1.4 Anesthetist's assessment of analgesia, all factors, mean % of time satisfactory, n (%): 0-59: G1: 11(44) G2: 4 (16) 60-69: G1: 2 (8) G2: 4 (16) 70-79: G1: 2 (8) G2: 2 (8) 80-89: G1: 6 (24) G2: 5 (20) 90-100: G1: 4 (15) G2: 10 (40)</p> <p>Labor progress: G1: NR¹ G2: NR¹</p>	<p>Satisfaction with pain management, n (%): Midwife report: Complete pain relief: G1: 2 (8) G2: 4 (16) Complete or considerable pain relief: G1: 18 (72) G2: 21 (84) Adequately cooperative: G1: 24 (96) G2: 24 (96) Satisfactory (restless assessment): G1: 15 (60) G2: 17 (68)</p> <p>Maternal report, immediately after delivery: Complete pain relief: G1: 4 (16) G2: 7 (28) Considerable pain relief: G1: 16 (64) G2: 14 (56) Slight pain relief: G1: 5 (20) G2: 4 (16) No pain relief: G1: 0 G2: 0</p> <p>Labor worse than expected, n (%): (36 to 48 hours after delivery) Time 1: G1: 10 (40) G2: 4 (16) G1/G2: <i>P</i> = NS Time 2: G1: 9 (36) G2: 2 (8) G1/G2: <i>P</i> < 0.05</p> <p>Labor better than previous labors, multiparae, n (%): (36 to 48 hours after delivery) Time 1:</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Jones et al., 1969 (continued)			Fetal status: NR Timeliness: NR Labor co-interventions: NR Adverse effects: NR Route of birth: NR	G1: 4 (25) G2: 9 (64) G1/G2: <i>P</i> = NS Time 2: G1: 12 (86) G2: 5 (31) G1/G2: <i>P</i> < 0.01 Maternal Status, n (%) : Remembered labor clearly (vs. hazily): G1: 17 (68) G2: 17 (68) Remembered actual delivery clearly: G1: 10 (40) G2: 17 (68) Thought they had fallen asleep during inhalation: G1: 8 (32) G2: 4 (16) Smell noted with inhalation: G1: 4 (16) G2: 25 (100) Dreams experienced: G1: 6 (24) G2: 4 (16) Other sensations: G1: 9 (36) G2: 2 (8) G1/G2: <i>P</i> < 0.05 Neonatal status: Apgar scores, 1-10 minutes after delivery: G1: NR ² G2: NR ² Adverse effects: Maternal: Blood loss, midwife estimate, ml, mean ± SD: G1: 144.0 ± 149 G2: 186.7 ± 101 Vomiting during labor (assessed immediately after delivery), n (%): G1: 2 (8) G2: 0

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Jones et al., 1969 (continued)				<p>Nausea during labor (assessed immediately after delivery), n (%): G1: 8 (32) G2: 0 G1/G2: $P < 0.01$</p> <p>Nausea or vomiting at some point during labor (assessed subsequently), n (%): G1: 8 (32) G2: 4 (16) G1/G2: $P = NS$</p> <p>Neonatal: NR Childhood: NR Occupational: NR</p>

Comments:

* Calculated by reviewer.

¹ The progress of labor in the two groups was similar, though the first stage of labor was shorter in G1

² There were no differences between the agents as demonstrated by the Apgar scores at 1, 2, 5 or 10 minutes.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Landon et al., 1992</p> <p>Country: United Kingdom</p> <p>Participant source: NR</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Healthy • Uncomplicated pregnancy <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Preeclampsia • Metabolic or haematological disease • IUGR • Abnormalities of the placenta • Pregnancy did not progress normally to full-term delivery 	<p>Groups: G1: Vaginal birth and Entonox G2: Vaginal birth without N₂O</p> <p>N at enrollment: G1: 45 G2: 13</p> <p>N at follow-up: G1: 45 G2: 13</p> <p>Age, mean yrs: G1: 27.5 G2: 29.4</p> <p>Race/ethnicity, n: Asian: G1: 16 G2: 3</p> <p>Parous, n: G1: 21 G2: 8</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress, Duration of labor, hours, mean ± SD: G1: 6.2 ± 2.8 G2: 5.5 ± 3.0</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n (%): Vaginal: G1: 45 (100) G2: 13 (100)</p> <p>Assisted: G1: 0 G2: 0</p> <p>Cesarean: G1: 0 G2: 0</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: Hb, g/dl, mean ± SD: G1: 12.8 ± 1.2 G2: 12.7 ± 0.67</p> <p>Mean cell volume, fl, mean ± SD: G1: 86.8 ± 14.5 G2: 90.4 ± 3.1</p> <p>Neonatal status: Birth weight, kg, mean ± SD: G1: 3.3 ± 0.45 G2: 3.1 ± 0.45</p> <p>Apgar score, mean ± SD: 1 minute: G1: 8.5 ± 1.1 G2: 8.5 ± 0.9 5 minutes: G1: 9.3 ± 0.5 G2: 9.4 ± 0.5</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Leong et al., 2000</p> <p>Country: Malaysia</p> <p>Participant source: Academic single setting</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort¹ *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Randomly selected healthy primigravid women at term (37-41 weeks) • Cervical dilation not exceeding 4 cm • Cephalic presentation • Presenting to labor between 0800 and 1000 hours <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Complications such as previous uterine surgery • Pre-existing illness • Hypertension • Abnormal admission cardiotocography • Contraindications to an epidural 	<p>Groups: G1: Inhalational Entonox (nitrous) and IM pethidine routine; 75-100 mg IM pethidine every 4-6 hours with Entonox (these patients declined an epidural) G2: Epidural with initial dose of 4-6 ml of 0.25% bupivacaine followed by maintenance dose of 6-10 ml/hour of 0.125% bupivacaine with 0.0002% fentanyl (selected by patients)</p> <p>N at enrollment: (enrolled in labor between 0800 and 1000 hours) G1: 68 G2: 55</p> <p>N at follow-up: G1: 68 G2: 50</p> <p>Age, mean yrs: G1: 24.9 G2: 25.5</p> <p>Race/ethnicity, %: Chinese: G1: 20.6 G2: 30.9 Indian: G1: 11.8 G2: 14.6 Malay: G1: 67.7 G2: 54.6</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress, mean duration of labor, min, mean: First stage: G1: 483.4 (n=65) G2: 565.8 G1/G2: $P < 0.02$ Second stage: G1: 36.3 (n=65) G2: 60.2 G1/G2: $P < 0.03$ Third stage: G1: 5.8 (n=65) G2: 6.3 G1/G2: $P = NS$ Total duration of labor: G1: 525.5 (n=65) G2: 631.6 G1/G2: $P < 0.03$</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions, n (%): Oxytocin augmentation: G1: 38 (55.9) G2: 48 (87.3) G1/G2: $P < 0.01$ Continuous cardiotocography: G1: 68 (100) G2: 55 (100)</p> <p>Adverse effects, n (%): Maternal: Ascension of epidural block to T3/T4: G1: 0 (NR) G2: 1 (NR) Spinal headache requiring blood patch: G1: 0 G2: 2 (3.6) Backache requiring oral analgesics: G1: 0 G2: 2 (3.6)</p>	<p>Satisfaction with pain management, n (%): (day after birth) Happy with method and would repeat in next pregnancy: G1: NR (35.3) G2: NR (69) Unhappy and unsatisfied with pain method: G1: 31 (45.6) G2: 3 (5.5)</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR²</p> <p>Neonatal status: NR³</p> <p>Adverse effects, n: Maternal: Voiding difficulties requiring repeat catheterization: G1: 0 G2: 2 Neonatal: NR Childhood: NR Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Leong et al., 2000 (continued)			<p>Neonatal: Occipito-transverse position in second stage of labor: G1: 0 G2: 8 (1.8)</p> <p>Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 56 (82.4) G2: 28 (50.9)</p> <p>Forceps assisted: G1: 5 (7.3) G2: 13 (23.6)</p> <p>Vacuum assisted: G1: 4 (5.9) G2: 9 (16.5)</p> <p>Cesarean: G1: 3 (4.4) G2: 5 (9.0) G1/G2: <i>P</i> = NS</p> <p>Total instrumental delivery rate: G1: NR (13.2) G2: NR (40.1) G1/G2: <i>P</i> < 0.01</p>	

Comments:

¹ Patients were randomly selected from those meeting inclusion criteria, but chose whether to be in epidural group.

² No significant difference in time to full ambulation or time to spontaneously void urine.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Marx et al., 1970</p> <p>Country: US</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Parturients with unremarkable prenatal courses <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: Vaginal delivery G2: Elective repeat cesarean section</p> <p>N at enrollment: G1: 26 G2: 14</p> <p>N at follow-up: G1: 26 G2: 14</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: G1: N₂O (ranging from 50-70%) and O₂ by mask in a semiclosed system with circle absorber plus local anesthesia G2: Anesthetized with 150-250 mg thiopental followed by N₂O-O₂ via endotracheal tube and 0.1% succinylcholine by IV infusion</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n: Vaginal: G1: 16 G2: 0</p> <p>Assisted, forceps: G1: 10 G2: 0</p> <p>Cesarean: G1: 0 G2: 14</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Umbilical vein blood N₂O levels, vol % range: Total: 11.2-28.8</p> <p>Apgar score < 6, 1 minute, n: 6 or less: G1: 3 G2: 1</p> <p>Apgar score 9-10, 5 minutes, n (%): Total: 40 (100)</p> <p>Adverse effects: Maternal: NR</p> <p>Neonatal, n: Severe fetal acidosis: G1: 3 G2: 0 High fetal N₂O level with normal acid-base values: G1: 0 G2: 1</p> <p>Childhood: NR</p> <p>Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: McAneny and Doughty 1963</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Nonrandomized trial *****</p> <p>Inclusion criteria: • English speaking women in labor</p> <p>Exclusion criteria: • See inclusion criteria</p>	<p>Groups: G1: 50% N₂O in O₂ G2: 60% N₂O in O₂ G3: 70% N₂O in O₂ G4: 75% N₂O in O₂ G5: 80% N₂O in O₂</p> <p>N at enrollment: G1: 101 G2: 101 G3: 100 G4: 101 G5: 98 Total: 501</p> <p>N at follow-up: G1: 101 G2: 101 G3: 100 G4: 101 G5: 98</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primigravidae: Total: 342 (68.3)</p> <p>Multigravidae: Total: 159 (31.7)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, %: Multiple analgesics by injection: G1: 30.0 G2: 26.0 G3: 22.0 G4: 29.0 G5: 33.0</p>	<p>Pain, %: Considerable and complete relief, mothers report: G1: 52.0 G2: 64.0 G3: 74.0 G4: 76.0 G5: 75.5 G1/G3: <i>P</i> < 0.01</p> <p>First stage, midwife report: Complete relief: G1: 8.0 G2: 6.0 G3: 14.0 G4: 12.0 G5: 7.0 Complete or adequate relief: G1: 92.0 G2: 92.0 G3: 90.0 G4: 88.0 G5: 92.0</p> <p>Second stage, midwife report: Complete relief: G1: 18.0 G2: 10.0 G3: 12.0 G4: 9.0 G5: 11.0 Complete or adequate relief: G1: 94.0 G2: 92.0 G3: 94.0 G4: 92.0 G5: 93.0</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal, (%):</p>	<p>Satisfaction with pain management: One day after labor: Only 2 mothers reported no pain during labor</p> <p>About 40% of mothers reported that the pain was worse than expected</p> <p>Satisfaction with birth experience, %: One day after labor: Would tolerate the same labor again: G1: 82.0 G2: 81.0 G3: 89.0 G4: 87.0 G5: 75.5 G3/G5: <i>P</i> < 0.02</p> <p>Were comfortable late in 1st stage of labor: G1: 55.0 G2: 66.0 G3: 63.0 G4: 56.0 G5: 60.0</p> <p>Were comfortable while pushing in 2nd stage: G1: 72.0 G2: 74.0 G3: 74.0 G4: 73.0 G5: 74.0</p> <p>Were comfortable at the actual birth: G1: 76.0 G2: 82.0 G3: 86.0 G4: 88.0 G5: 83.0</p> <p>Maternal status: NR</p> <p>Neonatal status: Mean Apgar score: G1: 9.1 G2: 8.6 G3: 8.9 G4: 8.6</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
McAney and Doughty 1963 (continued)			<p>Unconsciousness: G1: 1.0 G2: 3.0 G3: 1.0 G4: 5.0 G5: 5.0</p> <p>Restless or noisy: G1: 21.0 G2: 14.0 G3: 15.0 G4: 16.0 G5: 23.0</p> <p>Any complications: G1: 25.0 G2: 27.0 G3: 20.0 G4: 19.0 G5: 24.5</p> <p>Hemorrhage: G1: 8.5 G2: 8.5 G3: 6.5 G4: 4.0 G5: 5.0</p> <p>Hazy or no memory of labor: G1: 43.0 G2: 53.0 G3: 57.0 G4: 53.0 G5: 49.0</p> <p>Hazy or no memory of birth: G1: 15.0 G2: 25.0 G3: 26.0 G4: 31.0 G5: 26.0 G1/G4: $P < 0.02$</p> <p>Dreamed while breathing gas: G1: 8.0 G2: 12.0 G3: 18.0 G4: 21.0 G5: 26.0 G1/G5: $P < 0.001$</p> <p>Nausea or vomiting: G1: 16.0 G2: 15.0 G3: 22.0 G4: 22.0 G5: 18.5</p>	<p>G5: 8.9</p> <p>Adverse effects: Maternal: NR</p> <p>Neonatal: Death: G1: One neonatal death 9 hours after delivery</p> <p>Childhood: NR</p> <p>Occupational: NR</p>
			<p>Neonatal: NR</p> <p>Occupational: NR</p>	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
McAney and Doughty 1963 (continued)			Route of birth, %: Vaginal: NR Assisted: ¹ G1: 15.0 G2: 18.0 G3: 11.5 G4: 10.5 G5: 17.0 Cesarean: NR	

Comments:

¹ Forceps

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: McGuiness and Rosen, 1984</p> <p>Country: United Kingdom</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Crossover RCT</p> <p>At onset of regular uterine contractions, each participant was randomly administered one agent during 3 consecutive uterine contractions, followed by the other agent for 3 further contractions (the agent was concealed to the operator).</p>	<p>Groups: G1: Women delivered two gas mixtures via the same tubing and mouthpiece Ga: Entonox (50% N₂O in O₂) Gb: Enflurane 1% in air (delivered from a low resistance drawover Cyprane vaporizer) Gc: No analgesia</p> <p>N at enrollment: (during early normal labor) G1: 20</p> <p>N at follow-up: G1: 20</p> <p>Age, range yrs: G1: 20-33</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: Linear analog score, median (range): G1a: 52 (29-79) G1b: 50 (13-79) G1c: 61 (47-87) G1a/G1b: $P < 0.02$ G1a/G1c: $P = \text{NR}^1$ G1b/G1c: $P = \text{NR}^1$</p> <p>Linear analog score, n (%): 0-20: G1a: 0 G1b: 1 (5.0) G1c: 0 20-40: G1a: 4 (20.0) G1b: 7 (35.0) G1c: 0 40-60: G1a: 10 (50.0) G1b: 6 (30.0) G1c: 10 (50.0) 60-80: G1a: 6 (30.0) G1b: 6 (30.0) G1c: 6 (30.0) 80-100: G1a: 0 G1b: 0 G1c: 4 (20.0)</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: Drowsiness, linear analog score, median (range): G1a: 26 (0-68) G1b: 38 (0-88) G1a/G1b: $P < 0.02$ Slightly nauseous, n (%): G1a: 1 (5.0) G1b: 3 (15.0)</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
McGuinness and Rosen, 1984 (continued)			Neonatal: NR Occupational: NR Route of birth, n (%): Vaginal: G1: 15 (75.0) Assisted, forceps: G1: 2 (10.0) Cesarean: G1: 3 (15.0)	

Comments:

¹ The authors state that the difference is significant, but do not report the significance level used.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: McLeod et al., 1985</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Crossover RCT *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Women aged 18-38 • ASA group I • Normal labor <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Use of any other analgesic or sedative agent during labor 	<p>Groups: G1: Women given both agents in random sequence during 5 consecutive uterine contractions, with a break of 2 contractions to allow for elimination of first agent Ga: Entonox (50% N₂O in O₂) Gb: Isoflurane (0.75% in O₂)</p> <p>Both self-administered using separate facemasks</p> <p>N at enrollment: (in established labor) G1: 32</p> <p>N at follow-up: (end of trial) G1: 32</p> <p>Age, range yrs: G1: 18-38</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: Linear analog scores, mean (range): Prior to analgesia: G1: 75.4 (44-99) Post analgesia: G1a: 63.0 (24-92) G1b: 46.6 (19-86) G1a/G1b: <i>P</i> < 0.001</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal:¹ Drowsiness, assessed by midwife and patient: More drowsy when using Entonox: G1: 3 (9.7) More drowsy when using isoflurane: G1: 18 (58.1) Equal between agents: G1: 10 (32.2) Nausea, n: G1a: 1 G1b: 1 Dizziness, n: G1a: 2 G1b: 0 Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 32 (100) Assisted: G1: 0 Cesarean: G1: 0</p>	<p>Satisfaction with pain management, n (%): Preference at the end of the trial: Entonox: G1: 8 (25.0) Isoflurane: G1: 22 (68.8) No preference: G1: 2 (6.3)</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Comments:

¹ Results of 31 participants included.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Mills et al., 1996</p> <p>Country: United Kingdom</p> <p>Participant source: Multi-site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> •Midwives working in labor wards in one of two selected UK hospitals <p>Exclusion criteria:</p> <ul style="list-style-type: none"> •See inclusion criteria 	<p>Groups: Midwives working in labor wards at one of two hospitals (DRI and BDGH) and wearing N₂O personal sampling devices</p> <p>N at enrollment: DRI: 5 midwives/shift BDGH: 4 midwives/shift</p> <p>N at follow-up: 242 total shifts analyzed</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty, %: Midwives: 100</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR Occupational: N₂O exposure, mean ppm (range): DRI: 45 (0-413) BDGH: 124 (0-1638) Total: 86 (0-1638)</p> <p>In 111 shifts worked in rooms where Entonox was not used: Mean ppm (range): Total: 22 (0-233)</p> <p>Exceed exposure level, n (%): > 100 ppm: Total: 4 (3.6) > 25 ppm: Total: 21 (18.9)</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Morgan et al., 1982</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Cross-sectional *****</p> <p>Inclusion criteria: • Vaginal delivery of a live child</p> <p>Exclusion criteria: • See inclusion criteria</p>	<p>Groups: G1: Entonox, self administered G2: 100 mg Pethidine and 25 mg promethazine IM G3: Entonox and pethidine G4: Pudendal block G5: Epidural G6: Epidural and Entonox G7: Epidural and pethidine G8: Miscellaneous (ineffective epidural blocks or other analgesia, various IM and IV opiates, and regional blocks) G9: None</p> <p>N at enrollment: Total: 1,000 G1: 128 G2: 120 G3: 88 G4: 24 G5: 423 G6: 38 G7: 47 G8: 52 G9: 80</p> <p>N at follow-up: (within 48 hours of delivery) Total: 1,000</p> <p>Age, mean yrs ± SD: Total: 28 ± 4.8</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Total: 496 (49.6)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, n (%): Entonox: Total: 128 (12.8) Pethidine: Total: 120 (12.0) Entonox and pethidine: Total: 88 (8.8) Pudendal block: Total: 24 (2.4) Epidural: Total: 423 (42.3) Epidural and Entonox: Total: 38 (3.8) Epidural and pethidine: Total: 47 (4.7) Miscellaneous: Total: 52 (5.2) None: Total: 80 (8.0)</p>	<p>Pain: (linear analogue scale 0-100 mm)¹ Linear analogue score, mean ± SD: G1: 61 ± 3.1 G2: 58 ± 3.1 G3: 57 ± 3.4 G4: 68 ± 1.9 G5: 29 ± 3.7 G6: 51 ± 4.2 G7: 30 ± 3.8 G8: 69 ± 3.3 G9: 70 ± 2.6</p> <p>Painless labor, n (%): G1: 15 (11.7) G2: 15 (12.5) G3: 16 (18.2) G4: 2 (8.3) G5: 251 (59.3) G6: 13 (34.2) G7: 29 (61.7) G8: 7 (13.5) G9: 6 (7.5)</p> <p>Duration of pain, minutes, mean: G1: 47 G2: 66 G3: 71 G4: 73 G5: 35 G6: 66 G7: 56 G8: 75 G9: 50</p> <p>Labor progress, n (%): Induced: G1: 21 (16.4) G2: 22 (18.3) G3: 16 (18.2) G4: 4 (16.7) G5: 148 (35.0) G6: 12 (31.6) G7: 12 (25.5) G8: 21 (40.4) G9: 9 (11.3)</p> <p>Duration, hours, mean ± SD: G1: 6.7 ± 3.0 G2: 7.3 ± 3.2 G3: 7.6 ± 4.1 G4: 5.6 ± 4.2</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Morgan et al., 1982 (continued)			G5: 10.5 ± 4.6 G6: 8.6 ± 4.7 G7: 13.1 ± 6.1 G8: 10.7 ± 4.9 G9: 5.2 ± 3.5	
			Fetal status: NR	
			Timeliness: NR	
			Labor co-interventions: NR	
			Adverse effects: NR	
			Route of birth, n (%): Vaginal:* G1: 120 (93.7) G2: 111 (92.5) G3: 83 (94.3) G4: 20 (83.3) G5: 206 (48.7) G6: 23 (60.5) G7: 22 (46.8) G8: 11 (21.2) G9: 79 (98.7)	
			Assisted: G1: 8 (6.3) G2: 9 (7.5) G3: 5 (5.7) G4: 4 (16.7) G5: 217 (51.3) G6: 15 (39.5) G7: 25 (53.2) G8: 41 (78.8) G9: 1 (1.3)	
			Cesarean: Total: 0	

Comments:

* Calculated by reviewer

¹ 0 (no pain) to 100 mm (as much pain as is possible to imagine)

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Murphy et al., 1984</p> <p>Country: United Kingdom</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 1970 to 1979</p> <p>Design: Retrospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Live births from 1970-1979 • Data from Cardiff Births Survey • Residents of South Glamorgan <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: N₂O 50%/O₂ 50% (Entonox) used for maternal analgesia, administration not specified G2: Drugs and N₂O (Entonox) used for maternal analgesia G3: Drugs only (mainly pethidine) used for maternal analgesia G4: Epidural block used for maternal analgesia G5: No analgesia used</p> <p>Ga: Gave birth from 1970-1974 Gb: Gave birth from 1975-1979</p> <p>N at enrollment: G1: 8,392 G1a: 3,798 G1b: 4,594 G2: 21,121 G2a: 12,375 G2b: 8,746 G3: 3,749 G3a: 2,855 G3b: 894 G4: 4,435 G4a: 1,235 G4b: 3,200 G5: 2,440 G5a: 1,562 G5b: 878</p> <p>N at follow-up: G1: 8,392 G2: 21,121 G3: 3,749 G4: 4,435 G5: 2,440</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n:¹ Primiparae: G1a: 642 G1b: 894 G2a: 5,667</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, singletons with no congenital anomalies, n: Vaginal (vertex): Total: 30,172 Ga: 16,619 Gb: 13,553</p> <p>Assisted, forceps: Total: 5,737 Ga: 2,752 Gb: 2,985</p> <p>Cesarean: Total: 2,482 Ga: 1,038 G1b: 1,444</p> <p>Elective: Total: 856 Ga: 411 Gb: 445</p> <p>Emergency: Total: 1,626 Ga: 627 Gb: 999</p> <p>Singleton births: G1: 8,145 G1a: 3,697 G1b: 4,448 G2: 20,670 G2a: 12,084 G2b: 8,586 G3: 3,644 G3a: 2,770 G3b: 874 G4: 4,307 G4a: 1,223</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status, n (%): Lower of 1 and 5 minute Apgar scores, singletons with no congenital anomalies: 1-3: G1a: 66 (1.8) G1b: 63 (1.4) G2a: 330 (2.7) G2b: 220 (2.6) G3a: 121 (4.4) G3b: 25 (2.7) G4a: 38 (3.1) G4b: 48 (1.5) G5a: 26 (1.7) G5b: 13 (1.5)</p> <p>4-7: G1a: 389 (10.5) G1b: 388 (8.7) G2a: 2270 (18.8) G2b: 1594 (18.6) G3a: 586 (21.2) G3b: 149 (17.0) G4a: 274 (22.4) G4b: 509 (16.5) G5a: 183 (121) G5b: 72 (8.5)</p> <p>8-10: G1a: 3242 (87.7) G1b: 3997 (89.9) G2a: 9484 (78.5) G2b: 6772 (78.8) G3a: 2063 (74.4) G3b: 700 (80.3) G4a: 911 (74.5) G4b: 2527 (82.0) G5a: 1299 (86.1) G5b: 767 (90.0)</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Murphy et al., 1984 (continued)	G2b: 3,806 G3a: 1,211 G3b: 313 G4a: 837 G4b: 2,101 G5a: 315 G5b: 125 Ga: 8,672 Gb: 7,239 Multiparae: G1a: 3,120 G1b: 3,644 G2a: 6,599 G2b: 4,893 G3a: 1,616 G3b: 577 G4a: 397 G4b: 1,048 G5a: 1,185 G5b: 753 Ga: 12,917 Gb: 10,915		G4b: 3,084 G5: 2,360 G5a: 1,508 G5b: 852	

Comments:

¹ Parity was not known for 236 of women in Ga and 158 women in Gb.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Newton et al., 1999</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Cross-sectional</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Midwife participating in the care of women using Entonox during labor in a specific UK hospital <p>Exclusion criteria: See inclusion criteria</p>	<p>Groups: G1: Midwives participating in the care of women wearing samplers to measure N₂O levels over 8 hrs</p> <p>N at enrollment: 16</p> <p>N at follow-up: 15</p> <p>Age, mean yrs : NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: Midwife: 16 (100)</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: NR</p> <p>Neonatal: NR</p> <p>Occupational: No midwife was exposed to levels of N₂O greater than 100ppm</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Nyberg et al., 1992</p> <p>Country: Sweden</p> <p>Participant source: Other (see inclusion criteria)</p> <p>Setting: Other (see inclusion criteria)</p> <p>Enrollment period: 1945 to 1966</p> <p>Design: Case control</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Amphetamine or opiate addict • Brought to Stockholm City Custody • Opiate addict from autopsy victims at the State Institute of Forensic Medicine in Stockholm • Opiate addict accepted for the methadone program at Ulleraker Hospital <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1a: Amphetamine addicts G1b: Control siblings G2a: Opiate addicts G2b: Control siblings</p> <p>N at enrollment: G1a: 200 G1b: NR G2a: 200 G2b: NR</p> <p>N at follow-up: G1a: 73 G1b: 109 G2a: 139 G2b: 230</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR</p> <p>Childhood: Amphetamine addiction in offspring, relative risk for exposure to N₂O (95% CI): ≥ 4.5 hrs: G1: 4.4 (1.2,15.8) ≥ 2.5 to < 4.5 hrs: G1: 3.1 (1.2,7.9) > 1 to < 2.5 hrs: G1: 2.1 (1.11, 4.0) > 0.25 to ≤ 1 hr: G1: 1.5 (1.06, 2.0) 0 to ≤ 0.25 hr: G1: 1.0</p> <p>Opiate addiction in offspring, relative risk for exposure to N₂O (95% CI): G2: NR¹</p> <p>Occupational: NR</p>

Comments:

¹ In group G2, nitrous oxide is combined with opiate and barbiturate exposure. After controlling for socio-economic level and civil status of the mother at time of delivery, the conditional logistic regression analysis confirms that administration of opiate or barbiturate or nitrous oxide during delivery is a risk factor for adult amphetamine addiction in offspring, and that the number of administrations of either opiates, barbiturates or nitrous oxide for >1 hour, or any combination thereof, is a risk factor for opiate addiction.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Paech, 1991</p> <p>Country: Australia</p> <p>Participant source: NR</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Cross-sectional *****</p> <p>Inclusion criteria: • Vaginal birth</p> <p>Exclusion criteria: • See inclusion criteria</p>	<p>Groups:* G1: N₂O alone G2: Pethidine and N₂O G3: N₂O and epidural G4: Pethidine alone G5: Pethidine and epidural G6: Epidural alone G7: Several methods¹ G8: Non-pharmacological Ga: N₂O Gb: Pethidine Gc: Epidural Gd: No epidural</p> <p>N at enrollment: (day after vaginal birth) G1: 220 G2: 175 G3: 84 G4: 83 G5: 86 G6: 112 G7: 100 G8: 140 Ga: NR* Gb: NR* Gc: NR* Gd: NR*</p> <p>N at follow-up: G1: 220 G2: 175 G3: 84 G4: 83 G5: 86 G6: 112 G7: 100 G8: 140 Ga: NR¹ Gb: NR¹ Gc: NR¹ Gd: NR¹</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primipara: G1: 50 (23) G2: 86 (49) G3: 40 (48)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Antenatal preparation classes, on-demand epidural service, along with noted available treatments</p> <p>G8: Transcutaneous nerve stimulation (TENS)</p> <p>Pain management: NR</p>	<p>Pain, n (%): VAS < 25: G1: NR² G4: NR² G6: NR² G8: NR² G6/G1: <i>P</i> < 0.0001 G6/G4: <i>P</i> < 0.0001 G6/G8: <i>P</i> < 0.0001 Gc/Gd: <i>P</i> < 0.0001</p> <p>VAS < 50: G1: NR² G4: NR² G6: NR² G8: NR² G6/G1: <i>P</i> < 0.0001 G6/G4: <i>P</i> < 0.0001 G6/G8: <i>P</i> < 0.0001 Gc/Gd: <i>P</i> < 0.0001</p> <p>More than expected: G1: 93 (42) G2: 97 (55) G3: 38 (45) G4: 47 (57) G5: 40 (47) G6: 33 (29) G7: 60 (60) G8: 46 (33)</p> <p>Labor progress: Duration of labor, minutes, mean ± SD: First stage: G1: 291 ± 191 G2: 338 ± 200 G3: 397 ± 189 G4: 328 ± 195 G5: 501 ± 250 G6: 397 ± 223 G7: 507 ± 292 G8: 244 ± 155</p> <p>Second stage: G1: 29 ± 32 G2: 40 ± 37 G3: 79 ± 60 G4: 36 ± 35 G5: 98 ± 70 G6: 73 ± 58 G7: 87 ± 67 G8: 24 ± 31</p> <p>Fetal status: NR</p>	<p>Satisfaction with pain management: VAS > 75: G1: NR² G4: NR² G6: NR² G8: NR² Gc: NR² Gd: NR² G6/G1: <i>P</i> < 0.0001 G6/G4: <i>P</i> < 0.0001 G6/G8: <i>P</i> < 0.0001 Gc/Gd: <i>P</i> < 0.0001</p> <p>VAS = 100: G1: NR² G4: NR² G6: NR² G8: NR² Gc: NR² Gd: NR² G6/G1: <i>P</i> < 0.0001 G6/G4: <i>P</i> < 0.0001 G6/G8: <i>P</i> < 0.0001 Gc/Gd: <i>P</i> < 0.0001</p> <p>Satisfaction with birth experience, n (%): (day after birth) Dissatisfied: Total: 51 (5.1) Gc: NR (7) Gd: NR (4) Gc/Gd: <i>P</i> = NS</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Paech, 1991 (continued)	G4: 38 (46) G5: 66 (77) G6: 56 (50) G7: 82 (82) G8: 22 (16) Multipara: G1: 170 (77) G2: 89 (51) G3: 44 (52) G4: 45 (54) G5: 20 (23) G6: 56 (50) G7: 18 (18) G8: 118 (84)		Timeliness: NR Labor co-interventions, n (%): Induced or augmented: G1: 91 (41) G2: 99 (57) G3: 65 (77) G4: 31 (37) G5: 69 (80) G6: 90 (80) G7: 80 (80) G8: 43 (31) Adverse effects, %: Maternal: Inadequate pain relief: Ga: 21 Gb: 27 Gc: 7 G8: 6 Gc/Ga: $P < 0.0001$ Gc/Gb: $P < 0.0001$ G8/Ga: $P < 0.0001$ G8/Gb: $P < 0.0001$ Reduced awareness of experience: Ga: 18 Gb: 16 Gc: 2 G8: 0 Nausea and vomiting: Ga: 13 Gb: 16 Gc: 14 G8: 0 Dizziness: Ga: 5 Gb: 6 Gc: 0 G8: 0 Drowsiness Ga: 4 Gb: 11 Gc: 0 G8: 0 Mask phobia: Ga: 5 Gb: 0 Gc: 0 G8: 0 Shivering: Ga: 0 Gb: 0 Gc: 19 G8: 0	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Paech, 1991 (continued)			<p>Back pain: Ga: 0 Gb: 0 Gc: 14 G8: 0</p> <p>Difficulty moving: Ga: 0 Gb: 0 Gc: 14 G8: 0</p> <p>Pruritus: Ga: 0 Gb: 0 Gc: 8 G8: 0</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 204 (93) G2: 152 (87) G3: 49 (58) G4: 76 (92) G5: 47 (55) G6: 58 (52) G7: 56 (56) G8: 135 (96)</p> <p>Assisted: G1: 16 (7) G2: 23 (13) G3: 35 (42) G4: 7 (8) G5: 39 (45) G6: 54 (48) G7: 44 (44) G8: 5 (4)</p> <p>Cesarean: Total: 0</p>	

Comments:

¹ The author states that almost all women in G7 had pethidine and nitrous oxide, followed by epidural analgesia. If this was the case for all women in G7, then the number of women in Ga, Gb and Gc would be 579, 444 and 382, respectively.

² Results only displayed graphically.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Phillips and Macdonald, 1971</p> <p>Country: United Kingdom</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Fetus at extra risk of intrapartum hypoxia during labor • Primigravidae aged ≥ 35 or multigravidae aged ≥ 40 • Previous stillbirth due to intrauterine hypoxia • Pregnancy prolonged beyond 41 weeks • Maternal diabetes, preeclampsia, threatened abortion or antepartum hemorrhage during current pregnancy • Small-for-dates fetus, or • Low urinary estrogen excretion <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: 50% N₂O/50% O₂ (Entonox; delivery NR) and pethidine G2: Pethidine alone (no inhaled analgesia) G3: Trichloroethylene and pethidine</p> <p>N at enrollment: G1: 50 G2: 51 G3: 51</p> <p>N at follow-up: (neonatal capillary blood collected) G1: 30 G2: 30 G3: 28</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: Fetal scalp blood pH, mean \pm SD: Before inhaled analgesia: G1: 7.253 \pm 0.065 (n=49) G2: 7.256 \pm 0.064 (n=50) G3: 7.256 \pm 0.053 After inhaled analgesia: G1: 7.244 \pm 0.071 (n=49) G2: 7.241 \pm 0.066 (n=50) G3: 7.216 \pm 0.057</p> <p>Fetal scalp blood PCO₂, mean \pm SD: Before inhaled analgesia: G1: 37.0 \pm 8.1 (n=49) G2: 39.8 \pm 6.1 G3: 34.9 \pm 5.9 After inhaled analgesia: G1: 35.0 \pm 7.0 (n=49) G2: 41.8 \pm 4.8 G3: 41.3 \pm 7.7</p> <p>Fetal scalp blood base deficit, mean \pm SD: Before inhaled analgesia: G1: -9.3 \pm 3.7 G2: -10.2 \pm 2.1 G3: -8.6 \pm 2.2 After inhaled analgesia: G1: -9.7 \pm 2.4 G2: -11.6 \pm 1.9 G3: -10.7 \pm 1.6</p> <p>Fetal scalp blood PO₂, mean \pm SD: Before inhaled analgesia: G1: 27.8 \pm 4.6 G2: 26.1 \pm 6.5 (n=50) G3: 30.0 \pm 5.8 After inhaled</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Apgar score, mean: 1 minute: G1: 7.42 G2: 6.70 G3: 6.17 5 minutes: G1: 9.20 G2: 8.85 G3: 8.43</p> <p>Apgar score, 1 minute, n: 4: G1: 0 G2: 3 G3: 9 5: G1: 0 G2: 0 G3: 1 6: G1: 21 G2: 27 G3: 27 7: G1: 0 G2: 0 G3: 0 8: G1: 20 G2: 21 G3: 14 9: G1: 5 G2: 0 G3: 0 10: G1: 4 G2: 0 G3: 0</p> <p>Apgar score, 5 minutes, n: 4-5: G1: 0 G2: 0</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Phillips and Macdonald, 1971 (continued)			analgesia: G1: 28.7 ± 6.2 G2: 22.7 ± 5.7 (n=50) G3: 24.6 ± 4.0 Timeliness: NR Labor co-interventions: NR Adverse effects: NR Route of birth: NR	G3: 0 6: G1: 0 G2: 1 G3: 5 7: G1: 0 G2: 1 G3: 0 8: G1: 19 G2: 18 G3: 30 9: G1: 2 G2: 15 G3: 0 10: G1: 29 G2: 16 G3: 16 Fetal and neonatal capillary blood pH, mean (SE): Before treatment: G1: 7.249 (0.012) G2: 7.233 (0.011) G3: 7.259 (0.011) After treatment: G1: 7.246 (0.011) G2: 7.226 (0.009) G3: 7.235 (0.010) 45/60 minutes after birth: G1: 7.274 (0.009) G2: 7.250 (0.007) G3: 7.188 (0.012) Fetal and neonatal capillary blood base excess, mean (SE): Before treatment: G1: -8.8 (0.06) G2: -11.0 (0.4) G3: -8.2 (0.3) After treatment: G1: -9.1 (0.5) G2: -12.2 (0.3) G3: -10.7 (0.3) 45/60 minutes after birth: G1: -9.1 (0.5) G2: -8.2 (0.3) G3: -11.4 (0.3) Fetal and neonatal capillary blood PO ₂ , mean (SE):

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Phillips and Macdonald, 1971 (continued)				Before treatment: G1: 27.0 (1.1) G2: 26.8 (1.1) G3: 31.7 (1.2) After treatment: G1: 29.3 (0.9) G2: 21.6 (0.8) G3: 25.3 (1.1) 45/60 minutes after birth: G1: 64.0 (2.0) G2: 46.4 (1.2) G3: 44.8 (0.9) Adverse effects: NR

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Ranta et al., 1995</p> <p>Country: Finland</p> <p>Participant source: Academic multi-site Community</p> <p>Setting: Hospitals</p> <p>Enrollment period: 04/1992 to 07/1992</p> <p>Design: Cross-sectional *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> All pregnant women admitted for vaginal delivery during the study period <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Elective cesareans 	<p>Groups: G1: 50/50 N₂O/ O₂ mix by face mask G2: Pethidine 50-75 mg IM administered by midwife G3: Paracervical block with 0.25% bupivacaine 5 ml on each side of cervix, administered by obstetrician G4: Segmental epidural analgesia administered by an anesthetist; initially bupivacaine 0.25% 5-10 ml with intermittent top-ups in 42% and continuous infusion in 52%. G5: No analgesia Ga: Primiparous Gb: Multiparous, 2-4 Gc: Multiparous, 5-17</p> <p>N at enrollment: (admitted to delivery room at the beginning of labor) Total: 1,091 G1: NR¹ G2: NR¹ G3: NR¹ G4: NR¹ G5: 213 Ga: 360 Gb: 468 Gc: 45</p> <p>N at follow-up: (pain score measurements were obtained in the delivery room) Total: 833 (post-partum follow-up) Total: 1,024</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: Primiparous:</p>	<p>Provider preferences: NR</p> <p>Provider specialty, %: Midwife: Total: 100</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, %: N₂O/ O₂ mix: Ga: 20 Gb: 23 Gc: 18</p> <p>Pethidine: Ga: 2 Gb: 0.4 Gc: 0</p> <p>Paracervical block: Ga: 24 Gb: 24 Gc: 20</p> <p>Epidural: Ga: 39 Gb: 5.3 Gc: 1</p> <p>No analgesia: Ga: 17 Gb: 48 Gc: 61</p>	<p>Pain, %: (11-point Box Scale 1-10) High pain score (8-10) after analgesia in first stage of labor: G1: 46 G2: 5 G3: 23 G4: 5</p> <p>Low pain score (0-2) after analgesia in first stage of labor: G1: 35 G2: 4 G3: 27 G4: 57</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions, %: Induction of labor: Total: 8.7</p> <p>Adverse effects, %: Maternal: Episiotomy: Total: 45</p> <p>Peeineal laceration: Total: 29</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth, %: Vaginal, normal: Total: 80</p> <p>Assisted: Total: 4.2</p> <p>Cesarean, non-elective: Total: 7</p>	<p>Satisfaction with pain management, %: First stage: Very Good: Total: 45 Moderate: Total: 37 Poor: Total: 18</p> <p>Second stage: Satisfied: Total: 53</p> <p>Satisfaction with birth experience, %: Satisfied: Total: 95 Dissatisfaction to some degree: Total: 4 Compete dissatisfaction: Total: 1</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Ranta et al., 1995 (continued)	Total: 360 G5: 30 Multiparous, 2-4: Total: 360 Multiparous, 5-17: Total: 360			

Comments:

¹ Numbers of patients in groups G1-4 can be calculated (approximately) from the percentages for pain management by parity group.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Ranta et al., 1994</p> <p>Country: Finland</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 1992</p> <p>Design: Prospective cohort</p> <p>Patients selected pain relief methods in agreement with obstetric staff.</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Intended to deliver vaginally <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Elective cesarean 	<p>Groups:</p> <p>G1: 50% N₂O and O₂ administered by midwife</p> <p>G2: Water block using 0.1 ml intracutaneous injections of sterile water at four points in lower back administered by midwife</p> <p>G3: IM pethidine 1 mg/kg administered by midwife</p> <p>G4: Paracervical block with bilateral injection of 0.25% bupivacaine 5 ml</p> <p>G5: Epidural catheter induced with initial doses of 5-7 ml 0.25% bupivacaine (divided doses) and continued with 5 ml/hour infusion of same solution or further 5 ml top-ups, withheld after cervix was 8-10 cm dilated.</p> <p>G6: Several forms of analgesia¹</p> <p>G7: No analgesia</p> <p>N at enrollment: (patients who had attended antenatal clinics, selected pain relief method and consented to participation)</p> <p>G1: 210 G2: 69 G3: 50 G4: 128 G5: 82 G6: 339 G7: 213</p> <p>N at follow-up: (during first, second and third stage)</p> <p>G1: 200 G2: 68 G3: 44 G4: 119 G5: 80 G6: 151 G7: 171</p>	<p>Provider preferences: NR</p> <p>Provider specialty:</p> <p>G1: Midwives administered N₂O</p> <p>G2: Midwives administered water blocks</p> <p>G3: Midwives administered pethidine</p> <p>G4: Obstetricians administered paracervical blocks</p> <p>G5: Anesthetists administered epidural</p> <p>G6: NR</p> <p>G7: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain, median (IQR): (VAS from 0=no pain to 10=intolerable pain)</p> <p>First stage, before treatment (baseline):</p> <p>G1: 6 (5-7) G2: 6 (5-7) G3: 5 (4-7) G4: 7 (6-8) G5: 7 (6-8) G6: 7 (5-8) G7: 6 (5-7)</p> <p>G4/G1-3: <i>P</i> < 0.01 G4/G7: <i>P</i> < 0.01 G5/G1-3: <i>P</i> < 0.01 G5/G7: <i>P</i> < 0.01 G6/G1-3: <i>P</i> < 0.01 G6/G7: <i>P</i> < 0.01</p> <p>First stage, after treatment:</p> <p>G1: 8 (6-9) G2: 7 (6-8) G3: 8 (7-8) G4: 6 (4-8) G5: 2 (1-4) G6: 7 (5-7) G7: NR</p> <p>G1/BL: <i>P</i> < 0.01 G2/BL: <i>P</i> < 0.01 G3/BL: <i>P</i> < 0.01 G4/BL: <i>P</i> < 0.01 G5/BL: <i>P</i> < 0.0001</p> <p>Second stage:</p> <p>G1: 8 (6-9) G2: 7 (5-9) G3: 8 (5-9) G4: 8 (5-9) G5: 7 (4-9) G6: 7 (5-9) G7: 7 (5-9)</p> <p>Third stage:</p> <p>G1: 3 (1-5) G2: 2 (1-4) G3: 2 (1-4) G4: 2 (1-4) G5: 2 (1-5) G6: 2 (1-4) G7: 2 (0-4)</p> <p>Labor progress: Duration of labor, hours, mean ± SD:</p> <p>G1: 6.0 ± 3.3 G2: 5.8 ± 3.2 G3: 7.1 ± 4.5 G4: 6.7 ± 3.9</p>	<p>Satisfaction with pain management, %: (Verbal scale 0-5) Total pain experience, reported on the third day after delivery: No or mild (0-1):</p> <p>G1: 3 G2: 4 G3: 0 G4: 4 G5: 5 G6: 2 G7: 4</p> <p>Moderate to severe (2-3):</p> <p>G1: 50 G2: 78 G3: 67 G4: 57 G5: 36 G6: 47 G7: 74</p> <p>Very severe to intolerable (4-5):</p> <p>G1: 49 G2: 28 G3: 34 G4: 39 G5: 60 G6: 51 G7: 22</p> <p>G5/G1-4: <i>P</i> < 0.01 G5/G6-7: <i>P</i> < 0.01</p> <p>Adequacy of pain relief method: Good:</p> <p>G1: 33 G2: 59 G3: 60 G4: 59 G5: 94 G6: 32 G7: Not applicable</p> <p>Moderate:</p> <p>G1: 39 G2: 26 G3: 23 G4: 26 G5: 6 G6: 43 G7: Not applicable</p> <p>Poor:</p> <p>G1: 28</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Ranta et al., 1994 (continued)	<p>Age, mean yrs (range): Total: 28.6 (16-47)</p> <p>Race/ethnicity: NR</p> <p>Parous, %: Primiparous: G1: 27 G2: 14 G3: 26 G4: 23 G5: 71 G6: 49 G7: 13</p>		<p>G5: 10.8 ± 4.9 G6: 9.3 ± 4.9 G7: 6.5 ± 2.9</p> <p>Fetal status: pH < 7.15, umbilical artery, % (N=616): G1: 9 G2: 15 G3: 6 G4: 6 G5: 4 G6: 4 G7: 9</p> <p>Timeliness, %: Received analgesia within ½ hour of request: G1-4: 72 G5: 63</p> <p>Had to wait more than one hour for analgesia after requesting it: G1: 19 G2: 10 G3: 5 G4: 9 G5: 26 G6: NR</p> <p>Labor co-interventions, %: Induced labor: G1: 10 G2: 3 G3: 9 G4: 13 G5: 15 G6: 11 G7: 5</p> <p>Adverse effects: NR</p> <p>Route of birth, %: Vaginal: G1: 95 G2: 90 G3: 91 G4: 93 G5: 80 G6: 86 G7: 94</p> <p>Assisted, vacuum extraction: G1: 2 G2: 3</p>	<p>G2: 15 G3: 17 G4: 15 G5: 0 G6: 15 G7: Not applicable G5/G1-4: <i>P</i> < 0.01 G5/G6-7: <i>P</i> < 0.01</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status, %: Apgar score ≤ 7: 1 minute: G1: 7 G2: 10 G3: 9 G4: 3 G5: 6 G6: 6 G7: 11 5 minutes: G1: 1 G2: 3 G3: 0 G4: 3 G5: 4 G6: 3 G7: 1</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Ranta et al., 1994 (continued)			G3: 2 G4: 4 G5: 11 G6: 7 G7: 1 Cesarean: G1: 3 G2: 7 G3: 7 G4: 3 G5: 9 G6: 7 G7: 5	

Comments:

* Calculated by reviewer.

¹ Authors state that almost all patients in G6 first received water blocks and/or pethidine and/or N₂O followed by a paracervical (n=123, 36%) or epidural (n=84, 25%) block.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Reed et al., 1989</p> <p>Country: United Kingdom</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Case series</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Caucasian • Normal medical and obstetric histories • Did not intend to request extradural analgesia <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Those who subsequently received extradural analgesia • Those who delivered within one hour 	<p>Groups:¹</p> <p>G1a: N₂O (Entonox, 50% N₂O in O₂) only in the first stage of labor</p> <p>G1b: Pethidine plus N₂O (Entonox) in the first stage of labor</p> <p>G2: Pethidine only in first stage of labor</p> <p>G3: No analgesia</p> <p>N at enrollment: Total: 41</p> <p>N at follow-up:</p> <p>G1a: 6</p> <p>G1b: 20</p> <p>G2: 7</p> <p>G3: 0</p> <p>Age: NR</p> <p>Race/ethnicity, %: Caucasian: Total: 100</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: See groups.</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: Hypoxic episodes: G1a: 5/6 G1b: 9/20 G2: 2/7 Duration of monitoring, minutes:* G1a: 520 G1b: 1,819 G2: 1,677 G3: 2,452 Hypoxic episodes per hour of monitoring:* G1a: 0.57 G1b: 1.4 G2: 0.43 G3: 0.049</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Comments:

¹ Participants assigned to groups *a posteriori*. Indicated results refer to total minutes in which analgesia was nitrous oxide, pethidine, nitrous oxide plus pethidine, or no analgesia.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Rosen et al., 1972</p> <p>Country: United Kingdom</p> <p>Participant source: Academic multi-site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: RCT</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> NR for either study within this paper <p>Exclusion criteria:</p> <ul style="list-style-type: none"> NR for either study in the paper 	<p>Groups: G1: Study 1 G2: Study 2</p> <p>Ga: N₂O mix and delivery 50% N₂O and 50% O₂ (Entonox)</p> <p>Gb: Methoxyflurane 0.35%</p> <p>N at enrollment: (day prior to labor) G1a: 25 G1b: 25 (day of discharge from labor ward) G2a: 100 G2b: 100</p> <p>N at follow-up: (entire 6 days) G1a: 19 G1b: 20 G2a: 100 G2b: 100</p> <p>Age, mean yrs ± SD: G1a: 23.6 ± 5.4 G1b: 26.9 ± 7.1 G2a: 25.5 ± 5.9 G2b: 24.5 ± 5.3</p> <p>Race/ethnicity: NR</p> <p>Parous, n: Primagravidas: G1a: 18 G1b: 15 G2a: 36 G2b: 47</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, mean ± SD: Maternal: Blood urea, mg/100 ml, before delivery: G1a: 16.0 ± 4.5 G1b: 16.3 ± 7.3 G1a/G1b: P = NS Urinary/blood urea ratio, before delivery: G1a: 71.0 ± 22.3 G1b: 80.8 ± 43.2 G1a/G1b: P = NS Serum osmolality, before delivery, mOsm/kg: G1a: 289.7 ± 7.7 G1b: 290.7 ± 7.5 G1a/G1b: P = NS Urinary/serum osmolality ratio, before delivery: G1a: 1.88 ± 0.68 G1b: 1.92 ± 0.93 G1a/G1b: P = NS Packed cell volume, before delivery, mean % ± SD: G1a: 38.6 ± 2.5 G1b: 37.5 ± 3.1 G1a/G1b: P = NS Neonatal: NR Occupational: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status, n (%): Blood urea, mg/100 ml, mean ± SD: 1st day after delivery: G1a: 20.0 ± 6.9 G1b: 16.6 ± 5.2 G1a/G1b: P = NS 2nd-3rd day after delivery: G1a: 21.4 ± 5.7 G1b: 21.3 ± 6.3 G1a/G1b: P = NS 4th-6th day after delivery: G1a: 21.0 ± 5.2 G1b: 20.8 ± 4.4 G1a/G1b: P = NS Day of discharge: G2a: NR* G2b: NR* G2a/G2b: P = NS Urinary/blood urea ratio, mean ± SD: 1st day after delivery: G1a: 57.3 ± 27.1 G1b: 55.2 ± 31.8 G1a/G1b: P = NS 2nd-3rd day after delivery: G1a: 73.4 ± 27.3 G1b: 70.5 ± 28.6 G1a/G1b: P = NS 4th-6th day after delivery: G1a: 81.4 ± 24.9 G1b: 67.2 ± 29.1 G1a/G1b: P = NS Day of discharge: G2a: NR¹ G2b: NR¹ G2a/G2b: P = NS Serum osmolality, mOsm/kg, mean ± SD: 1st day after delivery: G1a: 288.5 ± 7.1</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Rosen et al., 1972 (continued)				<p>G1b: 291.8 ± 5.7 G1a/G1b: <i>P</i> = NS 2nd-3rd day after delivery: G1a: 294.5 ± 4.4 G1b: 294.6 ± 5.9 G1a/G1b: <i>P</i> = NS 4th-6th day after delivery: G1a: 294.7 ± 3.8 G1b: 295.4 ± 5.0 G1a/G1b: <i>P</i> = NS</p> <p>Urinary/serum osmolality ratio, mean ± SD: 1st day after delivery: G1a: 1.69 ± 0.85 G1b: 1.49 ± 0.62 G1a/G1b: <i>P</i> = NS 2nd-3rd day after delivery: G1a: 2.17 ± 0.75 G1b: 2.09 ± 0.66 G1a/G1b: <i>P</i> = NS 4th-6th day after delivery: G1a: 2.22 ± 0.59 G1b: 2.04 ± 0.61 G1a/G1b: <i>P</i> = NS</p> <p>Packed cell volume, mean % ± SD: 1st day after delivery: G1a: 38.5 ± 4.8 G1b: 37.8 ± 3.8 G1a/G1b: <i>P</i> = NS 2nd-3rd day after delivery: G1a: 35.5 ± 4.4 G1b: 34.6 ± 5.2 G1a/G1b: <i>P</i> = NS 4th-6th day after delivery: G1a: 37.2 ± 3.1 G1b: 35.2 ± 5.7 G1a/G1b: <i>P</i> = NS</p> <p>Mean hospital stay, days: G2a: 5.5 G2b: 5.3</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Comments:

¹ Results only displayed graphically.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Rosen et al., 1969</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Maternity units</p> <p>Enrollment period: NR</p> <p>Design: Nonrandomized trial</p> <p>Choice of drug for the day was randomized on a calendar present in labor room, with Sundays labeled as open choice of midwife.</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Mothers <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: N₂O 50% /O₂ 50% given by Entonox apparatus G2: Trichloroethylene (0.5% and 0.35% in air) G3: Methoxyflurane (0.35% in air)</p> <p>N at enrollment: G1: 265 G2: 394 G3: 598</p> <p>N at follow-up: G1: 265 G2: 394 G3: 598</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Multiparae: G1: 130 (49) G2: 226 (57.5) G3: 347 (58)</p>	<p>Provider preferences: Choice of agent on Sundays, n (%): G1: 47/180 (26) G2: 32/180 (18) G3: 101/180 (56)</p> <p>Midwives response to questionnaire (n=77): In favour of use, before trial began, %: G1: 85 G2: 50 G3: NR</p> <p>Methoxyflurane is improvement over chosen agent, after experience of trial, %: G1: 53 G2: 78 G3: NA</p> <p>Provider specialty, %: Midwife: Total: 100</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management, n (%): No additional drugs: G1: 87 (33) G2: 151 (38) G3: 238 (40)</p> <p>Pethidine: G1: 166 (63) G2: 228 (58) G3: 333 (56)</p> <p>Others: G1: 12 (4) G2: 15 (4) G3: 27 (4)</p> <p>Duration of inhalation, minutes, mean: G1: 103.14 G2: 97.15 G3: 91.19</p>	<p>Pain relief, n (%): (scale NR) Maternal report, immediately after delivery: Complete: G1: 29 (11) G2: 47 (12) G3: 69 (11.5) Considerable: G1: 161 (61) G2: 235 (60) G3: 352 (59) Slight: G1: 66 (25) G2: 98 (25) G3: 154 (26) None: G1: 9 (3) G2: 14 (3) G3: 23 (3.5)</p> <p>Midwife report: Excellent:¹ G1: 19 (7) G2: 43 (11) G3: 81 (14) G1/G3: <i>P</i> < 0.01 Good:¹ G1: 92 (35) G2: 148 (38) G3: 235 (39) Adequate: G1: 129 (49) G2: 161 (41) G3: 225 (38) Inadequate: G1: 25 (9) G2: 42 (10) G3: 57 (9)</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n (%): Vaginal:</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth (labor) experience, n (%): Maternal report, multiparous: Better: G1: 45 (35) G2: 94 (42) G3: 189 (55) G1/G3: <i>P</i> < 0.001 G2/G3: <i>P</i> < 0.01 Same: G1: 33 (25) G2: 66 (29) G3: 62 (18) Worse: G1: 18 (14) G2: 29 (22) G3: 32 (9) Don't know: G1: 9 (3) G2: 44 (19) G3: 34 (26)</p> <p>Maternal status: NR</p> <p>Neonatal status: Apgar score, 1 minute, pethidine within 4 hours of inhalation: G1: NR² G2: NR² G3: NR²</p> <p>Adverse effects: Maternal: Nausea/felt sick, %: G1: 19 G2: 22 G3: 23</p> <p>Vomited, %: G1: 7.5 G2: 6 G3: 7.5</p> <p>Restlessness, midwife report, n (%): Never: G1: 95 (36) G2: 153 (39) G3: 242 (41) Short periods:</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Rosen et al., 1969 (continued)		<p>G1/G3: $P < 0.02$</p> <p>Midwives opinion on concentration of agents, n (%):</p> <p>Satisfied:</p> <p>G1: 213 (79) G2: 299 (76) G3: 412 (69)</p> <p>G1/G3: $P < 0.001$</p> <p>G2/G3: $P < 0.05$</p> <p>Requested stronger:</p> <p>G1: 36 (14) G2: 42 (11) G3: 72 (12)</p> <p>Requested weaker:</p> <p>G1: 5 (3) G2: 35 (9) G3: 64 (11)</p> <p>Don't know:</p> <p>G1: 11 (4) G2: 18 (4) G3: 50 (8)</p> <p>Reasons and incidence of inhalation abandoned, n (%):</p> <p>Ineffective:</p> <p>G1: 6 (2) G2: 6 (1.5) G3: 18 (9)</p> <p>Too powerful:</p> <p>G1: 1 (0.6) G2: 9 (2.2) G3: 12 (2)</p> <p>Obstetric reason:</p> <p>G1: 2 (0.8) G2: 6 (1.5) G3: 9 (1.5)</p> <p>Other:</p> <p>G1: 5 (1.8) G2: 33 (8) G3: 45 (7.5)</p> <p>Reasons and incidence of inhalation abandoned, also took pethidine, n (%):</p> <p>Ineffective:</p> <p>G1: 6/12 (50) G2: 4/37 (10.8) G3: 14/49 (28.5)</p> <p>Too powerful:</p> <p>G1: 1/12 (8.3) G2: 9/37 (24.3) G3: 5/49 (10.2)</p> <p>Obstetric reason:</p> <p>G1: 1/12 (8.3) G2: 3/37 (8.1)</p>	<p>G1: 235 (88.7) G2: 345 (87.6) G3: 525 (87.8)</p> <p>Assisted:</p> <p>G1: 30 (11.3) G2: 46 (11.7) G3: 68 (11.4)</p> <p>Cesarean:</p> <p>G1: 0 G2: 3 (0.8) G3: 5 (0.8)</p>	<p>G1: 157 (59) G2: 206 (52) G3: 310 (52)</p> <p>Long periods:</p> <p>G1: 13 (5) G2: 35 (9) G3: 46 (7)</p> <p>Cooperation, midwife report, n (%):</p> <p>Satisfactory:</p> <p>G1: 213 (81) G2: 298 (76) G3: 413 (69)</p> <p>G1/G3: $P < 0.001$</p> <p>G2/G3: $P < 0.05$</p> <p>Drowsy:</p> <p>G1: 38 (14) G2: 68 (17) G3: 135 (23)</p> <p>Too drowsy:</p> <p>G1: 6 (2) G2: 14 (4) G3: 29 (5)</p> <p>Asleep:</p> <p>G1: 1 (1) G2: 5 (1) G3: 13 (2)</p> <p>Uncooperative:</p> <p>G1: 7 (2) G2: 9 (2) G3: 8 (1)</p> <p>Neonatal, n (%):</p> <p>Apnoea, treatment: Artificial ventilation alone:</p> <p>G1: 8 (3.5) G2: 15 (3.5) G3: 13 (2.5)</p> <p>Artificial ventilation and tracheal intubation:</p> <p>G1: 6 (2) G2: 7 (2) G3: 19 (3)</p> <p>Apnoea, mortality:</p> <p>G1: 2 (0.5) G2: 3 (0.5) G3: 3 (0.5)</p> <p>Childhood: NR</p> <p>Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Rosen et al., 1969 (continued)		G3: 5/49 (10.2) Other: G1: 4/12 (33.3) G2: 34/37 (64.8) G3: 25/49 (51.0)		

Comments:

¹ **G3/G2:** $P < 0.01$ (excellent or good)

² Data only represented graphically. There were a significantly higher percentage of babies with a low Apgar score in G1 than in G2 ($P < 0.01$) or G3 ($P < 0.05$).

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Ross et al., 1999</p> <p>Country: Scotland</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Uncontrolled trial</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Mother in labor • Selection of mothers for isoflurane with nitrous left to discretion of midwives <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: 50% N₂O / 50% O₂ (Entonox) mixed with isoflurane (IN₂O), given through a gas scavenging system</p> <p>Ga: Apgar score < 8 at 1 minute</p> <p>Gb: Apgar score 8-10 at 1 minute</p> <p>Gc: No resuscitation required</p> <p>Gd: Resuscitation required</p> <p>N at enrollment: (consented early in labor prior to need for a stronger agent than Entonox)</p> <p>G1: 221</p> <p>N at follow-up: G1: 221 Ga: 74 Gb: 147 Gc: 162 Gd: 59</p> <p>Age, median yrs (range): G1: 29 (16-43)</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primiparous: G1: 126 (57)</p> <p>Multiparous: G1: 93 (43)</p> <p>Gestation, median weeks (range): G1: 40 (34-42)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Opioids (either diamorphine 10 mg or morphine 15 mg given by intramuscular injection), pethidine</p> <p>Pain management, n (%): Epidural: G1: 32 (14.8)</p> <p>Opioids: G1: 173 (78.3)</p> <p>Pethidine: G1: 4 (1.8)</p>	<p>Pain: NR</p> <p>Labor progress: Duration of first stage, hours, median (IQR): G1: 9.13 (5.62-13.13)</p> <p>Duration of second stage, hours, median (IQR): G1: 0.70 (0.25-1.86)</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal: Smelled: G1: 5 (2.3) Disliked: G1: 1 (0.4) Nausea: G1: 2 (0.9) Dizziness: G1: 2 (0.9) Drowsiness: G1: 2 (0.9)</p> <p>Neonatal: NR</p> <p>Occupational: NR</p> <p>Route of birth, n: Vaginal: G1: 151</p> <p>Assisted (forceps or ventouse): Primiparous: G1: 49 Multiparous: G1: 9</p> <p>Cesarean: Primiparous: G1: 12 Multiparous: G1: 0</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Apgar score < 8, 1 minute: G1: 74</p> <p>Apgar score < 8, 5 minutes: G1: 6</p> <p>Duration of IN₂O use, hours, median (IQR): G1a: 2.41 (1.15-4.12) G1b: 2.22 (0.90-4.23) G1c: 2.38 (0.92-4.38) G1d: 2.0 (1.15-4.0)</p> <p>IN₂O stopped less than 1 hour before delivery, n (%): G1a: 57 (33) G1b: 117 (67) G1c: 127 (73) G1d: 47 (27)</p> <p>IN₂O stopped more than 1 hour before delivery, n (%): G1a: 17 (36) G1b: 30 (67) G1c: 35 (75) G1d: 12 (25)</p> <p>Opioid use by mother, n (%): No opioid: G1a: 8 (17.6) G1b: 40 (83) G1c: 45 (94) G1d: 3 (6)</p> <p>Opioid less than 5 hrs before delivery, n (%): G1a: 40 (46) G1b: 48 (55) G1c: 48 (55) G1d: 40 (45)</p> <p>Opioid more than 5 hrs before delivery, n</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Ross et al., 1999 (continued)				(%): G1a: 26 (31) G1b: 59 (69) G1c: 69 (81) G1d: 16 (19) Adverse effects: Maternal: Blood loss, ml, median (IQR): G1: 200 (100-300) Blood loss, mean ml: G1: 241 Blood loss, n (%): 500-999 ml: G1: 26 (11.1) > 1000 ml: G1: 3 (1.3) Neonatal: Admission to special care baby unit, n: G1: 2 Tracheal tube, n: G1: 1 Mild respirator depression: G1: 1 Childhood: NR Occupational: NR

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Smith et al., 1968</p> <p>Country: US</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 08/1966 to 08/1967</p> <p>Design: Nonrandomized trial</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Multiparous (except for comparison group) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups:</p> <p>G1: N₂O (individualized, usual amount 2-4 L of 25-40% concentration)</p> <p>G2: Methoxyflurane (usual amount 12-30 ml, 0.2-0.5% setting on a Pentec vaporizer)</p> <p>G3: Cyclopropane (usual amount 60-300 ml, 1-5% concentration)</p> <p>G4: Pudendal</p> <p>G5: Spinal</p> <p>N at enrollment: (during labor if analgesia needed in addition to local or pudendal nerve block)</p> <p>G1: 553</p> <p>G2: 525</p> <p>G3: 279</p> <p>G4: 259</p> <p>G5: 450</p> <p>N at follow-up: NR¹</p> <p>Age, mean yrs: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%):</p> <p>Primiparous:</p> <p>G1: 0</p> <p>G2: 0</p> <p>G3: 0</p> <p>G4: 0</p> <p>G5: 450 (100)</p> <p>Multiparous:</p> <p>G1: 553 (100)</p> <p>G2: 525 (100)</p> <p>G3: 279 (100)</p> <p>G4: 259 (100)</p> <p>G5: 0</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain, %: (5 point scale 0-4)²</p> <p>Patient report:</p> <p>Score 0:</p> <p>G1: 4</p> <p>G2: 4</p> <p>G3: 4</p> <p>Score 1:</p> <p>G1: 8</p> <p>G2: 7</p> <p>G3: 8</p> <p>Score 2:</p> <p>G1: 10</p> <p>G2: 16</p> <p>G3: 14</p> <p>Score 3:</p> <p>G1: 27</p> <p>G2: 35</p> <p>G3: 33</p> <p>Score 4:</p> <p>G1: 50</p> <p>G2: 38</p> <p>G3: 40</p> <p>Patient report, < 5 minutes administration:</p> <p>Score 0:</p> <p>G1: 9</p> <p>G2: 8</p> <p>G3: 10</p> <p>Score 1:</p> <p>G1: 13</p> <p>G2: 12</p> <p>G3: 10</p> <p>Score 2:</p> <p>G1: 17</p> <p>G2: 17</p> <p>G3: 25</p> <p>Score 3:</p> <p>G1: 20</p> <p>G2: 32</p> <p>G3: 30</p> <p>Score 4:</p> <p>G1: 41</p> <p>G2: 31</p> <p>G3: 25</p> <p>Patient report, ≥ 5 minutes administration:</p> <p>Score 0:</p> <p>G1: 1</p> <p>G2: 1</p> <p>G3: 3</p> <p>Score 1:</p> <p>G1: 4</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status, mean:</p> <p>Apgar score, 1 and 5 minutes:³</p> <p>NR</p> <p>pO₂:</p> <p>G1: 19 (n=23)</p> <p>G2: 20 (n=30)</p> <p>G3: 23 (n=7)</p> <p>G4: 20 (n=17)</p> <p>pH:</p> <p>G1: 7.23 (n=23)</p> <p>G2: 7.25 (n=30)</p> <p>G3: 7.25 (n=7)</p> <p>G4: 7.29 (n=17)</p> <p>pCO₂:</p> <p>G1: 62 (n=23)</p> <p>G2: 55 (n=30)</p> <p>G3: 49 (n=7)</p> <p>G4: 46 (n=17)</p> <p>Buffer base:</p> <p>G1: 39 (n=23)</p> <p>G2: 38 (n=30)</p> <p>G3: 39 (n=7)</p> <p>G4: 40 (n=17)</p> <p>Standard bicarbonate:</p> <p>G1: 17 (n=23)</p> <p>G2: 17 (n=30)</p> <p>G3: 18 (n=7)</p> <p>G4: 18 (n=17)</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Smith et al., 1968 (continued)			<p>G2: 5 G3: 7 Score 2: G1: 6 G2: 16 G3: 11 Score 3: G1: 32 G2: 36 G3: 34 Score 4: G1: 57 G2: 42 G3: 44</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, %: Maternal: Amnesia: G1: 11 G2: 8 G3: 11</p> <p>Amnesia, < 5 minutes administration: G1: 16 G2: 4 G3: 5</p> <p>Amnesia, ≥ 5 minutes administration: G1: 7 G2: 10 G3: 13</p> <p>Nausea and vomiting: G1: 3 G2: 13 G3: 0.5 G1/G2: <i>P</i> < 0.05 G2/G3: <i>P</i> < 0.001</p> <p>Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 505 (91.3) G2: 441 (84.0)</p>	

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Smith et al., 1968 (continued)			G3: 185 (66.3) G4: 241 (93.1) G5: 0 Assisted, low forceps: G1: 36 (6.5) G2: 76 (14.5) G3: 73 (26.2) G4: 12 (4.6) G5: 448 (99.6) Assisted, breech: G1: 12 (2.2) G2: 8 (1.5) G3: 21 (7.5) G4: 6 (2.3) G5: 2 (0.4) Cesarean: Total: 0	

Comments:

¹ Results for analgesia and amnesia scores note they include “all vaginal vertex deliveries in multiparous patients” so presumably these results exclude breech births.

² Patient analgesia score scale: 0=didn't help or made it worse, 1=only helped a little, 2=the anesthetic helped, 3=only a little pain, 4=no pain at all.

³ Apgar scores at 1 and 5 minutes only displayed graphically.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Soyannwo, 1985</p> <p>Country: Nigeria</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Participants in established labor <p>Exclusion criteria:</p> <ul style="list-style-type: none"> See inclusion criteria 	<p>Groups: G1: Entonox administered via portable demand apparatus G2: 100 mg injection of pethidine or pethilorphan in early labor followed by Entonox inhalation</p> <p>N at enrollment: (during established labor) G1: 114 G2: 36</p> <p>N at follow-up: (after labor) G1: 114 G2: 36</p> <p>Age, mean yrs: Total: 27.2</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Total: 114 (76.0)</p>	<p>Provider preferences: NR</p> <p>Provider specialty, n (%): Resident anesthetist or midwife: Total: 150 (100)</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain, n (%): Excellent relief: G1: 24 (21.1) G2: 12 (33.3) Good relief: G1: 74 (64.9) G2: 24 (66.7) Fair relief: G1: 14 (12.3) G2: 0 Poor relief: G1: 2 (1.7) G2: 0</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal: Drowsiness: Mild: G1: 76 (66.7) G2: 20 (55.6) Moderate: G1: 36 (31.6) G2: 16 (44.4) Severe: G1: 2 (1.7) G2: 0</p> <p>Time for inhalation of Entonox, minutes, mean (range): Mild drowsiness: Total: 210 (45-320) Moderate drowsiness: Total: 340 (60-480)</p> <p>Vomiting:¹ Total: 4 (2.7)</p> <p>Unconsciousness:¹ Total: 1 (0.7)</p> <p>Neonatal: NR Occupational: NR</p>	<p>Satisfaction with pain management, n (%): (after delivery) Willing to use Entonox in subsequent deliveries: Total: 135 (90.0)</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status, n (%): Apgar score 8-10, vaginal deliveries: Total: 136 (97.1)</p> <p>Adverse effects: Maternal: NR Neonatal: Apgar score < 5, vaginal deliveries: Total: 4 (2.9)² Childhood: NR Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Soyannwo, 1985 (continued)			Route of birth, n (%): Vaginal: Total: 130 (86.7) Assisted, forceps or breech delivery: Total: 10 (6.7) Cesarean: Total: 10 (6.7)	

Comments:

¹ Groups unspecified but adverse effects due to Entonox inhalation.

² All breech deliveries and all resuscitated.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Stirk et al., 2002</p> <p>Country: United Kingdom</p> <p>Participant source: Community</p> <p>Setting: Hospital</p> <p>Enrollment period: 02/1998 to 10/1998</p> <p>Design: Prospective cohort</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Primigravida • ≥ 36 weeks' gestation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Caesarean sections 	<p>Groups: G1: Entonox (mix and delivery method NR) G2: Diamorphine only</p> <p>N at enrollment: (chart review) G1: 45 G2: 70</p> <p>N at follow-up: G1: 45 G2: 70</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primigravida: G1: 45 (100) G2: 70 (100)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: None</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: Duration of labor, hours:minutes, mean (range):¹ G1: 5:00 (0:45-12:15) G2: 8:40 (1:45-20:15)</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: NR</p> <p>Route of birth, n: Vaginal: NR Assisted: NR Cesarean: Total: 0</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: Apgar score, mean: 1 minute: G1: 8.2 G2: 8.3 5 minutes: G1: 9.6 G2: 9.4</p> <p>Length of hospital stay, days, mean: G1: 3 G2: 2</p> <p>Adverse effects, n (%): Maternal: NR Neonatal: Neonatal unit admission: G1: 7 (18.4)² G2: 2 (2.8) G1/G2: <i>P</i> < 0.027</p> <p>Given Narcan: G1: 5 (7) G2: 0</p> <p>Given facial oxygen and intermittent positive pressure ventilation: G1: 3 (4.2) G2: 0</p> <p>Childhood: NR Occupational: NR</p>

Comments:

¹ The text reports the mean duration of labor for G2 as 8:20, but Figure 3 reports the value as 8:40.

² Text notes 7 out of 38 in G1 (18.4%) group were admitted, but the Figure 1 indicates that 38 were *not* admitted, so the correct value could be 7 out of 45 (15.6%).

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Talebi et al., 2009</p> <p>Country: Iran</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 09/2004 to 09/2006</p> <p>Design: RCT</p>	<p>Groups: G1: 50% N₂O and O₂, self administered via facemask G2: 50% O₂, self administered via facemask</p> <p>N at enrollment:¹ (first request for analgesia) Total: 523</p> <p>N at follow-up:¹ G1: 260 G2: 249</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: (VAS, at onset of active labor and hourly at 1-5 hours afterward) NR²</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, %: Maternal: Nausea: G1: 8.4 G2: 0 G1/G2: <i>P</i> = 0.001 Vomiting: G1: 2.3 G2: 0 G1/G2: <i>P</i> = .030 Dizziness: G1: 22.6 G2: 0 G1/G2: <i>P</i> = 0.001 Dry mouth: G1: 8.3 G2: 0 G1/G2: <i>P</i> = 0.001 Pins and needles/numbness: G1: 4.1 G2: 0 G1/G2: <i>P</i> = .001 Drowsiness: G1: 15.4 G2: 0 G1/G2: <i>P</i> = 0.001 Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 260 (100) G2: 249 (100) Assisted: Total: 0</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: (SaO₂ levels measured at onset of active labor and hourly at 1-5 hours afterward) NR²</p> <p>Neonatal status: Apgar scores, mean ± SD: 1st min: G1: 8.5 ± 0.9 G2: 8.5 ± 0.8 5th min: G1: 9.5 ± 0.8 G2: 9.5 ± 0.7</p> <p>Adverse effects: NR</p>
<p>*****</p>	<p>Age, mean yrs ± SD: G1: 24.2 ± 4.0 G2: 24.9 ± 4.7</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): G1: 97 (37.3) G2: 123 (49.4)</p>			
<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • ASA I and II • 16 to 35 yrs old • Primigravid or second gravid, term (38 to 42 wks GA) parturients in active phase of labor (dilation > 4 cm) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Evidence of fetal distress or abnormal heart rate pattern • GA < 37 wks or > 42 wks • Maternal cardiorespiratory disease or any condition affecting the accuracy of pulse oximetry • History of taking opioids, administration of sedatives or regional analgesia • Unable to tolerate Entonox • Cesarean or forceps delivery 				

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Talebi et al., 2009 (continued)			Cesarean: Total: 0	

Comments:

¹Authors state that four patients were lost from the study, follow-up N from parity reported in Table 1.

²Results only displayed graphically. For pain, G1 values were significantly lower than G2 at all time points; for SaO2 levels, G2 levels were significantly higher than G1 at the first three time points.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Waldenstrom et al., 2006</p> <p>Country: Sweden</p> <p>Participant source: Antenatal clinics</p> <p>Setting: Other</p> <p>Enrollment period: 05/1999 to 01/2000</p> <p>Design: Trend *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Pregnant woman • Fluent in Swedish <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Miscarriage • Elective cesarean • Emergency cesarean not preceded by labor 	<p>Groups: G1: All women G1a: N₂O used during labor</p> <p>N at enrollment: (completed first questionnaire in early pregnancy) G1: 3,061</p> <p>N at follow-up: G1: 2,482 G1a: 1,997</p> <p>Age, mean yrs, %: < 25: G1: 15 25-35: G1: 75 > 35: G1: 10</p> <p>Race/ethnicity, %: Native-born Swedes: G1: 91</p> <p>Parous, n (%): Primipara: G1: 1,096 (44) G1a: 926 (46)</p> <p>Multipara: G1: 1,386 (55) G1a: 1,071 (54)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Epidural block, pethidine, paracervical block, pudental block, bath or shower, acupuncture, psychoprophylaxis, TENS, sterile water papules</p> <p>Pain management, %: Epidural block: G1: 31.1 N₂O: G1: 80.5 Pethidine: G1: 9.1 Paracervical block: G1: 3.3 Pudental block: G1: 4.4 No pharmacological pain management: G1: 14 Bath or shower: G1: 32.9 Acupuncture: G1: 21.5 Psychoprophylaxis: G1: 13.9 TENS: G1: 11.8 Sterile water papules: G1: 3.4 No pain management: G1: 9</p>	<p>Pain, n: (7 point scale ranging from 1 = no pain at all to 7 = worst imaginable pain, reported at two months post partum) 1-3: G1: 173 G1a: 88¹ 4: G1: 243 G1a: 174¹ 5: G1: 596 G1a: 471¹ 6: G1: 749 G1a: 637¹ 7: G1: 721 G1a: 627¹</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: Oxytocin: G1: NR</p> <p>Adverse effects: NR</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management, %: (scale created by author/researchers, reported two months after birth) Primiparas: Very effective: G1: 37.6 Some effect: G1: 45.6 No effect: G1: 16.8</p> <p>Multiparas: Very effective: G1: 49.0 Some effect: G1: 42.0 No effect: G1: 9.0</p> <p>Satisfaction with birth experience: Recollection of labor pain at 1 year: G1a: NR²</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Comments:

¹ Computed from overall numbers for G1 and percentages in Table III.

² Results only displayed graphically. The authors state that high rates of nitrous oxide were associated with remembering less pain.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Waldenstrom, 1999</p> <p>Country: Sweden</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: 10/1989 to 01/1992</p> <p>Design: Cross-sectional</p> <ul style="list-style-type: none"> Groups were randomized to either birth center or hospital birth initially, but treated as 1 group for this study <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Women giving birth between 10/1989 and 01/1992 Low medical risk Recruited from greater Stockholm area in early pregnancy <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Miscarriage, fetal or neonatal loss Elective cesarean 	<p>Groups: G1: Entire group consisted of women randomly assigned to either standard care or in-hospital birth center birth, but treated as one group for this study G1a: Positive group (6 or 7 on a 7-point overall birth experience scale 1 = very negative, 7 = very positive) G1b: Less positive group (1-5 on a 7-point overall birth experience scale)</p> <p>N at enrollment: (early pregnancy before randomization) G1: 1,230</p> <p>N at follow-up: (returned follow-up questionnaire) G1: 1,148</p> <p>(two months after birth, after exclusions) G1: 1,111 G1a: 790 G1b: 321</p> <p>Age, mean yrs ± SD: G1a: 30.2 ± 4.4 G1b: 30.5 ± 4.3</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primiparity: G1a: 47.1 G1b: 71.3 G1a/G1b: <i>P</i> < 0.001</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Epidural, pethidine</p> <p>Pain management, %: Nitrous: G1a: 25.9 G1b: 49.2 Ga/Gb: <i>P</i> < 0.001 Epidural: G1a: 5.6 G1b: 26.6 Ga/Gb: <i>P</i> < 0.001 Pethidine: G1a: 5.9 G1b: 14.9 Ga/Gb: <i>P</i> < 0.001</p>	<p>Pain: Pain intensity, mean ± SD (1 = none at all, 7 = worst imaginable): G1a: 4.8 ± 1.5 G1b: 5.6 ± 1.5</p> <p>Labor progress, duration of labor, mean ± SD:¹ G1a: 12.5 ± 9.2 G1b: 18.0 ± 12.7</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions, %: Induction of labor: G1a: 2.0 G1b: 7.2</p> <p>Augmentation of labor, %: G1a: 12.5 G1b: 37.8</p> <p>Adverse effects, mean ± SD: Maternal: Anxiety (where 1 = not at all anxious, and 7 = very anxious): G1a: 2.1 ± 1.5 G1b: 3.6 ± 1.9</p> <p>Neonatal: Transfer, %: G1a: 7.2 G1b: 16.8</p> <p>Occupational: NR</p> <p>Route of birth, %: Vaginal: G1a: NR G1b: NR Vacuum extraction: G1a: 1.3 G1b: 9.7 Emergency cesarean: G1a: 1.4 G1b: 14.3</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status, %: Apgar score < 7, 5 minutes: G1a: 0.4 G1b: 2.5</p> <p>Adverse effects: Maternal: NR</p> <p>Neonatal: See neonatal transfer in labor and intermediate outcomes column.</p> <p>Childhood: NR</p> <p>Occupational: NR</p>

Comments:

¹ Assumed to be hours, unit not provided.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Waldenstrom et al., 1996</p> <p>Country: Sweden</p> <p>Participant source: Academic multi-site Community</p> <p>Setting: Hospital</p> <p>Enrollment period: 11/1994 to 12/1994</p> <p>Design: Cross-sectional *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> All women who gave birth at any of three hospitals providing maternity care in the Gothenburg region in enrollment period <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Had a stillborn or severely ill baby Suffered from postpartum psychosis Did not have mastery of Swedish language Did not agree to participate or were not contacted due to very early discharge Underwent elective cesarean 	<p>Groups:¹</p> <p>G1: Entonox (50/50 N₂O and O₂ mix)</p> <p>G2: Epidural</p> <p>G3: Local infiltration</p> <p>G4: Acupuncture</p> <p>G5: Bath</p> <p>G6: Breathing technique (psycho-prophylaxis)</p> <p>Ga: Less severe pain (score=1-6)</p> <p>Gb: Severe pain (score=7)</p> <p>N at enrollment: (all births from 11/21 to 12/6/1994) Total: 385</p> <p>N at follow-up: (completed questionnaires 4 hours to 7 days after birth, mean 45 hours) Total: 278</p> <p>G1: 219 G2: 95 G3: 69 G4: 51 G5: 107 G6: 85 Ga: 165 Gb: 113</p> <p>Age, mean yrs ± SD: Ga: 29.5 ± 5.1 Gb: 28.9 ± 4.2 Ga/Gb: P = NS</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): Primiparas: Total: 134 (48) Ga: NR (45.5) Gb: NR (52.2)</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Pethidine, morphine, paracervical block, pudendal block, shower, massage, sterile water s.c., TENS, movement, music</p> <p>Pain management, %:</p> <p>Entonox: Total: 78.8 Ga: 70.9 Gb: 85.8</p> <p>Epidural block: Total: 34.2 Ga: 29.1 Gb: 38.9</p> <p>Pethidine, morphine: Total: 3.4</p> <p>Paracervical block: Total: 5.0</p> <p>Pudendal block: Total: 7.2</p> <p>Local infiltration: Total: 24.8 Ga: 21.8 Gb: 27.4</p> <p>No pharmacological analgesia: Total: 9.3</p> <p>Non-pharmacological methods: Tub bath: Total: 40.5 Ga: 33.3 Gb: 46.0 Shower: Total: 14.8 Massage:</p>	<p>Pain, n (%): (7 point scale 1-7)² Pain score, n (%): 7: Total: 113 (41) 1-6: Total: 165 (59)</p> <p>Pain score, mean: Primiparas: Total: 6.1 Multiparas: Total: 5.9</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions, %:</p> <p>Induction: Ga: 15.9 Gb: 19.8</p> <p>Augmentation: Ga: 36.4 Gb: 53.8</p> <p>Adverse effects: Maternal: Anxiety score, mean ± SD:³ Ga: 3.3 ± 1.8 Gb: 4.4 ± 2.1 Ga/Gb: P < 0.001</p> <p>Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: Total: 236 (84.9) Ga: NR (88.5) Gb: NR (79.6)</p> <p>Assisted: Total: 22 (7.5) Ga: NR (4.8) Gb: NR (12.4)</p> <p>Emergency cesarean: Total: 20 (6.8) Ga: NR (6.7) Gb: NR (8.0)</p>	<p>Satisfaction with pain management, n (%): Would use pain relief method in future labor: G1: 188 (69.9) G2: 122 (45.3) G3: 93 (34.6) G4: 55 (20.4) G5: 180 (66.9) G6: 110 (40.9)</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Waldenstrom et al., 1996 (continued)		Total: 28.4 Special breathing technique: Total: 32.2 Ga: 33.9 Gb: 25.7 Acupuncture: Total: 19.3 Ga: 14.5 Gb: 23.9 Sterile water s.c.: Total: 7.6 TENS: Total: 6.4 Movement (walking around): Total: 39.8 Music: Total: 16.3		

Comments:

¹ Groups are not exclusive.

² 1=no pain at all; 7=worst imaginable pain

³ 1=not at all anxious, 7=very anxious

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Westberg et al., 2008</p> <p>Country: Sweden</p> <p>Participant source: NR</p> <p>Setting: Hospital</p> <p>Enrollment period: 03/2003 to 05/2004</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> All subjects available during the selected shifts were included. <p>Exclusion criteria: NR</p>	<p>Groups: G1: Midwives G2: Assistant midwives</p> <p>N at enrollment: G1: 25 G2: 11 Total: 36</p> <p>N at follow-up: NR</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: NR Neonatal: NR Occupational: Air concentrations (mg/m³) of 8 h time-weighted averages nitrous oxide levels in delivery suite, geometric mean ± geometric standard deviation (range): G1: 17 ± 4.4 (2.5-260) G2: 42 ± 4.7 (< 3.5-220) Total: 22 ± 4.7 (2.5-260)</p> <p>Route of birth: NR</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Westling et al., 1992</p> <p>Country: Sweden</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Crossover RCT *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Healthy • Normal singleton pregnancy • Vertex presentation <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1a: Intermittent N₂O/O₂ (40/60) G1b: Intermittent N₂O/O₂ (70/30) G1c: Continuous N₂O/O₂ (40/60) G1d: Intermittent O₂</p> <p>Intervention delivered via face mask</p> <p>N at enrollment: (labor) G1: 24</p> <p>N at follow-up: G1: 24</p> <p>Age, mean yrs ± SD: G1: 26.8 ± 0.9</p> <p>Race/ethnicity: NR</p> <p>Parous, n (%): G1: 12 (50)</p>	<p>Provider preferences: NR</p> <p>Provider specialty, n (%): Midwife: G1: 24 (100)</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: None</p> <p>Pain management: NR</p>	<p>Pain: VAS, participant report, mean: G1: NR¹</p> <p>VAS, midwife report, mean: G1: NR¹</p> <p>Labor progress, Cervical dilation, mean ± SD: Before measurements: G1: 5.8 ± 0.4</p> <p>After measurements: G1: 7.9 ± 0.4</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n (%): Maternal: Nausea G1a: 0 G1b: 0 G1c: 1 (4) G1d: 0 Vomiting: G1: 0 Loss of consciousness: G1: 0 Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal: G1: 23 (96) Assisted: G1: 0 Cesarean: G1: 1 (4)</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: Heart rate, mean: G1: NR¹</p> <p>Stroke volume, mean: G1: NR¹</p> <p>Cardiac output, mean: G1: NR¹</p> <p>Systolic arterial pressure, mean: G1: NR¹</p> <p>Diastolic arterial pressure, mean: G1: NR¹</p> <p>Mean arterial pressure: G1: NR¹</p> <p>Total peripheral vascular resistance, mean: G1: NR¹</p> <p>Neonatal status: Weight, g, mean ± SD: G1: 3,652 ± 121</p> <p>Apgar score, mean ± SD: 1 minute: G1: 9.2 ± 0.6 5 minutes: G1: 10.0 ± 0.2 10 minutes: G1: 10.0 ± 0</p> <p>Umbilical cord pH, mean ± SD: G1: 7.29 ± 0.05</p> <p>Adverse effects: NR</p>

Comments:

¹ Data only displayed graphically.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Yeo et al., 2007</p> <p>Country: United Kingdom</p> <p>Participant source: NR</p> <p>Setting: NR</p> <p>Enrollment period: NR</p> <p>Design: Crossover RCT *****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Active labor • GA > 36 weeks <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Major uterine abnormalities • Multiple gestation • CV or respiratory instability • Acute/chronic OB pathology/disease • Received any prior form of analgesia 	<p>Groups: G1: ESE¹ (double cross-over) G2: SES¹ (double cross-over)</p> <p>Ga: Entonox (E) Gb: Sevoflurane (S)</p> <p>N at enrollment: G1: 16 G2: 16</p> <p>N at follow-up: G1: 8 G2: 14</p> <p>Age, mean yrs: Total: 32</p> <p>Race/ethnicity: NR</p> <p>Parous, %: Nulliparous: Total: 91</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: Epidural</p> <p>Pain management, n (%): Epidural: G1a: 4² G1b: 0 G2a: 2 G2b: 0</p>	<p>Pain: (100 mm VAS) VAS score, mean difference (95% CI): Pain intensity, 1st cross-over period: Gb/Ga: 5 (0.2,11) Gb/Ga: <i>P</i> = 0.0395 Pain relief, 2nd cross-over period: Gb/Ga: 2 (-2,6) Gb/Ga: <i>P</i> = 0.0006 Pain relief, 1st cross-over period: Gb/Ga: 12 (3,21) Gb/Ga: <i>P</i> = 0.0115 Pain relief, 2nd cross-over period: Gb/Ga: 18 (8,28) Gb/Ga: <i>P</i> = NS Pain relief, VAS score, median (IQR): Ga: 51 (32-65) Gb: 67 (55-74)</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects, n: Maternal: Vomiting: Ga: 4 Gb: 0 Nausea: Ga: 8 Gb: 1 Ga/Gb: <i>P</i> = 0.004 Neonatal: NR Occupational: NR</p> <p>Route of birth, n (%): Vaginal spontaneous: Total: 21 (68) Assisted vaginal: Total: 6 (19)</p>	<p>Satisfaction with pain management, % (95% CI): Preferred sevoflurane to Entonox: Total: 97 (84,99) Ga/Gb: <i>P</i> < 0.0001</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: (100 mm VAS) VAS score, mean difference (95% CI): Mood, 1st cross-over period: Gb/Ga: 3 (-3,8) Gb/Ga: <i>P</i> = NS Mood, 2nd cross-over period: Gb/Ga: 10 (3,19) Gb/Ga: <i>P</i> = 0.0088 Coping, 1st cross-over period: Gb/Ga: 0.2 (-6,6) Gb/Ga: <i>P</i> = NS Coping, 2nd cross-over period: Gb/Ga: 3 (-4,10) Gb/Ga: <i>P</i> = NS</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Yeo et al., 2007 (continued)			Cesarean: Total: 4 (13)	

Comments:

¹ E: nitrous mix (Entonox by piped gas supply and demand valve); S: sevoflurane with O₂ via draw-over vaporizer.

² All were in the last phase.

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Zack et al., 1991</p> <p>Country: Sweden</p> <p>Participant source: Other (registry data)</p> <p>Setting: Not applicable (registry data)</p> <p>Enrollment period: 1973 to 1984</p> <p>Design: Case control</p> <p>*****</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Born between 1973 and 1984 • Registered at birth in the Swedish Medical Birth Register • Diagnosed with leukemia • Enrolled in Swedish National Cancer Registry <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • See inclusion criteria 	<p>Groups: G1: Has leukemia G2: Control matched for sex, birth year, and birth month</p> <p>N at enrollment: G1: 411 G2: 2,055</p> <p>N at follow-up: G1: 411 G2: 2,055</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: Not applicable</p>	<p>Provider preferences: Not applicable</p> <p>Provider specialty: Not applicable</p> <p>Cost of intervention: Not applicable</p> <p>Other pain management methods available: Not applicable</p> <p>Pain management, nitrous oxide, n (%): G1: 245 (60) G2: 1,118 (54)</p>	<p>Pain: Not applicable</p> <p>Labor progress: Not applicable</p> <p>Fetal status: Not applicable</p> <p>Timeliness: Not applicable</p> <p>Labor co-interventions: Not applicable</p> <p>Adverse effects: Not applicable</p> <p>Route of birth, n: Vaginal: NR Assisted: G1: 22 G2: 116 Cesarean: G1: 39 G2: 201</p>	<p>Satisfaction with pain management: Not applicable</p> <p>Satisfaction with birth experience: Not applicable</p> <p>Maternal status: Not applicable</p> <p>Neonatal status: Not applicable</p> <p>Adverse effects: Maternal: Not applicable Neonatal: Not applicable Childhood leukemia, odds ratio for N₂O analgesia, (95% CI): G1/G2: 1.3 (1.0,1.6) Occupational: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
<p>Author: Zelcer et al., 1989</p> <p>Country: Australia</p> <p>Participant source: Academic single site</p> <p>Setting: Hospital</p> <p>Enrollment period: NR</p> <p>Design: Prospective cohort *****</p> <p>Inclusion criteria: • First stage of labor</p> <p>Exclusion criteria: • Analgesic group changed during recording • Distressed and did not want to continue study</p>	<p>Groups: G1: N₂O for every contraction, no pethidine G2: N₂O during every contraction and received intramuscular pethidine within the previous 150 minutes G3: No analgesia (control) G4: Good analgesia from epidural block, no opioid in preceding 150 minutes G5: Intramuscular pethidine within the previous 150 minutes, no N₂O</p> <p>N at enrollment: (first stage of labor) Total: 75</p> <p>N at follow-up: G1: 10 G2: 10 G3: 10 G4: 10 G5: 10</p> <p>Age: NR</p> <p>Race/ethnicity: NR</p> <p>Parous: NR</p>	<p>Provider preferences: NR</p> <p>Provider specialty: NR</p> <p>Cost of intervention: NR</p> <p>Other pain management methods available: NR</p> <p>Pain management: NR</p>	<p>Pain: NR</p> <p>Labor progress: NR</p> <p>Fetal status: NR</p> <p>Timeliness: NR</p> <p>Labor co-interventions: NR</p> <p>Adverse effects: Maternal: Inspired oxygen, FiO₂, mean: G1: 0.69 G2: 0.65 G3: 0.21 G4: 0.21 G5: 0.21</p> <p>Oxygen saturation, 5 contractions, mean %: Maximum: G1: 100 G2: 100 G3: 99 G4: 99 G5: 99</p> <p>Minimum: G1: 94 G2: 91 G3: 94 G4: 94 G5: 92 G2/G3: <i>P</i> < 0.05</p> <p>Average maximum: G1: 100 G2: 99 G3: 99 G4: 99 G5: 98</p> <p>Average Minimum: G1: 96 G2: 94 G3: 96 G4: 96 G5: 96 G2/G3: <i>P</i> < 0.05</p> <p>Difference between maximum and minimum (Max-Min): G1: 6</p>	<p>Satisfaction with pain management: NR</p> <p>Satisfaction with birth experience: NR</p> <p>Maternal status: NR</p> <p>Neonatal status: NR</p> <p>Adverse effects: NR</p>

Evidence Table: Nitrous Oxide for Management of Labor Pain (continued)

Study Description	Intervention & Population	Aspects of Care	Labor and intermediate outcomes	Birth and long-term outcomes
Zelcer et al., 1989 (continued)			G2: 9 G3: 5 G4: 5 G5: 7 G2/G3: $P < 0.05$ Neonatal: NR Occupational: NR Route of birth: NR	

Appendix D. Applicability and Quality Tables

Table 1. Key Question 1--Applicability

Table 2. Key Question 2--Applicability

Table 3. Key Question 3--Applicability

Table 4. Key Question 4--Applicability

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials

Table 6. Quality Ratings for Randomized Controlled Trials

Table 7. Quality Ratings for Cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials)

Table 8. Quality Ratings for Case-control Studies

Table 1. Key Question 1--Applicability

Domain	Description of applicability of evidence compared to question
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. In addition, mechanical equipment for delivery of N2O in labor and delivery has very limited availability in the U.S.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and non-pharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	The most frequent outcome was an assessment of pain, generally during labor. Some studies retrospectively assessed pain in the immediate postpartum period and/or weeks to months after birth. The methods of pain assessment were heterogeneous. Those assessing outcomes included participants, obstetricians, midwives, and anesthesia providers.
Setting	Only five of 21 studies were conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S. All of the studies were conducted in hospitals, thus the effectiveness of the intervention in birth centers and the home setting has not been reported.

Table 2. Key Question 2--Applicability

Domain	Description of applicability of evidence compared to question
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. In addition, mechanical equipment for delivery of N ₂ O in labor and delivery has very limited availability in the U.S.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and non-pharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	Satisfaction with pain management and the birth experience were the outcome measures, as reported by the women.
Setting	Only three of nine studies were conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S. All of the studies were conducted in hospitals, thus the satisfaction with the intervention in birth centers and the home setting has not been reported.

Table 3. Key Question 3--Applicability

Domain	Description of applicability of evidence compared to question
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. In addition, mechanical equipment for delivery of N2O in labor and delivery has very limited availability in the U.S.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and non-pharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	The outcomes were vaginal birth, assisted vaginal birth, and cesarean. None of the studies had a cesarean birth rate greater than 10%, which is much lower than the most recently reported U.S. rate of 32%. ¹
Setting	Only one of six studies was conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S. All of the studies were conducted in hospitals, thus the route of birth in birth centers and the home setting has not been reported.

Table 4. Key Question 4--Applicability

Domain	Description of applicability of evidence compared to question
Population	The study populations were healthy women in labor who should be similar to the target population. The eligibility criteria and participant characteristics were not always explicitly detailed. Some participants were excluded due to choice of alternate pain management methods.
Intervention	Most studies used a 50/50 mix of nitrous and oxygen, often premixed in the form of Entonox. The 50/50 mix is available, although Entonox is not used in the U.S, and not currently approved by the FDA. The intervention varied significantly in terms of dose, frequency, and duration. In many studies participants received unspecified amounts of narcotics and/or sedating agents. Studies prior to 1980 are not applicable to current guidelines for clinical use.
Comparators	The comparators include standard pain management methods, such as epidural, narcotics, and non-pharmacologic methods such as TENS. However, some comparators are not commonly used and/or available for laboring women in the U.S., such as other inhalational anesthetic gases.
Outcomes	The most frequent outcomes were assessments of nausea, vomiting, dizziness, drowsiness, hypoxia, oxygen saturation, Apgar scores, and cord blood gases. Apoptosis was not addressed because there are no human studies.
Setting	Only six of 48 studies were conducted in the U.S. The standards of care are not comparable because nitrous is widely available outside of the U.S.

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials

RANDOM SEQUENCE GENERATION Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.	
<p>Criteria for a judgment of 'Low risk' of bias.</p>	<p>The investigators describe a random component in the sequence generation process such as:</p> <ul style="list-style-type: none"> • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. <p>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.</p>
<p>Criteria for the judgment of 'High risk' of bias.</p>	<p>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:</p> <ul style="list-style-type: none"> • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. <p>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:</p> <ul style="list-style-type: none"> • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
<p>Criteria for the judgment of 'Unclear risk' of bias.</p>	<p>Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.</p>

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials (continued)

ALLOCATION CONCEALMENT	
Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	
Criteria for a judgment of 'Low risk' of bias.	<p>Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:</p> <ul style="list-style-type: none"> • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
Criteria for the judgment of 'High risk' of bias.	<p>Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:</p> <ul style="list-style-type: none"> • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
Criteria for the judgment of 'Unclear risk' of bias.	<p>Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.</p>
SELECTIVE REPORTING	
Reporting bias due to selective outcome reporting.	
Criteria for a judgment of 'Low risk' of bias.	<p>Any of the following:</p> <ul style="list-style-type: none"> • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgment of 'High risk' of bias.	<p>Any one of the following:</p> <ul style="list-style-type: none"> • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgment of 'Unclear risk' of bias.	<p>Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.</p>

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials (continued)

OTHER BIAS Bias due to problems not covered elsewhere in the table.	
Criteria for a judgment of 'Low risk' of bias.	The study appears to be free of other sources of bias.
Criteria for the judgment of 'High risk' of bias.	There is at least one important risk of bias. For example, the study: <ul style="list-style-type: none"> • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
Criteria for the judgment of 'Unclear risk' of bias.	There may be a risk of bias, but there is either: <ul style="list-style-type: none"> • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: <ul style="list-style-type: none"> • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: <ul style="list-style-type: none"> • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: <ul style="list-style-type: none"> • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.

Table 5. The Cochrane Risk of Bias Tool for Randomized Controlled Trials (continued)

BLINDING OF OUTCOME ASSESSMENT	
Detection bias due to knowledge of the allocated interventions by outcome assessors.	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: <ul style="list-style-type: none"> No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: <ul style="list-style-type: none"> No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: <ul style="list-style-type: none"> Insufficient information to permit judgment of 'Low risk' or 'High risk'; The study did not address this outcome.
INCOMPLETE OUTCOME DATA	
Attrition bias due to amount, nature or handling of incomplete outcome data.	
Criteria for a judgment of 'Low risk' of bias.	Any one of the following: <ul style="list-style-type: none"> No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods.
Criteria for the judgment of 'High risk' of bias.	Any one of the following: <ul style="list-style-type: none"> Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; Potentially inappropriate application of simple imputation.
Criteria for the judgment of 'Unclear risk' of bias.	Any one of the following: <ul style="list-style-type: none"> Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided);

- | | |
|--|---|
| | <ul style="list-style-type: none">• The study did not address this outcome. |
|--|---|

Thresholds for converting the Cochrane Risk of Bias tool to AHRQ standards (good, fair, and poor):

Good quality: All criteria met (i.e. low for each domain)

Using the Cochrane ROB tool, it is possible for a criterion to be met even when the element was technically not part of the method. For instance, a judgment that knowledge of the allocated interventions was adequately prevented can be made even if the study was not blinded, if EPC team members judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.

Fair quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was **unlikely** to have biased the outcome, and there is no known important limitation that could invalidate the results

Poor quality: One criterion not met (i.e. high risk of bias for one domain) or two criteria unclear, and the assessment that this was **likely** to have biased the outcome, and there are important limitations that could invalidate the results

Poor quality: Two or more criteria listed as high or unclear risk of bias

Table 6. Quality ratings for randomized control trials

Citation	Quality rating	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Talebi et al., ² 2009	Poor	L	U	L	U	U	U	U
Yeo et al., ³ 2007	Poor	U	H	H	U	H	H	L
Einarsson et al., ⁴ 1996	Poor	U	U	L	U	U	U	L
Abboud et al., ⁵ 1995	Poor	L	L	L	L	H	H	L
Carstoniu et al., ⁶ 1994	Poor	L	H	L	L	H	H	L
Westling et al., ⁷ 1992	Poor	H	H	L	U	H	H	L
Chia et al., ⁸ 1990	Poor	H	H	L	H	H	H	L
Abboud et al., ⁹ 1989	Poor	U	U	L	L	H	H	L
McLeod et al., ¹⁰ 1985	Poor	U	U	L	U	L	U	L
McGuinness and Rosen, ¹¹ 1984	Poor	U	U	L	U	U	L	L
Abboud et al., ¹² 1981	Poor	U	U	L	U	H	H	L
Rosen et al., ¹³ 1972	Poor	H	U	L	L	H	U	L
Phillips and Macdonald, ¹⁴	Poor	U	U	L	H	U	U	H
Bergsjo and Lindbaek, ¹⁵ 1971	Poor	L	L	L	U	U	U	L
NA, ¹⁶ 1970	Fair	U	L	L	L	L	L	L
Jones et al., ¹⁷ 1969	Poor	U	U	L	U	U	U	L

Table 6. Quality ratings for randomized control trials (continued)

Citation	Quality rating	Random sequence generation	Allocation concealment	Selective reporting	Other sources of bias	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data
Jones et al., ¹⁸	Poor	U	U	L	U	L	U	L
Constantine et al., ¹⁹ 1989	Poor	U	H	L	U	H	H	L
Arora et al., ²⁰	Fair	L	L	L	U	L	L	L

H = high; L = low; U = unclear

Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Representativeness of the exposed cohort
 - a) Truly representative **(one star)**
 - b) Somewhat representative **(one star)**
 - c) Selected group
 - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort **(one star)**
 - b) Drawn from a different source
 - c) No description of the derivation of the non exposed cohort
- 3) Ascertainment of exposure
 - a) Secure record (e.g., surgical record) **(one star)**
 - b) Structured interview **(one star)**
 - c) Written self report
 - d) No description
 - e) Other
- 4) Demonstration that outcome of interest was not present at start of study
 - a) Yes **(one star)**
 - b) No

Comparability

- 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
 - The study controls for age, sex and marital status **(one star)**
 - Study controls for other factors (list) _____ **(one star)**
 - Cohorts are not comparable on the basis of the design or analysis controlled for confounders
 - No comparison group*
 - N/A*

Outcome

- 1) Assessment of outcome
 - a) Independent blind assessment **(one star)**
 - b) Record linkage **(one star)**
 - c) Self report
 - d) No description
 - e) Other
- 2) Was follow-up long enough for outcomes to occur
 - Yes **(one star)**
 - No

Indicate the median duration of follow-up and a brief rationale for the assessment above: _____

- 3) Adequacy of follow-up of cohorts
 - a) Complete follow up- all subject accounted for **(one star)**
 - b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. **(one star)**
 - c) Follow up rate greater than 80% and no description of those lost
 - d) No statement

*Added by Vanderbilt EPC

Newcastle-Ottawa Quality Assessment Form for Case-control Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

- 1) Is the case definition adequate?
 - a) Yes, with independent validation **(one star)**
 - b) Yes, e.g., record linkage or based on self report
 - c) No description
- 2) Representativeness of the cases
 - a) Consecutive or obviously representative series of cases **(one star)**
 - b) Potential for selection biases or not stated
- 3) Selection of controls
 - a) Community controls **(one star)**
 - b) Hospital controls
 - c) No description
- 4) Definition of controls
 - a) No history of disease (endpoint) **(one star)**
 - b) No description of source

Comparability

- 1) Comparability of cases and controls on the basis of the design or analysis controlled for confounders
 - The study controls for age, sex and marital status **(one star)**
 - Study controls for other factors (list) _____ **(one star)**
 - Cohorts are not comparable on the basis of the design or analysis controlled for confounders
 - No comparison group*
 - N/A*

Exposure

- 1) Ascertainment of exposure
 - a) Secure record (e.g., surgical record) **(one star)**
 - b) Structured interview where blind to case/control status **(one star)**
 - c) Interview not blinded to case/control status
 - d) Written self report or medical record only
 - e) No description
- 2) Same method of ascertainment for cases and controls
 - Yes **(one star)**
 - No
- 3) Non-response rate
 - a) Same rate for both groups **(one star)**
 - b) Non-respondents described
 - c) Rate different between cases and controls with no description

*Added by Vanderbilt EPC

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

The Vanderbilt EPC included two additional options in the comparability domain not generally included in the Newcastle-Ottawa scales: “no comparison group” and “not applicable”. This was necessary because the review included single-arm studies for both the effectiveness and harms assessments.

Studies of the effectiveness of nitrous oxide for the management of labor pain that included only one study arm were marked as “no comparison group”, which equates to receiving no stars and an automatic rating of poor quality.

Cross sectional studies used to identify potential harms and measures of environmental exposure could appropriately have no comparison group, and were marked for comparability as “not applicable.” The quality scores for these studies were downgraded to account for their non-comparative study designs. For example, a study with three or four stars in the selection domain and two or three stars in the outcome/exposure domain, which would normally equate to a “good” quality rating, would be deemed “fair” quality if the comparability domain response was “not applicable”.

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials)

Citation	Quality rating	Selection (0-4 stars)				Comparability (n/a, 0-2 stars)	Outcome (0-3 stars)		
		Representativeness of exposed cohort	Selection of non exposed	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts	Assessment	Long enough followup	Adequacy of follow up
Waldenstrom and Irestedt, ²¹ 2006	Fair	a)truly representative	a)drawn from same community	c) written self report	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias -
Henry and Nand, ²² 2004	Poor	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias
Henderson et al., ²³ 2003	Fair	a)truly representative	a)drawn from same community	a)secure record	b) no	N/A	a)independent assessment	a) yes	a)complete follow up
Leong et al., ²⁴ 2000	Good	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	both	c) self report	a) yes	b)unlikely to introduce bias
Waldenstrom, ²⁵ 1999	Fair	b)somewhat representative	a)drawn from same community	a) secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias -
Ross et al., ²⁶ 1999	Poor	c)selected group	c)no description	a)secure record	a) yes	NC	b) record linkage	a) yes	b)unlikely to introduce bias
Bodin et al., ²⁷ 1999	Poor	c)selected group	a)drawn from same community	c)written self report	a) yes	no	b)record linkage	a) yes	b)unlikely to introduce bias lost
Ahlborg et al., ²⁸ 1996	Fair	c)selected group	a)drawn from same community	c)written self report	a) yes	N/A	c)self report	a) yes	b)unlikely to introduce bias

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

Citation	Quality rating	Selection (0-4 stars)				Comparability (n/a, 0-2 stars)	Outcome (0-3 stars)		
		Representativeness of exposed cohort	Selection of non exposed	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts	Assessment	Long enough followup	Adequacy of follow up
Axelsson et al., ²⁹ 1996	Poor	c)selected group	a)drawn from same community	c)written self report	a) yes	N/A	c)self report	a) yes	b)unlikely to introduce bias
Arfeen et al., ³⁰ 1994	Poor	a)truly representative	a)drawn from same community	a)secure record	a) yes	no	b)record linkage	a) yes	b)unlikely to introduce bias
Landon et al., ³¹ 1992	Poor	a)truly representative	a)drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Peach, ³² 1999	Fair	a)truly representative	a)drawn from same community	a)secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias lost
Zelcer et al., ³³ 1989	Poor	d)no description	c)no description	a)secure record	a) yes	no	b) record linkage	a) yes	b)unlikely to introduce bias
Reed et al., ³⁴ 1988	Poor	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Deckardt et al., ³⁵ 1987	Poor	d)no description	a)drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Harrison et al., ³⁶ 1987	Poor	b)somewhat representative	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

Citation	Quality rating	Selection (0-4 stars)				Comparability (n/a, 0-2 stars)	Outcome (0-3 stars)		
		Representativeness of exposed cohort	Selection of non exposed	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts	Assessment	Long enough followup	Adequacy of follow up
Soyannwo, ³⁷ 1985	Poor	d)no description	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up
Morgan et al., ³⁸ 1982	Poor	a)truly representative	a)drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up
Arthurs et al., ³⁹ 1979	Poor	d)no description	a)drawn from same community cohort	a)secure record	a) yes	no	c) self report	a) yes	a)complete follow up for
Holdcroft and Morgan, ⁴⁰ 1974	Poor	b)somewhat representative	a) drawn from same community	c)written self report	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias
Marx et al., ⁴¹ 1970	Poor	c)selected group	a) drawn from same community	a)secure record	a) yes	NC	b) record linkage	a) yes	d) no statement
Rosen et al., ⁴² 1969	Poor	a)truly representative	a) drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias -
Clark et al., ⁴³ 1967	Fair	d) no description	c) no description	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up
Beppu ⁴⁴ 1968	Poor	d) no description	c) no description	a)secure record	a) yes	NC	b) record linkage	a) yes	a)complete follow up

Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

Citation	Quality rating	Selection (0-4 stars)				Comparability (n/a, 0-2 stars)	Outcome (0-3 stars)		
		Representativeness of exposed cohort	Selection of non exposed	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts	Assessment	Long enough followup	Adequacy of follow up
Smith et al., ⁴⁵ 1968	Poor	a) truly representative	a) drawn from same community	a)secure record	a) yes	no	a)independent assessment	a) yes	b)unlikely to introduce bias
Stirk et al., ⁴⁶ 2002	Poor	b)somewhat representative	a) drawn from same community	a)secure record	a) yes	no	b) record linkage	a) yes	a) complete follow up
Westberg et al., ⁴⁷ 2008	Fair	c)selected group	a) drawn from same community	a)secure record	a) yes	N/A	b) record linkage	a) yes	a)complete follow up
Waldenstrom et al., ⁴⁸ 1996	Fair	a) truly representative	a) drawn from same community	a)secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias
Ranta et al., ⁴⁹ 1995	Fair	a) truly representative	a) drawn from same community	a)secure record	a) yes	N/A	c) self report	a) yes	b)unlikely to introduce bias
Ranta et al., ⁵⁰ 1994	Poor	b)somewhat representative	a) drawn from same community	a)secure record	a) yes	no	c) self report	a) yes	b)unlikely to introduce bias
Harrison and Cullen ⁵¹ 1986	Poor	b)somewhat representative	a) drawn from same community	a) secure record	a) yes	no	a)independent assessment	a) yes	a)complete follow up
Murphy et al., ⁵² 1984	Poor	a) truly representative	a) drawn from same	a)secure record	a) yes	no	b) record linkage	a) yes	a)complete follow up

			community						
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Table 7. Quality ratings for cohort studies (including case series, cross-sectional, uncontrolled and nonrandomized trials) (continued)

Citation	Quality rating	Selection (0-4 stars)				Comparability (n/a, 0-2 stars)	Outcome (0-3 stars)		
		Representativeness of exposed cohort	Selection of non exposed	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts	Assessment	Long enough followup	Adequacy of follow up
McAney and Doughty, ⁵³ 1963	Poor	d) no description	a) drawn from same community	a)secure record	a) yes	no	a)independent blind assessment	a) yes	b)unlikely to introduce bias
Mills et al., ⁵⁴ 1996	Fair	c)selected group	a) drawn from same community	a)secure record	a) yes	N/A	b) record linkage	a) yes	a)complete follow up
Newton et al., ⁵⁵ 1999	Fair	c)selected group	a) drawn from same community	a)secure record	a) yes	N/A	b) record linkage	a) yes	b)unlikely to introduce bias

Table 8. Quality ratings for case-control studies

Citation	Quality rating	Selection (0-4 stars)				Comparability (n/a, 0-2 stars)	Outcome (0-3 stars)		
		Adequate case definition	Representativeness of cases	Selection of Controls	Definition of Controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment	Non-Response rate
Nyberg et al., ⁵⁶ 1992	Poor	b) yes, e.g., record linkage or based on self report	a) consecutive or obviously representative series of cases	a)community	a) no history of disease (endpoint)	no	a) secure record	a) yes	a) same
Zack et al., ⁵⁷ 1991	Good	b) yes, e.g., record linkage or based on self report	a) consecutive or obviously representative series of cases	a)community	a) no history of disease (endpoint)	other	a) secure record	a) yes	a) same
Jacobson et al., ⁵⁸ 1990	Poor	b) yes, e.g., record linkage or based on self report	b) potential for selection biases or not stated	a)community	a) no history of disease (endpoint)	no	a) secure record	a) yes	a) same
Jacobson et al., ⁵⁹ 1988	Poor	b) yes, e.g., record linkage or based on self report	b) potential for selection biases or not stated	a)community	a) no history of disease (endpoint)	no	a) secure record (a) yes	a) same

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Appendix E. List of Excluded Studies

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Appendix F: Regulatory Considerations of Nitrous Oxide

Nitrous oxide is used in the US for both medical and non-medical purposes. The following section will focus on the regulation of nitrous oxide used as analgesia for labor pain. Nitrous oxide as a labor analgesia is governed by a limited patchwork of laws, regulations, and standards.

Regulation by federal entities

Like all medical gases, nitrous oxide is regulated by the U.S. Food and Drug Administration (FDA) as a prescription drug.¹ Title 21 of the Code of Federal Regulations describes the required manufacturing (Good Manufacturing Practices) and distribution practices for prescription drugs, performance standards for medical gas delivery devices, and safety requirements for medical gas containers. There are only a few FDA regulations that specifically or solely apply to nitrous oxide. These regulations describe labeling requirements, manufacturing requirements, and performance standards for delivery systems.²

Nitrous oxide also falls under the purview of the United States Pharmacopeia (USP). The USP is a scientific nonprofit organization that sets standards for the quality, purity, identity, and strength of medicines and food ingredients distributed and consumed worldwide. USP standards are enforced by the FDA.

Two federal agencies have weighed in on the use of nitrous oxide in the workplace. The National Institute for Occupational Health and Safety (NIOSH), the federal agency responsible for conducting research and making recommendations to prevent injury and illness in the workplace, has established a recommended exposure limit (REL) for nitrous oxide of 25 parts per million as an eight hour time weighted average. In 1994, NIOSH published an alert (DHHS (NIOSH) Publication No. 94-100) that provided guidance on how to control workplace exposures to nitrous oxide during anesthetic administration.³

The Occupational Safety and Health Administration (OSHA) is the federal agency that sets and enforces workplace health and safety standards. OSHA has not set a threshold standard for nitrous oxide exposures in the workplace,³ but is developing requirements for monitoring workplace exposures to nitrous oxide.⁴ OSHA has addressed public safety by requiring all piped systems that transfer and distribute nitrous oxide to comply with safety standards set by the Compressed Gas Association.⁵

Companies that sell nitrous oxide and facilities that store nitrous oxide are subject to certain environmental regulations. The U.S. Environmental Protection Agency (EPA) maintains and publishes every two years a list of chemicals sold in the U.S. This list, the Toxic Substances Control Act (TSCA) inventory, includes nitrous oxide. Facilities that use and store nitrous oxide must submit material safety data sheets and report nitrous oxide inventories to the local emergency planning commission, the organization responsible for local emergency preparedness and response.

Regulation by state legislatures and agencies

In addition to the federal regulations that govern the manufacture, distribution, and storage of nitrous oxide, there are state laws that are meant to promote the safe use, storage, and delivery of nitrous oxide. An increasing number of states have enacted legislation that attempt to limit youth access to nitrous oxide in order to reduce the prevalence of nitrous oxide abuse by young people. Some state legislatures and licensing boards have enacted legislation or rules that define who

may administer or assist in administering nitrous oxide in a medical setting. Some states have enacted community and worker right to know laws. These laws mandate reporting of environmental exposures (accidental releases and on-site storage exposures) to a local agency and mandate notice of exposures to employees and community residents. Finally, it is not uncommon for state and local governments to regulate and enforce building codes that address the installation, testing, and maintenance of pipelines used to deliver nitrous oxide to medical facilities.

Regulation by national organizations

Professional organizations are an integral part of the regulator environment for nitrous oxide. The American Conference of Governmental Industrial Hygienists (ACGIH) is a professional association of industrial hygiene personnel within government agencies. ACGIH establishes the Threshold Limit Values (TLVs) for chemical substances and physical agents and Biological Exposure Indices (BEIs) as guidelines for use in the industrial hygiene field. This group has set a threshold limit value (TLV) for nitrous oxide of 50 ppm of air as an eight hour time weighted average.⁶

The Compressed Gas Association (CGA) writes regulations and standards for compressed gases. Title 41 of the Code of Federal Regulations applies to federal contracts and requires that “the pipe systems for the in-plant transfer and distribution of nitrous oxide shall be designed, installed, maintained and operated in accordance with Compressed Gas Association Pamphlet G8.11964.”⁷ OSHA has also adopted the CGA code for piped systems that deliver and transfer nitrous oxide.⁵

The National Fire Protection Association (NFPA) develops and writes consensus standards for medical gas delivery systems (pipelines) in healthcare facilities. NFPA 99 sets standards for monitoring and testing of nitrous oxide delivery systems. The Joint Commission for the Accreditation of Healthcare Organizations (JCAHO) requires healthcare facilities to comply with NFPA 99 (Annex C). The American Welding Society, the Manufacturers’ Standardization Society of the Valve and Fittings Industry, the American Society of Mechanical Engineers, and the American National Standard Institute (ANSI) all have set standards for the installation, design and testing of medical gas pipelines.

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