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Maternal Oxygen Supplementation Compared With Room Air for Intrauterine Resuscitation
A Systematic Review and Meta-analysis

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IMPORTANCE Supplemental oxygen is commonly administered to pregnant women at the time of delivery to prevent fetal hypoxia and acidemia. There is mixed evidence on the utility of this practice.

OBJECTIVE To compare the association of peripartum maternal oxygen administration with room air on umbilical artery (UA) gas measures and neonatal outcomes.

DATA SOURCES Ovid MEDLINE, Embase, Scopus, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials were searched from February 18 to April 3, 2020. Search terms included *labor* or *obstetric delivery* and *oxygen therapy* and *fetal blood* or *blood gas* or *acid-base imbalance*.

STUDY SELECTION Studies were included if they were randomized clinical trials comparing oxygen with room air at the time of scheduled cesarean delivery or labor in patients with singleton, nonanomalous pregnancies. Studies that did not collect paired umbilical cord gas samples or did not report either UA pH or UA Pao_2 results were excluded.

DATA EXTRACTION AND SYNTHESIS Data were extracted by 2 independent reviewers. The analysis was stratified by the presence or absence of labor at the time of randomization. Data were pooled using random-effects models.

MAIN OUTCOMES AND MEASURES The primary outcome for this review was UA pH. Secondary outcomes included UA pH less than 7.2, UA Pao_2, UA base excess, 1- and 5-minute Apgar scores, and neonatal intensive care unit admission.

RESULTS The meta-analysis included 16 randomized clinical trials (n = 1078 oxygen group and n = 974 room air group). There was significant heterogeneity among the studies (I^2 = 49.88%; P = .03). Overall, oxygen administration was associated with no significant difference in UA pH (weighted mean difference, 0.00; 95% CI, −0.01 to 0.01). Oxygen use was associated with an increase in UA Pao_2 (weighted mean difference, 2.57 mm Hg; 95% CI, 0.80-4.34 mm Hg) but no significant difference in UA base excess, UA pH less than 7.2, Apgar scores, or neonatal intensive care unit admissions. Umbilical artery pH values remained similar between groups after accounting for the risk of bias, type of oxygen delivery device, and fraction of inspired oxygen. After stratifying by the presence or absence of labor, oxygen administration in women undergoing scheduled cesarean delivery was associated with increased UA Pao_2 (weighted mean difference, 2.12 mm Hg; 95% CI, 0.09-4.15 mm Hg) and a reduction in the incidence of UA pH less than 7.2 (relative risk, 0.63; 95% CI, 0.43-0.90), but these changes were not noted among those in labor (Pao_2: weighted mean difference, 3.60 mm Hg; 95% CI, −0.30 to 7.49 mm Hg; UA pH<7.2: relative risk, 1.34; 95% CI, 0.58-3.11).

CONCLUSIONS AND RELEVANCE This systematic review and meta-analysis suggests that studies to date showed no association between maternal oxygen and a clinically relevant improvement in UA pH or other neonatal outcomes.

Supplemental content

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Maternal oxygen supplementation is a widely used intrauterine resuscitation technique recommended by the American College of Obstetricians and Gynecologists for the management of abnormal fetal heart rate tracings.[1] In the presence of fetal heart rate patterns that may represent fetal hypoxia,[2] oxygen is administered to the mother with the intent of increasing placental oxygen transfer and preventing neonatal acidemia. This use of oxygen for fetal resuscitation is so widespread that 2 of 3 women in labor in the US will receive oxygen at some point during labor.[3]

Umbilical artery (UA) gas samples obtained at the time of delivery provide an objective assessment of in utero fetal oxygenation and metabolic status.[4] Umbilical artery gas analysis provides measurements of pH, Pao_2, $Paco_2$, and base excess. These measurements are used by clinicians to assess neonatal acidemia and estimate short- and long-term morbidity.[5,6]

A 2016 Cochrane review of 2 trials investigating the use of intrapartum oxygen for intrauterine resuscitation concluded that there was insufficient evidence to evaluate the effectiveness of oxygen in that setting.[7] A separate 2012 Cochrane review specifically assessing the use of supplemental oxygen at the time of cesarean delivery (CD) concluded that oxygen was associated with higher maternal and neonatal blood gas values with otherwise no evidence of clinical benefit or harm.[8] Subsequent to these Cochrane reviews, additional trials showing mixed results in investigation of peripartum oxygen administration have been published.[9-14] Although some studies suggested fetal benefit with increased UA Pao_2 and UA pH levels,[10,15] others demonstrated harm with oxygen, including a higher proportion of neonates with acidemia and requiring delivery room resuscitation compared with those exposed to room air.[16] Moreover, the timing and setting of oxygen administration varied among these studies, with some evaluating oxygen during labor and others in the absence of labor. This distinction is important because the physiologic characteristics of placental oxygen transfer and, hence, UA gases may differ based on the presence or absence of regular uterine contractions.

The objectives of this study were to synthesize data from randomized clinical trials comparing peripartum oxygen supplementation with room air and investigate the association between oxygen administration at the time of labor or planned CD and UA gas measures and other neonatal outcomes.

Key Points

Question Is maternal oxygen supplementation at the time of delivery associated with improved umbilical artery gas measures and neonatal outcomes?

Findings In this systematic review and meta-analysis of 16 randomized clinical trials, peripartum maternal oxygen supplementation was associated with an improvement in umbilical artery Pao_2 but no significant difference in umbilical artery pH compared with room air. Other umbilical artery gas measures, rates of neonatal intensive care unit admission, and Apgar scores were similar between the oxygen and room air groups.

Meaning This systematic review and meta-analysis found no association between maternal oxygen supplementation and a clinically relevant improvement in umbilical artery pH or other neonatal outcomes.

Data Sources

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline for meta-analyses and the *Cochrane Handbook for Systematic Reviews of Interventions*.[17] We used an a priori research protocol that defined the research question, inclusion and exclusion criteria, population, exposures, and risk of bias criteria.

The literature was searched using strategies created by a medical librarian (M.M.D.) for administration of maternal oxygen during delivery and umbilical cord gas measures. The search strategies were implemented in Ovid MEDLINE 1946-, Embase 1947-, Scopus, ClinicalTrials.gov, and Cochrane Central Register of Controlled Trials, without a language limit, and were established using a combination of standardized terms and key words including, but not limited to, *labor* or *obstetric delivery* and *oxygen therapy* and *fetal blood* or *blood gas* or *acid-base imbalance*. The search syntax appears in the eAppendix in the Supplement. A sensitive search filter was used to limit for randomized clinical trials. All databases were searched from February 18 to April 3, 2020.

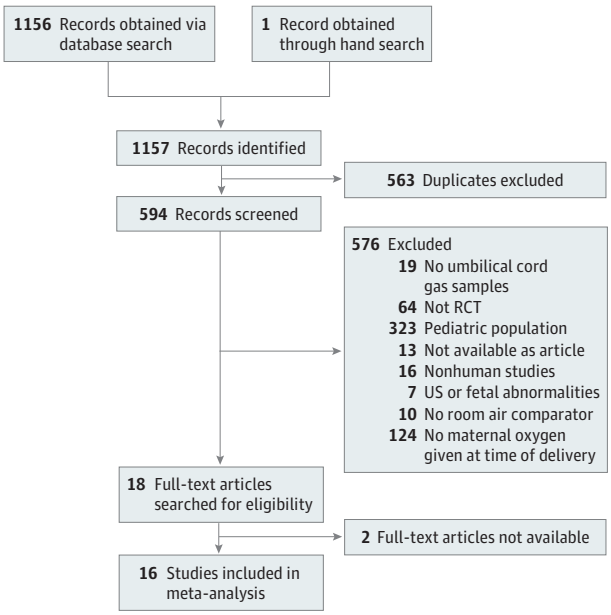
Study Selection

Studies were included if they were randomized clinical trials comparing maternal oxygen supplementation with room air at the time of delivery in patients with singleton, nonanomalous pregnancies. All routes and doses of oxygen delivery were included. Studies that did not collect paired cord gas samples or did not have either UA pH or UA Pao_2 results were excluded. We excluded nonrandomized studies, case reports or series, and studies published only in abstract form. The primary outcome for this review was UA pH. Secondary outcomes were UA pH less than 7.2, UA pH less than 7.1, UA Pao_2, UA base excess, 1- and 5-minute Apgar scores, neonatal intensive care unit admission, and oxidative stress markers.

Titles and abstracts from the initial search result were independently reviewed by 2 of us (N.R. and L.A.T.). Full-text articles were obtained if there was uncertainty about inclusion based on the abstract. Discrepancies were resolved by the senior author (M.G.T.). Two of us (N.R. and L.A.T.) independently abstracted data into standard extraction forms. Discrepancies in data abstraction were resolved by discussion or by the senior author. Details regarding oxygen administration were collected. Nasal cannulas and simple face masks were categorized as low-flow devices, whereas nonrebreathers, Venturi masks, and anesthetic masks were considered high-flow devices.

We categorized studies as low or high risk for bias using 3 factors considered most likely to limit the validity of study results[18-20]: valid randomization method, loss to follow-up less than 15%, and analysis using the intention-to-treat principle. All 3 criteria had to be met for a study to be labeled as

Figure 1. Randomized Clinical Trials Included in the Meta-analysis



RCT indicates randomized clinical trial; US, ultrasonography.

low risk for bias. Studies that did not have adequate information to determine the answers to the above criteria were considered to be at high risk for bias. Valid randomization included the use of random number tables, computer-generated sequences, and other accepted methods of random allocation.

Statistical Analysis

Mean values were estimated from median values using the method published by Hozo et al.[21] Umbilical artery Pa_{O_2} results reported in kilopascals were converted to millimeters of mercury using the formula millimeters of mercury = kilopascals × 7.50. The results for each outcome were stratified by the presence or absence of labor (labor or scheduled CD). We performed additional stratified analyses by risk of bias, fraction of inspired oxygen (F_{IO_2}), and type of oxygen delivery device for the primary outcome.

The Higgins I^2 test and Cochrane Q test were used to quantify and assess heterogeneity.[22] Heterogeneity was considered significant at $P < .10$ for the Q tests or $I^2 > 30\%$. Using random-effects models, raw data from the studies were pooled to obtain relative risks (RRs) with 95% CI for categorical outcomes and weighted mean difference (WMD) with 95% CI for continuous outcomes. Random-effects models were used because of the significant heterogeneity among the studies. To assess for publication bias, we visually inspected funnel plots and performed the Egger test for small study effect.[23] A 2-sided $P < .05$ was considered statistically significant for pooled analyses. Statistical analyses were performed using Stata, version 16.1 (StataCorp LLC).

Results

A total of 1156 references were obtained from the initial electronic database search. One additional reference was obtained from a hand search of the citations. After removing 563 duplicates, a total of 594 references were screened. We eliminated 576 of these references for not being relevant or meeting exclusion criteria. Of the 18 full-text articles searched for eligibility, 2 did not have full text available for review, and 16 were included in the final meta-analysis (**Figure 1**).

Ten trials were performed in patients undergoing scheduled CD with regional anesthesia[10,14,24-31] and 4 trials were performed in women in labor.[11-13,16] One trial included both scheduled CD and emergent CD during labor,[9] and another trial[15] only included patients undergoing emergency CD during labor. In both of these trials, data from the patients undergoing emergency CD were abstracted and categorized in the subgroup of labor. Detailed information on the characteristics of the included studies is provided in **Table 1**. A total of 1078 patients were randomized to the oxygen group (622 at time of scheduled CD and 456 in labor) and 974 patients were randomized to the room air group (561 at the time of a scheduled CD and 413 during labor).

Eight trials were considered at low risk for bias.[9,12-14,16,27,29,31] Three studies did not report or lacked valid randomization methods.[10,24,26] Only 1 trial had loss to follow-up greater than 15%.[11] Four trials did not perform or specifically report an intention-to-treat analysis.[15,24,28,30]

Fourteen trials reported results for UA pH—the primary outcome of this review.[7,9-14,16,25-27,29-31] One of these trials[9] had a cohort of patients randomized at the time of the scheduled CD and another cohort randomized at the time of an emergent CD during labor. There was significant heterogeneity between studies (I^2 = 49.88%; P = .03). Overall, there was no significant difference in mean UA pH between the room air and oxygen groups (15 studies: WMD, 0.00; 95% CI, −0.01 to 0.01). The mean difference in UA pH between the oxygen and room air groups did not appear to be impacted by the presence (5 studies: WMD, −0.01; 95% CI, −0.03 to 0.00) or absence (10 studies: WMD, 0.00; 95% CI, −0.01 to 0.01) of labor (**Figure 2**). There was no evidence of publication bias from visual inspection of the funnel plot and the Egger test (P = .45) (eFigure 1 in the Supplement).

After stratifying by risk of bias, F_{IO_2}, and oxygen delivery device, heterogeneity was reduced for studies that used high-flow oxygen devices (I^2 = 0.11%; P = .93). In stratified analysis, there remained no significant difference in UA pH between oxygen and room air at the time of a scheduled CD or during labor (eTable in the Supplement).

Six studies reported UA pH less than 7.2 as an outcome.[10,12,14-16,28] Overall, there was no significant difference in UA pH less than 7.2 between oxygen and room air groups (6 studies: relative risk [RR], 0.87; 95% CI, 0.58-1.32). After stratifying by the presence or absence of labor, oxygen administration was associated with a reduction in the risk of UA pH less than 7.2 at the time of scheduled CD (3 studies: RR, 0.63; 95% CI, 0.43-0.90) with no evidence of heterogeneity

Table 1. Characteristics of Randomized Clinical Trials Comparing Peripartum Maternal Oxygen Supplementation With Room Air

Source	Country	Inclusion criteria	Exclusion criteria	Patient population	Exposure (No. of patients)	Risk of bias	Outcomes
Ahuja et al,[9] 2018	India	ASA I-II, term, elective or emergency CD with subarachnoid block	ASA >II, preoperative receipt of oxygen, multiple gestation, no regional anesthesia, BMI>45, arterial injury, arterial disease, prematurity, fetal anomaly	Labor followed by emergent CD, scheduled CD	Venturi mask, 50% (30 [initial labor], 30 [scheduled CD]), room air (30)	Low	UA malondialdehyde,[a] UV malondialdehyde, UA total antioxidant status, UV total antioxidant status, cord gases
Biswas et al,[10] 2019	India	ASA I-II, term, elective CD with subarachnoid block	Fetal anomaly, maternal medical problem affecting placental perfusion, skin incision to delivery >30 min, uterine incision to delivery >5 min	Scheduled CD	Nasal cannula (61), room air (66)	High	UA Pao_2,[a] cord gases, neonatal outcomes
Castro et al,[25] 2009	Brazil	Term, scheduled CD	Maternal disease that affects fetal oxygenation (eg, preeclampsia, hypertension, and diabetes), intraoperative events that compromise fetal oxygenation	Scheduled CD	Nonrebreather, 60% (12), room air (8)	Low	Maternal Pao_2,[a] UA Pao_2
Cogliano et al,[26] 2002	UK	Elective CD with spinal anesthesia	Age <18 y, height <152 cm, weight >85 kg, history of fetal compromise, coexisting medical condition, non-English speaking	Scheduled CD	Nasal cannula (23), simple face mask, 40% (23), room air (23)	High	UV Pao_2,[a] cord gas measures, Apgar scores, patient comfort
Gunaydin et al,[27] 2011	Turkey	Elective CD with spinal anesthesia, term, singleton, vertex	Not specified	Scheduled CD	Nasal cannula, 32% (30), simple face mask, 30% (30), room air (30)	Low	Maternal and neonatal cerebral oximetry,[a] Apgar scores, cord gas measures
Khaw et al,[29] 2002	China	ASA I-II, no labor, term, elective CD with spinal anesthesia	Not specified	Scheduled CD	Venturi mask, 60% (22), room air (22)	Low	Maternal and UA malondialdehyde,[a] cord gas measures, Apgar scores, maternal arterial blood gas measures
Khaw et al,[28] 2004	China	ASA I-II, no labor term, elective CD with spinal anesthesia	Not specified	Scheduled CD	Venturi mask, 40% (44), Venturi mask, 60% (60), room air (55)	High	UV oxygen content,[a] Apgar scores, UA pH, uterine incision to delivery time, UV Pao_2, oxyhemoglobin saturation
Khaw et al,[15] 2009	China	ASA I-II, term, singleton, emergent CD after labor with regional anesthesia	Fetal anomaly, fetal growth restriction, preeclampsia, general anesthesia for fetal compromise	Labor followed by emergent CD	Venturi mask, 60% (61), room air (64)	High	UV oxygen content,[a] umbilical 8-isoprostane, uterine incision to delivery time, UA and UV Pao_2
Moors et al,[11] 2020	Netherlands	Term, labor, singleton, cephalic, age >18 y, abnormal fetal heart rate in second stage of labor	Tobacco, drug, alcohol use; cardiac disease; pulmonary disease; diabetes; hyperthyroidism; anemia; corticosteroid, antihypertensive, or magnesium treatment; medications associated with free radicals; congenital malformation; infection in labor; prolonged bradycardia; normal or preterminal fetal heart rate pattern	Labor	Nonrebreather, 80% (57), room air (60)	High	Change of fetal heart rate pattern,[a] Apgar scores, cord gas measures, NICU admission, perinatal death
Qian et al,[12] 2017	China	Age <35 y, term, singleton, nulliparous, cephalic, spontaneous or induction of labor, normal fetal heart rate pattern in first stage of labor, normal labor at onset of second stage	Pregestational and gestational diabetes, hypertension, preeclampsia, eclampsia, oligohydramnios, abruption, fetal growth restriction, cephalopelvic disproportion, meconium, tachysystole, oxygen in first stage of labor, history of prior uterine incision, respiratory or cardiovascular disease, anemia, fever, disorder in oxygen saturation, hypotension, tobacco and alcohol use	Labor	Nasal cannula (219), room air (224)	Low	UA pH,[a] maternal satisfaction, mode of delivery, fetal heart rate pattern, tachysystole, hypotension, meconium, use of oxytocin, duration of second stage of labor, maternal arterial blood gas measures, cord gas measure, postpartum hemoglobin, neonatal outcomes
Raghuraman et al,[13] 2018	US	Term, singleton, admitted for labor or induction of labor, category II requiring resuscitation	Fetal anomalies, multiple gestation, maternal hypoxia	Labor	Nonrebreather, 80% (48), room air (51)	Low	UA lactate,[a] cord gas measures, CD for nonreassuring fetal status, operative vaginal delivery

(continued)

Table 1. Characteristics of Randomized Clinical Trials Comparing Peripartum Maternal Oxygen Supplementation With Room Air (continued)

Source	Country	Inclusion criteria	Exclusion criteria	Patient population	Exposure (No. of patients)	Risk of bias	Outcomes
Ramanathan et al,[24] 1982	US	Term, elective repeat CD, epidural anesthesia without obstetric complications	None specified	Scheduled CD	Anesthetic face mask with circle absorber, 47% (10), anesthetic face mask with circle absorber, 74% (10), anesthetic face mask with circle absorber, 100% (10), room air (10)	High	UA and UV Pao_2, maternal arterial blood gases, fetal and maternal oxyhemoglobin saturation
Simon et al,[14] 2018	US	Term, singleton, age >18 y, planned CD, with regional anesthesia	Chronic hypertension, maternal lung disease, preeclampsia, fetal growth restriction, fetal anomalies, multiple gestation, breech	Scheduled CD	Simple face mask (33), room air (32)	Low	UA pH, cord gas measures,[a] composite maternal complications, composite neonatal complications
Siriussawakul et al,[31] 2014	Thailand	Term, singleton, adult, elective CD with spinal anesthesia	Maternal hypoxemia, diabetes, hypertension, heart disease, obesity, previa, premature rupture of membranes, fetal growth restriction	Scheduled CD	Nasal cannula (163), room air (163)	Low	Maternal oxygen saturation,[a] cord gas measures
Thorp et al,[16] 1995	US	Spontaneous or induced labor, normal labor at onset of second stage	Maternal respiratory disease, diabetes, hypertension, preeclampsia, no significant fetal heart rate tracing abnormalities	Labor	Simple face mask, 81% (41), room air (44)	Low	UA pH,[a] cord gas measures
Palacio et al,[30] 2008	Spain	Term, received prenatal care, ASA I, CD under spinal	Fetal anomalies, maternal health problems	Scheduled CD	Venturi mask, 40% (62), room air (62)	High	Maternal pulse oximetry,[a] cord gas measures

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CD, cesarean delivery; Fio_2, fraction of inspired oxygen; UA, umbilical artery; UV, umbilical vein.

[a] Primary outcome identified in the study.

(I^2 = 0.00%; P = .62). In contrast, there was no significant difference in UA pH less than 7.2 between oxygen and room air among women in labor (3 studies: RR, 1.34; 95% CI, 0.58-3.11) (eFigure 2 in the Supplement). In the 3 studies that reported UA pH less than 7.1 as an outcome,[11,12,16] there was no significant difference between the oxygen and room air groups (3 studies: RR, 3.16; 95% CI, 0.64-15.50).

Thirteen studies reported the outcome of UA Pao_2. Nine included patients with a scheduled CD,[10,14,24-27,29-31] 3 included women who were in labor,[13,15,16] and 1 included both scheduled CD and labor groups that were analyzed separately.[9] There was significant heterogeneity among all studies (I^2 = 90.37%; P < .01). Overall, oxygen administration was associated with an increase in UA Pao_2 compared with room air (14 cohorts: WMD, 2.57 mm Hg; 95% CI, 0.80-4.34 mm Hg). After the results were stratified by the presence or absence of labor, the significant association between oxygen and UA Pao_2 was limited to women undergoing scheduled CD (10 studies: WMD, 2.12 mm Hg; 95% CI, 0.09-4.15 mm Hg), but not among those during labor (4 studies: WMD, 3.60 mm Hg; 95% CI, −0.30 to 7.49 mm Hg) (eFigure 3 in the Supplement).

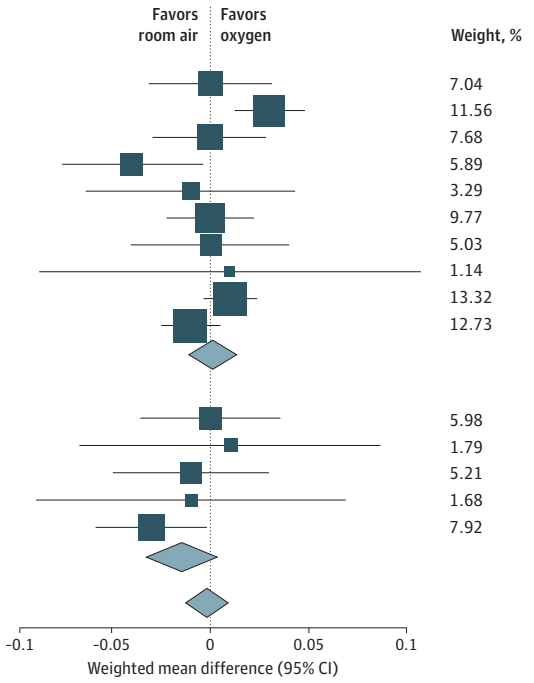
Eleven studies reported results for the outcome of UA base excess. Six were in women with scheduled CD,[14,24,27,29-31] 4 were in women in labor,[11-13,16] and 1 included both groups.[9] There was significant heterogeneity between studies (I^2 = 94.63%; P < .01). There was no significant difference in UA base excess between the oxygen and room air groups overall (12 studies: WMD, −0.13; 95% CI, −0.74 to 0.49) and after stratifying by the presence or absence of labor (scheduled CD, 7 studies: WMD, −0.54; 95% CI, −1.49 to 0.41; labor, 5 studies: WMD, −0.21; 95% CI, −0.16 to 0.58) (eFigure 4 in the Supplement). **Table 2** summarizes the pooled results for all UA gas measures.

Seven studies reported 1- and 5- minute Apgar scores,[9-11,27-29,31] 1 of which included both women in labor and those scheduled for CD and analyzed the results separately.[9] Overall, there were no significant differences in Apgar scores between groups. However, after stratifying by the presence or absence of labor, infants of mothers receiving oxygen during scheduled CD had slightly lower 1-minute Apgar scores than those whose mothers were receiving room air (6 studies: WMD, −0.20; 95% CI, −0.40 to −0.01). There was no statistically significant difference in 5-minute Apgar scores. All Apgar scores were similar in the oxygen and room air groups among infants of mothers who were in labor (**Table 3**; eFigure 5 and eFigure 6 in the Supplement).

Neonatal intensive care unit admission was reported in 4 studies,[9,11,12,16] 3 of which were performed in women during labor. There was no significant difference in the rate of neonatal intensive care unit admission between all oxygen and room air groups (4 studies: RR, 0.87; 95% CI, 0.44-1.73), patients undergoing scheduled CD (1 study: RR, 1.00; 95% CI, 0.02-48.82), or patients in labor (3 studies: RR, 0.87; 95% CI, 0.44-1.73) (Table 3; eFigure 7 in the Supplement).

The association between oxygen administration and oxidative stress was investigated in 4 studies.[9,11,15,28] Maternal and/or UA malondialdehyde was the most commonly

Figure 2. Maternal Oxygen Supplementation vs Room Air and Umbilical Artery (UA) pH



Source	UA pH with oxygen No.	UA pH with oxygen Mean (SD)	UA pH with room air No.	UA pH with room air Mean (SD)	Weighted mean difference (95% CI)	Weight, %
Scheduled CD						
Ahuja et al,[9] 2018	30	7.20 (0.07)	30	7.20 (0.05)	0.00 (-0.03 to 0.03)	7.04
Biswas et al,[10] 2019	61	7.22 (0.05)	66	7.19 (0.05)	0.03 (0.01 to 0.05)	11.56
Cogliano et al,[26] 2002	46	7.27 (0.06)	23	7.27 (0.05)	0.00 (-0.03 to 0.03)	7.68
Gunaydin et al,[27] 2011	60	7.27 (0.09)	30	7.31 (0.06)	-0.04 (-0.08 to -0.00)	5.89
Khaw et al,[29] 2002	22	7.24 (0.09)	22	7.25 (0.09)	-0.01 (-0.06 to 0.04)	3.29
Khaw et al,[28] 2004	104	7.28 (0.06)	55	7.28 (0.08)	0.00 (-0.02 to 0.02)	9.77
Ramanathan et al,[24] 1982	30	7.33 (0.04)	10	7.33 (0.09)	0.00 (-0.04 to 0.04)	5.03
Simon et al,[14] 2018	33	7.29 (0.20)	32	7.28 (0.20)	0.01 (-0.09 to 0.11)	1.14
Siriussawakul et al,[31] 2014	162	7.31 (0.06)	163	7.30 (0.06)	0.01 (-0.00 to 0.02)	13.32
Palacio et al,[30] 2008	62	7.30 (0.03)	62	7.31 (0.05)	-0.01 (-0.02 to 0.00)	12.73
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 56.16\%$, $H^2 = 2.28$ Test of $\theta_i = \theta_j$: $Q_9 = 19.39$, $P = .02$					0.00 (-0.01 to 0.01)	
Labor						
Ahuja et al,[9] 2018	30	7.20 (0.09)	30	7.20 (0.04)	0.00 (-0.04 to 0.04)	5.98
Moors et al,[11] 2020	57	7.22 (0.21)	60	7.21 (0.21)	0.01 (-0.07 to 0.09)	1.79
Qian et al,[12] 2017	219	7.26 (0.21)	224	7.27 (0.21)	-0.01 (-0.05 to 0.03)	5.21
Raghuraman et al,[13] 2018	48	7.25 (0.20)	51	7.26 (0.20)	-0.01 (-0.09 to 0.07)	1.68
Thorp et al,[16] 1995	41	7.26 (0.07)	44	7.29 (0.06)	-0.03 (-0.06 to -0.00)	7.92
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.08\%$, $H^2 = 1.00$ Test of $\theta_i = \theta_j$: $Q_4 = 2.32$, $P = .68$					-0.01 (-0.03 to 0.00)	
Overall					-0.00 (-0.01 to 0.01)	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 49.88\%$, $H^2 = 2.00$ Test of $\theta_i = \theta_j$: $Q_{14} = 25.25$, $P = .03$ Test of group differences: $Q_{b1} = 2.06$; $P = .15$ Random-effects REML model						

Pooled relative risk estimates for the association between oxygen or room air and UA pH stratified by the presence or absence of labor. CD indicates cesarean delivery; REML, residual maximum likelihood.

Table 2. Pooled and Stratified Results of the Effect of Maternal Oxygen Supplementation vs Room Air on UA Gas Measures

Characteristic	No. of studies	No. of patients: Oxygen	No. of patients: Room air	Measure of effect	Effect size (95% CI)	I^2 value	*P* value
All studies							
UA pH	15	1005	902	WMD	0.00 (−0.01 to 0.01)	49.88	.03
UA pH <7.2	6	512	487	RR	0.87 (0.58-1.32)	34.87	.11
UA pH <7.1[a]	3			RR	3.16 (0.64-15.50)	0.00	>.99
UA Pao_2	13	698	635	WMD	2.57 (0.80-4.34)	90.37	.005
UA base excess	11	794	758	WMD	−0.13 (−0.74 to 0.49)	94.63	<.001
Scheduled CD							
UA pH	10	610	493	WMD	0.00 (−0.01 to 0.01)	56.16	.02
UA pH <7.2	3	198	155	RR	0.63 (0.43-0.90)	0.00	.62
UA Pao_2	10	518	446	WMD	2.12 (0.09-4.15)	84.33	<.001
UA base excess	7	399	349	WMD	−0.54 (−1.49 to 0.41)	88.12	<.001
Labor							
UA pH	5	395	409	WMD	−0.01 (−0.03 to 0.00)	0.08	.68
UA pH <7.2	3	260	268	RR	1.34 (0.58-3.11)	57.53	.10
UA Pao_2	4	180	189	WMD	3.60 (−0.30 to 7.49)	94.14	<.001
UA base excess	5	395	409	WMD	0.21 (−0.16 to 0.58)	78.51	<.001

Abbreviations: CD, cesarean delivery; RR, relative risk; UA, umbilical artery; WMD, weighted mean difference.

[a] All 3 trials in women in labor.

studied marker among these trials. Use of oxygen was associated with an increase in maternal malondialdehyde levels (3 studies: WMD, 0.37μM; 95% CI, 0.26-0.48μM) and no significant difference in the UA malondialdehyde level (4 studies: WMD, 0.16μM; 95% CI, −0.18 to 0.50μM).

Discussion

The results of this systematic review and meta-analysis suggest that maternal oxygen supplementation at the time of de-

Table 3. Pooled and Stratified Results for the Effect of Maternal Oxygen Supplementation vs Room Air on Neonatal Outcomes

Characteristic	No. of studies	No. of patients		Measure of effect	Effect size (95% CI)	I^2 value	*P* value
		Oxygen	Room air				
All studies							
1-min Apgar score	8	526	456	WMD	−0.13 (−0.30 to 0.04)	71.68	.001
5-min Apgar score	8	526	456	WMD	−0.12 (−0.27 to 0.04)	99.91	<.001
NICU admission	4	333	340	RR	0.87 (0.44-1.73)	0.00	.64
Scheduled CD							
1-min Apgar score	6	439	366	WMD	−0.20 (−0.40 to −0.01)	62.60	.02
5-min Apgar score	6	439	366	WMD	−0.16 (−0.36 to 0.04)	99.30	<.001
NICU admission	1	30	30	RR	1.00 (0.02-48.82)	NA	NA
Labor							
1-min Apgar score	2	87	90	WMD	0.08 (−0.02 to 0.19)	0.00	.32
5-min Apgar score	2	87	90	WMD	−0.12 (−0.27 to 0.04)	0.01	>.99
NICU admission	3	303	310	RR	0.87 (0.44-1.73)	0.00	.43

Abbreviations: CD, cesarean delivery; NA, not applicable; NICU, neonatal intensive care unit; RR, relative risk; WMD, weighted mean difference.

livery yields no substantial difference in UA pH compared with room air, despite an increase in UA Pao_2. The UA pH remained similar between the oxygen and room air groups even after accounting for risk of bias, use of low-flow devices, or FIO_2 less than 60%. Oxygen supplementation appeared to lower rates of UA pH less than 7.2 and increase UA Pao_2 compared with room air at the time of a scheduled CD. Trials including women in labor and data on neonatal outcomes were limited. One-minute Apgar scores were marginally lower in infants whose mothers were receiving oxygen at the time of a scheduled CD; however, the mean difference between oxygen and room air was less than 1 point. There were no statistically significant differences in other secondary outcomes. There was significant interstudy heterogeneity for most of the outcomes.

Similar to our results, a 2016 Cochrane review on supplemental oxygen at the time of elective CD with the use of regional anesthesia reported that oxygen administration was associated with a higher UA Pao_2 with no difference in UA pH.[7] Contrary to the Cochrane review's finding that Apgar scores were similar between the oxygen and room air groups, we observed a lower 1-minute Apgar score in infants exposed to oxygen at the time of a scheduled CD. We suspect that this lower score may be a spurious finding, particularly because it is inconsistent with the finding of oxygen administration reducing the incidence of UA pH less than 7.2 in the same cohort. Furthermore, a mean difference of 0.20 in 1-minute Apgar scores is unlikely to be clinically relevant, particularly when 5-minute Apgar scores were similar between groups.

A 2012 Cochrane review of 2 trials comparing room air with oxygen in women in labor found that oxygen was associated with an increased risk of UA pH less than 7.2 with no significant differences in UA oxygen content or Apgar scores.[8] Our review found no significant differences in UA pH less than 7.2 between oxygen and room air groups in women during labor. Although the overall number of trials in women during labor is limited, our review included 5 additional trials[9,11-13,15] in this group that were published subsequent to the 2012 Cochrane review and therefore provides a more comprehensive analysis of UA gases after oxygen exposure.

We stratified our analysis by the presence or absence of labor and observed that oxygen administration at the time of scheduled CD was associated with increased UA Pao_2 and a lower rate of UA pH less than 7.2. Spinal anesthesia at the time of CD has been associated with acute hypotension in 70% to 80% of patients.[32] The development of hypotension may result in decreased uteroplacental perfusion and impaired maternal-fetal gas exchange that women who receive epidural anesthesia during labor are less likely to experience. A meta-analysis comparing epidural, spinal, and general anesthesia reported that UA pH and base excess were significantly lower after spinal anesthesia than after general or epidural anesthesia.[33] Furthermore, the choice of vasopressor (ephedrine vs phenylephrine) to treat hypotension might play a role because ephedrine is associated with stimulation of fetal metabolism and, consequently, fetal acidemia.[34,35] Administration of oxygen to women may therefore improve fetal oxygenation and prevent acidemia in the setting of spinal anesthesia-associated hypotension. However, it remains to be determined whether such improvement will be noticeable in the current paradigm of preventing hypotension with a continuous phenylephrine infusion.[36]

Pooled results from all of the studies in this review showed increased UA Pao_2 but no significant differences in UA pH with the use of oxygen. Umbilical artery Pao_2 has been shown to be a poor estimator of neonatal morbidity[37] because the Pao_2 evaluated in a cord blood gas represents dissolved oxygen in the sample and does not reflect the amount of oxygen that is bound to hemoglobin.[38] Therefore, hypoxia or inadequate tissue oxygenation cannot be inferred from dissolved oxygen content alone. Prolonged tissue hypoxia leads to anaerobic metabolism, resulting in decreased pH, which is why UA pH ultimately serves as a better marker for prediction of neonatal morbidity. An intervention that increases the Pao_2 without concomitantly increasing the pH has limited clinical benefit, particularly because hyperoxemia is associated with the

production of free radicals and oxidative cell damage in adults and neonates.[3,39,40]

Strengths and Limitations

The strengths of this review include adherence to an a priori study protocol, inclusion of only randomized clinical trials, and assessment of heterogeneity for the primary outcome by using stratified analyses to address factors such as route and dose of oxygen administration. To our knowledge, this is the first meta-analysis to combine data from all trials investigating the utility of peripartum oxygen administration for fetal benefit.

This review has limitations. First, using our preestablished criteria, 50% of the studies were at high risk of bias. In a sensitivity analysis excluding these studies, we found no significant difference in the UA pH between groups. Another limitation is the heterogeneity of all the studies, particularly with regard to the way oxygen was administered. To account for the heterogeneity, we used random-effects models and performed stratified analyses by type of oxygen delivery device and FIO_2. Despite pooling data from existing trials, it is possible that our analysis was underpowered to detect differences in UA pH or other UA gas outcomes. Furthermore, only 1 trial in this review assessed oxygen administration for category II fetal tracings, which is the most common indication for oxygen use in labor and delivery settings.[13] Data on short- and long-term neonatal outcomes were limited, with few trials presenting results for neonatal intensive care unit admissions and Apgar scores. Although these 2 outcomes are commonly used to gauge neonatal risk, they poorly correlate with high-acuity illness, asphyxia, and long-term neurologic morbidity.[41-45]

Conclusions

The results of this systematic review and meta-analysis suggest that peripartum maternal oxygen supplementation is not associated with a clinically relevant improvement in the UA pH or other neonatal outcomes. However, the published studies on this topic are heterogeneous, lack important data on the association between oxygen supplementation and clinically relevant neonatal sequelae, and largely did not assess oxygen use for abnormal fetal heart rate tracings. A large, adequately powered trial is needed to investigate the effect of maternal oxygen supplementation in response to fetal heart rate tracings on short- and long-term neonatal morbidity. In the interim, prolonged oxygen use should be limited given lack of proven benefit and potential risk of harm. Future studies should also assess the optimal dose, duration, and route of peripartum oxygen administration.

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