OBSTETRICS

Effect of long-duration oxygen vs room air during labor on umbilical cord venous partial pressure of oxygen: a randomized controlled trial

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Yunhai Chuai, MS; Wen Jiang, MS; Lanmei Zhang, MD; Fang Chuai, BS; Xiuyan Sun, BS; Kefei Peng, BS; Jinfang Gao, BS; Tong Dong, MS; Lei Chen, MD; Yuanqing Yao, MD

BACKGROUND: There are limited data to guide the duration and dose of oxygen supplementation for pregnant women undergoing labor.

OBJECTIVE: To assess the effect of maternal long-duration high-concentration oxygen administration during labor on umbilical cord venous partial pressure of oxygen.

STUDY DESIGN: This randomized clinical trial was conducted between January and October of 2021 in the obstetrics wards of 3 tertiary teaching hospitals in Beijing, China. Women undergoing the latent phase of labor with no existing medical conditions or obstetrical complications who were admitted for delivery were eligible. The women who met inclusion criteria with category I fetal heart rate tracings in labor were randomized in a 1:1 ratio to oxygen or room air. The oxygen group received 10 L of oxygen per minute by simple, tight-fitting face mask until delivery. The room-air group received room air only, without a face mask. The primary outcome was the umbilical cord venous partial pressure of oxygen.

RESULTS: A total of 661 women were screened, and 521 were excluded; 140 participants with category I fetal heart rate tracings were enrolled and randomized to oxygen (N=70) or room air (N=70). A total of 135 women with valid paired umbilical cord venous and arterial gas values were included in the umbilical cord venous partial pressure of oxygen and arterial pH analyses. All 140 women were included in the fetal heart rate tracings analysis. Baseline characteristics were similar between the oxygen and room-air groups. The duration of oxygen exposure was approximately 322±147 minutes. There were no differences between the oxygen and room-air groups in the umbilical cord venous partial pressure of oxygen (mean difference, 1.1 mm Hg; 95% confidence interval, −1.0 to 3.2; *P*=.318) or the proportion of participants with category II fetal heart rate tracings (81.4% vs 78.6%; relative risk, 1.04; 95% confidence interval, 0.88−1.22; *P*=.672). However, the umbilical cord arterial pH was significantly lower in the oxygen group than in the room-air group (median, 7.23; interquartile range, 7.20−7.27 vs median 7.27; interquartile range, 7.20−7.30; *P*=.005).

CONCLUSION: Maternal long-duration high-concentration oxygen administration during labor did not affect either the umbilical cord venous partial pressure of oxygen or fetal heart rate pattern distribution but resulted in a deterioration of the umbilical cord arterial pH at birth.

Key words: high-concentration oxygen, long-duration, umbilical cord venous partial pressure of oxygen

Introduction

Maternal oxygen (O_2) administration has been the most common intervention for intrauterine fetal resuscitation; it has been estimated that more than half of all pregnant women have received O_2 at some point during labor, although they were not hypoxic.[1,2] Obstetricians and midwives hoped that the additional O_2 can improve the status of fetal acid-base metabolism and relieve suspicious or abnormal fetal heart rate (FHR) tracings.[1,2] However, there has been a great deal of controversy about the effects of therapeutic or prophylactic maternal O_2 inhalation therapy during labor on neonatal outcomes.[3,4] Systematic reviews have found low or very low-certainty evidence of hyperoxia-induced vasoconstriction in animal models and in healthy volunteers and patients.[5,6] The effects of hyperoxia on pregnancy hemodynamics were studied in a cohort study, which found that a supplemental 80% to 100% fraction of inspired O_2 (FiO_2) for 10 minutes decreased the cardiac index and increased systemic vascular resistance.[7] At present, there have been only 5 randomized clinical trials (RCTs) of prophylactic or therapeutic O_2 inhalation during labor showing that supplemental O_2 did not improve fetal acid-base status or other neonatal outcomes. In these trials, women received prophylactic O_2 during the second stage of labor (30%−80% FiO_2) or therapeutic O_2 (80% FiO_2) when they developed category II or III FHR tracings at any point in the active phase or the second stage of labor until delivery.[8−12]

An unproven hypothesis concerning O_2 for intrauterine resuscitation is that the supraphysiological O_2 can be transferred across the placenta to fetal circulation.[13,14] Fetal oxygenation was often tested by fetal pulse oximetry ($FSpO_2$), blood O_2 level-dependent magnetic resonance imaging (BOLD-MRI), and umbilical cord venous (Uv) partial pressure of O_2 (PO_2). For $FSpO_2$, Dildy et al[15] showed that supplemental 40% FiO_2 (20 or 45 minutes) resulted in no significant change in fetal O_2 saturation, but other studies showed that 40% to 100% FiO_2 (15−30 minutes) increased fetal O_2 saturation.[16−18] For BOLD-MRI, studies showed that a short time breathing 100% FiO_2 (6 minutes) increased cerebral blood oxygenation in

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AJOG at a Glance

Why was this study conducted?

This study aimed to investigate whether prolonged oxygen exposure in labor may be helpful in improving fetal oxygen content.

Key findings

In this randomized trial of 140 pregnant patients with category I fetal heart tracings in labor, prolonged oxygen exposure was not associated with higher fetal oxygen content or lower fetal distress risk; rather, this intervention was associated with a trend of fetal acidosis.

What does this add to what is known?

Excess oxygen may be useless and potentially harmful to fetuses.

fetuses with single ventricle or aortic obstruction, but 100% FiO_2 did not affect fetal brain oxygenation (6 and 40 minutes) or fetal liver oxygenation (15 minutes) in healthy fetuses.[19–21] Thorp et al[8] found no significant change in Uv PO_2 with maternal administration of 80% FiO_2 for a mean of 45 minutes during the second stage of labor, but Watkins et al[14] showed a significant decrease in Uv PO_2 (median 25.5 vs 32.5 mm Hg) with maternal administration of 80% FiO_2 over 176 minutes during the partial active phase and the second stage of labor.

In the real world, the duration of O_2 exposure ranged from a few minutes to several hours, and was based on clinical experience with no consensus.[14] We performed this trial to assess the effect of maternal, long-duration, high FiO_2 exposure during labor on Uv PO_2. The long-duration high FiO_2 was defined as supplementing with 60% to 80% FiO_2 during the major part of labor (ie, late latent phase, whole active phase, and second stage of labor), with a duration of usually >2 to 3 hours. To avoid pulmonary O_2 toxicity, supplemental high FiO_2 cannot exceed 24 hours,[22] and the total duration of O_2 exposure was not allowed to exceed 12 hours in our study.

Materials and Methods

Study design

The study was a 3-site (based in Beijing, China), randomized, open-label, parallel-group trial of women in the latent phase of labor who had category I FHR tracings from January 2021 to October 2021. The study was approved by the human research ethics committees at the Sixth Medical Center and Seventh Medical Center of the Chinese PLA General Hospital, and the PLA Strategic Support Force Characteristic Medical Center. The trial was registered on ClinicalTrials.gov with the identifier NCT03764696 before its commencement. After eligibility determination and before randomization, all participants completed informed consent in the labor units. The registered study protocol is available in the Appendix.

Study population

Study participants were women without existing medical conditions or obstetrical complications and with a high probability of vaginal delivery. The inclusion criteria were: at term (37–42 weeks), singleton, and cephalic presentation, spontaneous or induced labor, normal labor, category I FHR tracings, 2 to 3 cm of cervical dilation in nulliparas, 1 to 2 cm of cervical dilation in multiparas, and informed consent. Exclusion criteria included: respiratory or cardiovascular disease, diabetes mellitus or insulin-treated gestational diabetes mellitus, hypertension or preeclampsia, oligohydramnios, fetal growth restriction, placental abruption, cephalopelvic disproportion, meconium-stained amniotic fluid, tachysystole, having received O_2, uterine incision (myomectomy or perforation), anemia, fever, chorioamnionitis, tobacco or alcohol use, disorders in O_2 saturation, hypotension, and being uncomfortable with face masks. According to our experience, among those who were enrolled, the cesarean delivery rate was <5% and the median duration of first plus second stages of labor was approximately 8 to 9 hours.[10]

Randomization and intervention

Obstetricians assessed women for eligibility. Eligible women were randomized at 2 to 3 cm of cervical dilation in nulliparity and 1 to 2 cm of cervical dilation in multiparity in the latent phase of labor. Participants were randomly assigned to a computer-generated random sequence that used balanced variable blocks within each site in a ratio of 1:1. The random sequence was generated by 1 investigator at each site who took no further part in this study. Randomization was performed by the sequential opening of sealed numbered envelopes by 1 research nurse at each site.

Women were assigned to receive either O_2 via a tight-fitting simple face mask at a flow rate of 10 L per minute (FiO_2 was approximately 60%–80%[8,11,12]) until delivery, or room air only without a face mask. The face mask was applied by 1 research nurse to ensure that it was worn properly to cover the nose and mouth. Supplemental O_2 could be interrupted for certain reasons, including eating, drinking, and other related reasons, but the total duration could not exceed 15 minutes. To avoid O_2 toxicity, the total duration of O_2 exposure was not allowed to exceed 12 hours, otherwise the intervention would be terminated. All participants received standard intrapartum care and gave birth in a supine position. The FHR tracing was reviewed every 15 to 30 minutes in the first stage of labor and continuously during the second stage. We managed those who developed category II or III FHR tracings according to the guidelines of the American College of Obstetricians and Gynecologists (ACOG).[23] The initial evaluation included the following: a cervical examination, monitoring of the maternal blood pressure, and assessment of the uterine tachysystole. The methods of intrauterine resuscitation included changing the maternal position,

discontinuation of oxytocin, intravenous fluid bolus, and tocolytic agents.[23] Amnioinfusion was not used in this study, and O_2 was not used for resuscitation in the room-air group.

Outcomes and data collection

Baseline characteristics of study participants were collected, including maternal age, gestational age, nulliparity or multiparity, body mass index, antepartum hematocrit, spontaneous or induced labor, pain management, and augmentation of labor.

The primary outcome was the Uv PO_2. The paired Uv and umbilical cord arterial (Ua) blood samples were collected as recommended by ACOG.[24] A segment of umbilical cord (20 cm) was double-clamped and divided, and blood samples were obtained by trained technicians immediately after delivery. These samples were analyzed in the delivery units using the GEM Premier 4000 benchtop blood gas analyzer (Werfen, Bedford, MA). We validated the umbilical cord blood gases according to the criteria of Monneret et al,[25] who established 3 exclusion criteria: a Uv - Ua pH difference <0.02, a Ua - Uv partial pressure of carbon dioxide (PCO_2) <5.25 mm Hg, and a Uv PCO_2 <21.75 mm Hg.

The secondary outcomes were the Ua pH and the number of women who developed category II or III FHR tracings in labor. Two trained research nurses, unaware of the randomization assignments, independently assessed the FHR tracings in the storage compute, and resolved disagreements by discussion with a third nurse. The details of category II or III FHR tracings were recorded, including baseline, variability, and deceleration. Other secondary outcomes were other umbilical cord blood gas components, the duration of the first and second stages of labor, the time from randomization to delivery, the methods of delivery, the methods of intrauterine resuscitation, neonatal sex, birthweight, Apgar score, resuscitation, admission to the neonatal ward, and serious neonatal morbidity. All of the newborns were followed up during the 4 weeks after birth.

Participant protection

An ethical dilemma faced in this study was whether the prolonged O_2 administration in low-risk participants was justified. In January 2019, the institutional review board (IRB) approved the study on the basis of the results of randomized trials and real-world clinical practice. In the randomized trials, there was not enough evidence to conclude that maternal O_2 exposure was harmful to fetuses. We provided all of the 4 available RCTs concerning O_2 administration during labor to the review boards for reference [8−11]. In these trials, all participants had normal cardiac and pneumonic functions without hypoxia. Three of the trials included normal women with category I FHR tracings,[8−10] and 1 trial included normal women who had developed category II FHR tracings.[11] No statistical differences were found between the O_2 and air groups in the Ua pH.[8−11] The only reference for prolonged O_2 during labor (>2−3 hours) at the time was in 1 (99 participants) of these 4 RCTs, conducted by Raghuraman et al.[11] In the O_2 group, the median duration of O_2 exposure was 96 minutes, and a quarter of the participants received O_2 for >176 minutes; there were no differences between the 2 groups in the Ua lactate or pH.[11] In the real world, the duration of maternal O_2 exposure ranged from a few minutes to several hours, depending on clinical experience, without guidelines or consensus.[14] Obstetricians empirically believed that maternal O_2 inhalation could increase fetal O_2 content and lessen a nonreassuring fetal status, and therapeutic or prophylactic O_2 was widely used, with few realizing it could be potentially harmful.[1,2]

The main rationale for including normal women with category I FHR tracings was safety considerations, followed by practical significance. Assuming that prolonged O_2 exposure was potentially harmful, to reduce the incidence of fetal adverse events, the IRB recommended that we include very low-risk participants with category I FHR tracings rather than women with high-risk pregnancies. Our intention was to answer the question of how prolonged O_2 exposure during labor affected fetal O_2 content in a safe trial with a low probability of adverse events. Only approximately 16% of the women maintained category I FHR tracings throughout labor. A previous study reported only approximately 16% of the women maintained category I FHR tracings throughout labor, and most puerperae developed category II FHR tracings at some point during labor.[26] One reason might have been the widespread use of O_2 for intrauterine resuscitation, which is an empirical rather than evidence-based intervention. Given the lack of evidence and controversy concerning the use of O_2, it is still necessary to study normal participants with category I FHR tracings to provide a basis for formulating the O_2 supply parameters.

The IRB considered that prolonged O_2 during labor might cause pulmonary O_2 toxicity in women, and made it a rule that the total duration of maternal O_2 administration was not allowed to exceed 12 hours in this study. To expeditiously resolve the category III FHR tracings, we were able to perform operative vaginal or cesarean delivery in the labor room, and all 3 centers had standard operating rooms in the labor rooms, in addition to having neonatal intensive care unit departments. No maternal pulmonary O_2 toxicity events or fetal category III FHR tracing events occurred during our trial.

Statistical analysis

Sample size was calculated on the basis of the Uv PO_2. According to our institutional data and literature, we estimated a baseline Uv PO_2 mean±standard deviation (SD) of 27±6 mm Hg in term infants of nonpathologic pregnancies or deliveries uncomplicated during labor.[25] A Cochrane review showed an increase in Uv PO_2 (mean difference [MD], 8.2 mm Hg) with maternal FiO_2 of at least 60% during cesarean delivery.[27] An RCT showed no significant change in Uv PO_2 with maternal FiO_2 at 80% for a mean of 45 minutes during labor.[8] An analysis of nonrandom samples from a RCT showed a decrease in Uv PO_2 (median 25.5 vs 32.5 mm Hg) with maternal FiO_2 at 80% over 176 minutes during labor.[14] In the

present trial, a clinically significant change of Uv PO_2 was assumed to be 3 mm Hg units. To detect the 3-mm Hg difference in Uv PO_2 with 80% power and a 2-sided test of 0.05, we estimated that 64 women were needed in each group. We anticipated a 10% loss to unattainable paired cord gases, resulting in a plan to enroll 140 participants.

Data analysis was performed using the modified intention-to-treat principle. All randomized women received their assigned interventions without interruption or crossover; 96.4% (135/140) of participants with valid paired Uv and Ua gas values were included in the Uv PO_2 and Ua pH analyses, the values of the remaining 3.6% (5/140) were assumed to be missing at random, and all randomized women were included in the FHR tracings analysis. The distribution of continuous variables was analyzed using the Kolmogorov−Smirnov test, and the Student *t* test or Mann−Whitney *U* test were used as appropriate. Categorical variables were analyzed using the chi square test or Fisher exact test. Data were expressed as mean±SD, median and interquartile range (IQR), or number (%). All statistical analyses were performed using IBM SPSS Statistics, version 19 (IBM Corp, Armonk, NY).

Results

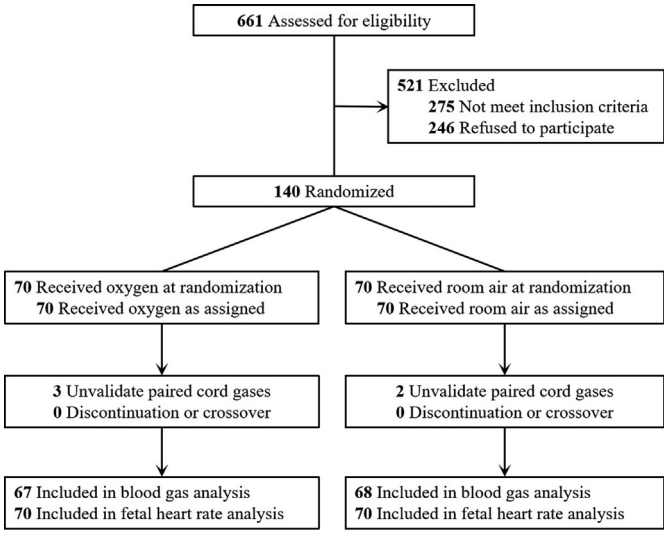
The Figure depicts the course of recruitment and follow-up of this study. Of the 661 women screened, 275 did not meet the inclusion criteria, 246 declined participation, and 140 were randomly assigned. There were 70 women who were assigned to 10 L of O_2 per minute by a simple, tight-fitting face mask and 70 who were assigned to room air only without a face mask; 96.4% (135/140) of participants were included in the umbilical cord gas analysis, and all randomized women were included in the FHR tracings analysis. The baseline characteristics were similar between the O_2 and room-air groups (Table 1).

There were no differences between the O_2 and room-air groups in labor outcomes, including duration of first stage (MD, 33 minutes; 95% confidence interval [CI], −34 to 101; *P*=.331), duration of second stage (median 50 minutes; IQR, 34−83 vs median 46 minutes; IQR, 27−67; *P*=.495), time from randomization to delivery (MD, 14 minutes; 95% CI, −31 to 60; *P*=.537), neonatal resuscitation (relative risk [RR], 1.5; 95% CI, 0.44−5.09; *P*=.512), and neonatal intensive care (RR, 1; 95% CI, 0.34−2.95; *P*=1.000) (Table 2). Operative vaginal delivery and cesarean delivery were rare in the trial (Table 2). There were no Apgar scores <7 or serious neonatal morbidity in either group (Table 2). In the O_2 group, the mean (SD) time from randomization to delivery was 322 (147) minutes: >120 minutes in 94% (63/67) of cases and >180 minutes in 88% (59/67) of cases.

There were no differences between the O_2 and room-air groups in the Uv PO_2 (MD, 1.1 mm Hg; 95% CI, −1.0 to 3.2; *P*=.318), the Ua PO_2 (MD, 0.09 mm Hg; 95% CI, −1.8 to 1.9; *P*=.927), or in some other components, including Uv/Ua O_2 saturation, Uv/Ua hemoglobin, and Uv PCO_2 (Table 3). Long-duration O_2 was associated with lower Ua pH (median 7.23; IQR, 7.20−7.27 vs median 7.27; IQR, 7.20−7.30; *P*=.005), Uv pH (median 7.29; IQR, 7.27−7.33 vs median 7.32; IQR, 7.30−7.35; *P*=.002), Uv/Ua base deficit, and Ua PCO_2, compared with room air (Table 3). There was no difference between the O_2 and room-air groups in the proportion of pH <7.2 (RR, 1.2; 95% CI, 0.6−2.3; *P*=.639) (sTable 1). To assess the dose-dependent effect of O_2 exposure on Ua/Uv pH, Ua/Uv pH was compared among the groups with duration of O_2 exposure <25th percentile, ≥25th (240 minutes) and <75th percentile, and ≥75th percentile (480 minutes). There were no differences in the Ua/Uv pH among these 3 groups (sTable 2).

There were no differences between the O_2 and room-air groups in the proportion of women with category II FHR tracings (RR, 1.04; 95% CI, 0.88−1.22; *P*=.672) (Table 4). The distribution of category II FHR tracings was similar between the 2 groups (sTable 3). There was no category III FHR tracing event in either group (Table 4). Alternate methods of intrauterine resuscitation were similar between the 2 groups (RR, 1.02; 95% CI, 0.83−1.25; *P*=.85) (Table 4).

FIGURE
Flow diagram of trial recruitment and follow-up



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Comment

Principal findings

Our trial showed that prolonged O_2 exposure was not associated with higher fetal O_2 content (Uv PO_2) or lower fetal distress risk (category II FHR tracing events) in normal women during labor, but that this intervention was instead

TABLE 1
Baseline characteristics of study participants

Characteristics	Oxygen (n=70)	Room air (n=70)
Maternal age, y	31.6±3.6	31.6±3.8
Gestational age, wk	39.8±1.0	39.7±0.9
Nulliparity (%)	59 (84.3)	55 (78.6)
Admission BMI, kg/m^2	26.0±2.6	25.8±2.6
Admission Hb, g/L	124.6±6.7	123.8±7.5
Induction of labor (%)	42 (60)	39 (55.7)
Epidural (%)	47 (67.1)	42 (60)
Augmentation of labor (%)	47 (67.1)	44 (62.9)
Amniotomy (%)	26 (37.1)	21 (30)
Oxytocin (%)	43 (61.4)	38 (54.3)

Data are expressed as mean±SD or number (percentage).

BMI, body mass index; *Hb*, hemoglobin; *SD*, standard deviation.

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associated with a trend of fetal acidosis (lower Ua pH).

Results in the context of what is known

It is generally believed that fetal distress or nonreassuring fetal status can be prevented and alleviated by increasing the available O_2 from the woman to the baby through the placenta. Consequently, maternal O_2 administration has become the most direct and common method of intrauterine resuscitation.[3,4] This study assessed the effects of long-duration (>2−3 hours), high-concentration (60%−80% FiO_2) maternal O_2 exposure. This trial differed from the 5 related RCTs mentioned previously,[8−12] in which O_2 exposure was studied for short durations (approximately 10 to several tens of minutes) with different concentrations (30% and 80% FiO_2).

Clinical implications

Physiologically, maternal uterine arterial PO_2 is approximately 100 mm Hg, the PO_2 of the intervillous space is 40 to 50 mm Hg, and the PCO_2 of the intervillous space is 38 to 42 mm Hg.[28] Fetal Ua PO_2 is 17 mm Hg and Ua PCO_2 is 55 mm Hg.[25] The primary site of maternal−fetal material exchange is the vasculosyncytial membrane (VSM), which is a 5-layer membrane structure that consists of syncytiotrophoblast cells, the syncytiotrophoblast basement membrane, villous stroma, the capillary basement membrane, and capillary endothelial cells.[28] O_2 and CO_2 penetrate the VSM by simple diffusion, and after exchanging, the fetal Uv PO_2 is 28 mm Hg and Uv PCO_2 is 41 mm Hg.[25] A Cochrane review

TABLE 2
Labor outcomes

Outcome	Oxygen (n=70)	Room air (n=70)	*P* value	MD or RR	95% CI
Duration of first stage, min	463±193	429±212	.331	33	−34 to 101
Duration of second stage, min	50 (34−83)	46 (27−67)	.495	—	—
Time from randomization to delivery, min	322±147	308±125	.537	14	−31 to 60
Operative vaginal delivery (%)	1 (1.4)	1 (1.4)	.476	1	0.06−15.67
Cesarean delivery (%)	3 (4.3)	1 (1.4)	.612	3	0.32−28.15
Female neonatal sex (%)	34 (48.6)	33 (47.1)	.866	1.03	0.73−1.46
Birthweight, g	3315±335	3416±402	.107	−102	−226 to 22
Neonatal resuscitation (%)	6 (8.6)	4 (5.7)	.512	1.5	0.44−5.09
Apgar score <7 at 1 min (%)	0 (0)	0 (0)	—	—	—
Apgar score <7 at 5 min (%)	0 (0)	0 (0)	—	—	—
Neonatal ward (%)	6 (8.6)	6 (8.6)	1.000	1	0.34−2.95
Serious morbidity[a] (%)	0 (0)	0 (0)	—	—	—

Data are expressed as mean±SD, number (percentage), or median (interquartile range).

CI, confidence interval; *MD*, mean difference; *RR*, relative risk; *SD*, standard deviation.

[a] Serious morbidity: life-threatening events occurred in the neonatal intensive care unit.

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TABLE 3
Paired umbilical cord venous and arterial blood gases

Outcomes	Oxygen (n=67)	Room air (n=68)	*P* value	MD	95% CI
Umbilical venous (Uv)					
Uv pH	7.29 (7.27–7.33)	7.32 (7.3–7.35)	.002	—	—
Uv PO_2, mm Hg	27.9±6.6	26.8±5.8	.318	1.1	−1.0 to 3.2
Uv PCO_2, mm Hg	42 (37.5–45)	39 (36–44)	.065	—	—
Uv base deficit	−6.4±2.8	−5.4±2.4	.021	−1.0	−1.9 to −0.2
Uv SO_2, %	58.4±18.6	57.3±17.3	.714	1.1	−5.0 to 7.2
Uv Hb, g/L	158±14.7	155.3±15.7	.286	2.8	−2.4 to 8.0
Umbilical arterial (Ua)					
Ua pH	7.23 (7.20–7.27)	7.27 (7.20–7.30)	.005	—	—
Ua PO_2, mm Hg	17.1±5.8	17.0±5.0	.927	0.09	−1.8 to 1.9
Ua PCO_2, mm Hg	57.2±10.5	52.7±8.6	.006	4.6	1.3–7.9
Ua base deficit	−5.6±3.2	−4.5±2.7	.048	−1.0	−2.0 to −0.01
Ua SO_2, %	29.2±15.8	29.8±15.0	.816	−0.6	−5.9 to 4.6
Ua Hb, g/L	160.6±14.5	157.1±14.5	.156	3.6	−1.4 to 8.5

Data are expressed as median (interquartile range) or mean±SD.

CI, confidence interval; *Hb*, hemoglobin; *MD*, mean difference; *PCO_2*, partial pressure of carbon dioxide; *PO_2*, partial pressure of O_2; *SD*, standard deviation; *SO_2*, O_2 saturation.

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(including 10 RCTs and 683 participants) showed that short-duration supplementary O_2 could significantly increase Uv PO_2 (FiO_2 at least 60%; MD, 8.19 mm Hg; and FiO_2 <60%; MD, 3.95 mm Hg) during cesarean deliveries, but provided very low-certainty evidence because of small-sample studies and high heterogeneity.[27] Two RCTs (200 participants) reported that short-duration 80% FiO_2 did not affect Uv/Ua PO_2 during labor,[8,14] whereas a secondary analysis of 1 trial (12 nonrandom samples) found that prolonged O_2 exposure (over 176 minutes) was associated with lower Uv PO_2 (median 25.5 vs 32.5 mm Hg).[14] In the present trial, the duration of O_2 exposure was approximately 322±147 minutes, and we found no differences in Uv/Ua PO_2 between the O_2 and room-air groups. We speculate that supraphysiological O_2 cannot freely pass through the VSM to fetal circulation, and the reasons may be hyperoxia-induced placental insufficiency or placental barrier function. Fetuses have a wider reference range of arterial PO_2 (17–41 mm Hg) than that found in adults (80–100 mm Hg).[25] Although the Uv PO_2 is relatively low, fetuses are not hypoxic because of the high O_2 carrying capacity and concentration of fetal hemoglobin ($\alpha 2\gamma 2$).[10] In general, O_2 supply to the fetus is oversupply, and fetal uptake is not affected even when the supply is reduced by half.[1] This implies that fetuses do not usually need excess O_2.

Despite the widespread use of prophylactic or therapeutic O_2, a recent systematic review (including 16 RCTs and 2052 participants) found no differences in the Ua pH between the O_2 and room-air groups (MD, 0.00; 95% CI, −0.01 to 0.01), and the Ua pH did not seem to be affected by either vaginal or cesarean delivery.[4] In the present trial, we found that prolonged O_2 exposure was associated with lower median Ua pH (7.23 vs 7.27), Uv pH (7.29 vs 7.32), and Uv/Ua base deficit compared with room air during labor (Table 3), and the deterioration of the Ua/Uv pH occurred approximately 2 to 3 hours after continuous O_2 inhalation (sTable 2). In the human circulatory system, 98.5% of O_2 is transported by binding to hemoglobin, with only 1.5% of O_2 being transported by physical dissolution.[29] Supplemental O_2 significantly increased maternal arterial PO_2, as breathing 50% FiO_2 increased maternal arterial PO_2 by >200 mm Hg in 5 minutes, and breathing 100% FiO_2 increased it by >300 mm Hg in 5 minutes.[1] Adult hemoglobin is saturated if the maternal PO_2 exceeds 150 mm Hg, and the unbound O_2 can only be transported by physical dissolution, which is an inefficient mode of transportation (0.03 mL O_2 per 1 mm Hg).[1,29] In addition, supraphysiological O_2 may trigger oxidative stress.[4,27] Two systematic reviews found that the use of O_2 was associated with an increase in maternal plasma concentrations of malondialdehyde or 8-isoprostane (2 markers of oxidative stress),[4,27] with one showing a significant increase in neonatal plasma (Uv/Ua) concentrations of malondialdehyde and 8-isoprostane,[27] and the other showing no difference in the Ua malondialdehyde level.[4] It has also been found that maternal arterial

TABLE 4
Fetal heart rate tracings and alternate methods of intrauterine resuscitation

Outcome	Oxygen (n=70)	Room air (n=70)	*P* value	RR	95% CI
FHR tracings (%)					
Category I FHR tracings	13 (18.6)	15 (21.4)	.672	0.87	0.45–1.68
Category II FHR tracings	57 (81.4)	55 (78.6)	.672	1.04	0.88–1.22
in the first stage	27 (38.6)	23 (32.9)	.48	1.17	0.75–1.84
in the second stage	48 (68.6)	47 (67.1)	.856	1.02	0.81–1.28
Category III FHR tracings	0 (0)	0 (0)	—	—	—
Intrauterine resuscitation (%)	51 (72.9)	50 (71.4)	.85	1.02	0.83–1.25
Changing maternal position	47 (67.1)	44 (62.9)	.595	1.07	0.84–1.36
Discontinuation of oxytocin	23 (32.9)	20 (28.6)	.583	1.15	0.7–1.89
Intravenous fluid bolus	6 (8.6)	4 (5.7)	.512	1.5	0.44–5.09
Tocolytic agents	0 (0)	1 (1.4)	.50	0.33	0.01–8.04

Data are expressed as number (percentage).

CI, confidence interval; *FHR*, fetal heart rate; *RR*, relative risk.

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hyperoxia might be associated with hemodynamic alterations, including a fall in cardiac output and a rise in systemic vascular resistance.[5–7] It should be recognized that maternal hyperoxia may be useless and potentially harmful for intrauterine resuscitation.

Research implications

The major outcomes were the Uv/Ua blood gases, which were laboratory findings rather than patient-relevant endpoints, and there was a weak-to-absent correlation between Uv/Ua blood gases and long- or short-term neonatal outcomes.[30,31] The optimal primary outcome may be serious neonatal morbidity. This study had a small sample size, and interventions are more likely to yield statistically significant results in small-sample studies.[32] To detect differences in serious neonatal morbidity, as many as 11,000 participants would be required.[1]

Strengths and limitations

The slight worsening of Ua pH was of questionable importance. There was no dose-dependent effect of O_2 exposure on Ua pH, which was compared between the duration of O_2 exposure in the <25th percentile, ≥25th (240 minutes) and <75th percentile, and ≥75th percentile groups (sTable 2). The low Ua pH events (<7.2) were recorded to be similar between the O_2 and air groups (sTable 1). In the O_2 group, most Ua pH values were still within the 95% reference percentiles (7.14–7.36).[25] These results might suggest that normal fetuses tolerated maternal hyperoxia well, or that the results of this study were spurious.

The applicability of our findings may be low. Our inclusion criteria were narrow, and the trial did not include any high-risk women with existing medical conditions, obstetrical complications, or category II or III FHR tracings. Although participants with category I FHR tracings were enrolled, 80% (112/140) of patients developed category II FHR tracings during labor in our study (Table 4), and they had a high probability of being given supplementary O_2 in the real world. Our results implied that intrapartum O_2 administration was not likely to be effective in those populations. The participants had very low-risk pregnancies, such that fetal acidosis and detecting marked detrimental effects on fetuses were considered unlikely, especially because some variables were unlikely related to O_2. In the real world, it is difficult to estimate the number of women exposed to prolonged O_2 (>2–3 hours) during labor. Prolonged O_2 administration was provided for only approximately a quarter of the women if the supply started at any point in the active phase of labor,[11,14] and rarely in cases where supply started in the second stage of labor.[8,10]

Conclusions

We conclude that maternal long-duration high-concentration O_2 administration in normal labor does not affect either the Uv PO_2 or FHR pattern distribution. However, the O_2 group was associated with a lower Ua pH compared with the room-air group. We do not seek to reach a conclusive recommendation regarding prolonged O_2 supplementaion in the absence of data on patient-relevant endpoints. Future trials should be cautious of the potentially harmful nature of O_2 administration in the same concentrations and duration as used in this study. ■

Acknowledgments

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References

1. Hamel MS, Anderson BL, Rouse DJ. Oxygen for intrauterine resuscitation: of unproved benefit and potentially harmful. Am J Obstet Gynecol 2014;211:124–7.
2. Reddy UM, Weiner SJ, Saade GR, et al. Intrapartum resuscitation interventions for category II fetal heart rate tracings and improvement to category I. Obstet Gynecol 2021;138:409–16.
3. Fawole B, Hofmeyr GJ. Maternal oxygen administration for fetal distress. Cochrane Database Syst Rev 2012;12:CD000136.
4. Raghuraman N, Temming LA, Doering MM, et al. Maternal oxygen supplementation compared with room air for intrauterine resuscitation: a systematic review and meta-analysis. JAMA Pediatr 2021;175:368–76.
5. Smit B, Smulders YM, Eringa EC, et al. Effects of hyperoxia on vascular tone in animal models: systematic review and meta-analysis. Crit Care 2018;22:189.
6. Smit B, Smulders YM, van der Wouden JC, Oudemans-van Straaten HM, Spoelstra-de Man AME. Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis. Crit Care 2018;22:45.
7. McHugh A, El-Khuffash A, Bussmann N, Doherty A, Franklin O, Breathnach F. Hyperoxygenation in pregnancy exerts a more profound effect on cardiovascular hemodynamics than is observed in the nonpregnant state. Am J Obstet Gynecol 2019;220:397.e1–8.
8. Thorp JA, Trobough T, Evans R, Hedrick J, Yeast JD. The effect of maternal oxygen administration during the second stage of labor on umbilical cord blood gas values: a randomized controlled prospective trial. Am J Obstet Gynecol 1995;172:465–74.
9. Sirimai K, Atisook R, Boriboonhirunsarn D. The correlation of intrapartum maternal oxygen administration and umbilical cord blood gas values. Acta Obstet Gynecol Scand Suppl 1997;76:90.
10. Qian G, Xu X, Chen L, et al. The effect of maternal low flow oxygen administration during the second stage of labour on umbilical cord artery pH: a randomised controlled trial. BJOG 2017;124:678–85.
11. Raghuraman N, Wan L, Temming LA, et al. Effect of oxygen vs room air on intrauterine fetal resuscitation: a randomized noninferiority clinical trial. JAMA Pediatr 2018;172:818–23.
12. Moors S, Bullens LM, van Runnard Heimel PJ, et al. The effect of intrauterine resuscitation by maternal hyperoxygenation on perinatal and maternal outcome: a randomized controlled trial. Am J Obstet Gynecol MFM 2020;2:100102.
13. Raghuraman N, López JD, Carter EB, et al. The effect of intrapartum oxygen supplementation on category II fetal monitoring. Am J Obstet Gynecol 2020;223:905.e1–7.
14. Watkins VY, Martin S, Macones GA, Tuuli MG, Cahill AG, Raghuraman N. The duration of intrapartum supplemental oxygen administration and umbilical cord oxygen content. Am J Obstet Gynecol 2020;223:440.e1–7.
15. Dildy GA, Clark SL, Loucks CA. Intrapartum fetal pulse oximetry: the effects of maternal hyperoxia on fetal arterial oxygen saturation. Am J Obstet Gynecol 1994;171:1120–4.
16. Simpson KR, James DC. Efficacy of intrauterine resuscitation techniques in improving fetal oxygen status during labor. Obstet Gynecol 2005;105:1362–8.
17. Haydon ML, Gorenberg DM, Nageotte MP, et al. The effect of maternal oxygen administration on fetal pulse oximetry during labor in fetuses with nonreassuring fetal heart rate patterns. Am J Obstet Gynecol 2006;195:735–8.
18. Aldrich CJ, Wyatt JS, Spencer JA, Reynolds EO, Delpy DT. The effect of maternal oxygen administration on human fetal cerebral oxygenation measured during labour by near infrared spectroscopy. Br J Obstet Gynaecol 1994;101:509–13.
19. Huen I, Morris DM, Wright C, Sibley CP, Naish JH, Johnstone ED. Absence of PO_2 change in fetal brain despite PO_2 increase in placenta in response to maternal oxygen challenge. BJOG 2014;121:1588–94.
20. You W, Andescavage NN, Kapse K, Donofrio MT, Jacobs M, Limperopoulos C. Hemodynamic responses of the placenta and brain to maternal hyperoxia in fetuses with congenital heart disease by using blood oxygen-level dependent MRI. Radiology 2020;294:141–8.
21. Morris DM, Ross JA, McVicar A, et al. Changes in foetal liver T2* measurements by MRI in response to maternal oxygen breathing: application to diagnosing foetal growth restriction. Physiol Meas 2010;31:1137–46.
22. Wang C, Gao Z. Internal medicine: respiratory and critical care medicine. Beijing, People's Republic of China. People's Health Publishing House; 2016.
23. ACOG Practice Bulletin No. 106. ACOG Practice Bulletin No. 106: intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009;114:192–202.
24. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 348, November 2006: umbilical cord blood gas and acid-base analysis. Obstet Gynecol 2006;108:1319–22.
25. Monneret D, Desmurs L, Zaepfel S, Chardon L, Doret-Dion M, Cartier R. Reference percentiles for paired arterial and venous umbilical cord blood gases: an indirect nonparametric approach. Clin Biochem 2019;67:40–7.
26. Jackson M, Holmgren CM, Esplin MS, Henry E, Varner MW. Frequency of fetal heart rate categories and short-term neonatal outcome. Obstet Gynecol 2011;118:803–8.
27. Chatmongkolchart S, Prathep S. Supplemental oxygen for caesarean section during regional anaesthesia. Cochrane Database Syst Rev 2016;2016:CD006161.
28. Shao X, Ye H, Qiu X. Practice of neonatology, 5th ed. Beijing, People's Republic of China: People's Health Publishing House; 2019.
29. Wang T. Physiology, 9th ed. Beijing, People's Republic of China: People's Health Publishing House; 2018.
30. Yeh P, Emary K, Impey L. The relationship between umbilical cord arterial pH and serious adverse neonatal outcome: analysis of 51,519 consecutive validated samples. BJOG 2012;119:824–31.
31. Johnson GJ, Salmanian B, Denning SG, Belfort MA, Sundgren NC, Clark SL. Relationship Between umbilical cord gas values and neonatal outcomes: implications for electronic fetal heart rate monitoring. Obstet Gynecol 2021;138:366–73.
32. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. Cochrane Handbook for Systematic Reviews of Interventions, 2nd Edition. Chichester, United Kingdom: John Wiley & Sons; 2019.

Author and article information

From the Chinese PLA General Hospital, Medical School of Chinese PLA, Beijing, China (Ms Y Chuai and Drs Chen and Yao); Department of Obstetrics and Gynaecology, Sixth Medical Center, Chinese PLA General Hospital, Beijing, China (Ms Y Chuai, Bs F Chuai, Bs Gao, Ms Dong, and Dr Chen); Department of Obstetrics and Gynaecology, Seventh Medical Center, Chinese PLA General Hospital, Beijing, China (Ms Jiang, Bs Sun, and Dr Yao); and Department of Obstetrics and Gynecology, PLA Strategic Support Force Characteristic Medical Center, Beijing, China (Dr Zhang and Bs Peng).

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Y.C., W.J., L.Z., and F.C. contributed equally to this work.

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Clinical trial information:

Date of registration: December 5, 2018;

Date of initial participant enrollment: January 1, 2021;

Clinical trial identification number: NCT03764696;

URL: https://clinicaltrials.gov/ct2/show/NCT03764696?term=NCT03764696&draw=2&rank=1;

Data sharing information: a. Individual participant data are available; b. All data will be shared; c. Study protocol and statistical analysis plan are available; d. When will data be available? After publication; e. How will data be shared? The data used in the present study is available from the corresponding author on reasonable request.

Corresponding authors: Lei Chen, MD. 3313400243@qq.com and Yuanqing Yao, MD. yqyao_ghpla@126.com

STABLE 1
Umbilical Cord Arterial pH Distribution

Outcomes	Oxygen (n = 67)	Room Air (n = 68)	*P*	RR	95% CI
Umbilical cord arterial pH	7.23 (7.20 - 7.27)	7.27 (7.20 - 7.30)	0.005	-	-
pH < 7.2 (%)	15 (22.4)	13 (19.1)	0.639	1.2	0.6 to 2.3
pH < 7.1 (%)	4 (5.97)	0 (0)	0.14	9.13	0.50 to 166.39
pH < 7.0 (%)	2 (2.99)	0 (0)	0.29	5.07	0.25 to 103.74

Data are expressed as median (interquartile range) or number (%).

RR, relative risk; CI, confidence interval.

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STABLE 2
Assessing dose dependent effect of Oxygen (O_2) exposure on umbilical cord pH

	Duration of O_2 exposure			
Outcomes	< 25th percentile (n = 17)	≥ 25th < 75th percentile (n = 33)	≥ 75th percentile (n = 17)	*P*
Umbilical cord venous pH	7.29 ± 0.09	7.29 ± 0.06	7.27 ± 0.09	0.57
Umbilical cord arterial pH	7.23 ± 0.09	7.22 ± 0.06	7.21 ± 0.09	0.747

Data are expressed as mean ± SD.

25th percentile = 240 minutes, 75th percentile = 420 minutes.

Duration of O_2 exposure < 25th percentile group: median 198 mins, interquartile range 124 - 217.

Duration of O_2 exposure ≥ 25th < 75^{th} percentile group: median 309 mins, interquartile range 256 - 373.

Duration of O_2 exposure ≥ 75th percentile group: median 469 mins, interquartile range 435 - 592.

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STABLE 3
Fetal Heart Rate (FHR) Tracings Distribution

Outcome	Oxygen (n = 70)	Room Air (n = 70)	*P*	RR	95% CI
Category I FHR tracings (%)	13 (18.6)	15 (21.4)	0.672	0.87	0.45 to 1.68
Category II FHR tracings (%)	57 (81.4)	55 (78.6)	0.672	1.04	0.88 to 1.22
Baseline bradycardia	0 (0)	1 (1.4)	0.50	0.33	0.01 to 8.04
Baseline tachycardia	5 (7.1)	1 (1.4)	0.211	5	0.6 to 41.7
Minimal or absent variability	9 (12.9)	8 (11.4)	0.796	1.13	0.46 to 2.75
Marked variability	1 (1.4)	1 (1.4)	0.476	1	0.06 to 15.7
Isolated variable deceleration	27 (38.6)	20 (28.6)	0.210	1.35	0.84 to 2.17
Recurrent variable decelerations	24 (34.3)	26 (37.1)	0.724	0.92	0.59 to 1.44
Isolated late deceleration	23 (32.9)	25 (35.7)	0.722	0.92	0.58 to 1.46
Recurrent late decelerations	10 (14.3)	11 (15.7)	0.813	0.9	0.4 to 2.0
Prolonged deceleration	9 (12.9)	10 (14.3)	0.805	0.9	0.4 to 2.1
Category III FHR tracings (%)	0 (0)	0 (0)	-	-	-

Data are expressed as number (%).

RR, relative risk; *CI*, confidence interval.

Minimal or absent variability: lasting 40 minutes or more.

Recurrent decelerations: more than 50% of uterine contractions were accompanied by decelerations for 20 minutes or more.

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Informed Consent Form

Study on the effect of prolonged oxygen inhalation on umbilical cord venous partial pressure of oxygen during labor

Research title: The Effect of Maternal Long Term High Flow Oxygen Administration During Labor on Umbilical Cord Blood Gases

Source: Application Research of Capital Clinical Characteristics from the Beijing Municipal Science & Technology Commission

Number : Z181100001718004

Sponsor: Sixth Medical Center of PLA General Hospital

Participating Centers: Seventh Medical Center of PLA General Hospital, PLA Strategic Support Force Characteristic Medical Center

Informed consent version number: 1.1

Informed consent version date: 2019-01-20

Dear Subject:

This informed consent form is for your consent. The following items describe the purpose, method, possible risks and benefits or inconveniences brought to you during the research, as well as your rights and interests, etc. Please read carefully before participating in the clinical research. The information provided to you in this informed consent form can help you decide whether to participate in this study. If you have any questions, please ask the investigator in charge of the study to ensure that you fully understand the content. Your participation in this study is voluntary. If you agree to participate in this clinical study, please sign the statement of informed consent.

1. Objective

To study whether prolonged oxygen inhalation during labor affects the umbilical venous partial pressure of oxygen, umbilical arterial pH value, and whether it affects the fetal heart rate monitoring pattern.

2. Study design

A total of 140 women undergoing the latent phase of labor with no existing medical conditions or obstetrics complications who are admitted for delivery are eligible. These women who meet inclusion criteria with normal fetal heart rate tracings in labor are randomized in a 1:1 ratio to oxygen or room air. The oxygen group receive 10 L of oxygen per minute by tight-fitting simple facemask until delivery. The room air group receive room air only without a facemask. Immediately after the delivery of the newborn, cord blood is collected for blood gas analysis. The The primary outcome are the umbilical cord venous partial pressure of oxygen and umbilical arterial pH.

3. Use of samples and information

Samples (umbilical artery 1ml, vein 1ml) and medical information is non-profit, and requires no payment from you. Your samples and information will be used for teaching and research on the occurrence and development of diseases related to this project. The remaining samples are not used for other studies.

Samples and information is subject to strict review procedures by the ethics committee to protect your rights, ensure the rationality and feasibility of scientific research, and comply with relevant ethical laws and regulations.

4. Potentially harmful

Some animal and clinical studies have shown that oxygen inhalation may

constrict uterine blood vessels, reduce blood flow to the placenta, and interfere with the oxygen supply to the fetus. There was no consensus on whether or not maternal oxygen administration was harmful. There were only four randomized controlled trials of prophylactic or therapeutic use of oxygen during labor involving a total of 787 women (Table 1). In these studies, there were no statistical differences between the oxygen and air groups in the umbilical arterial pH. There was also no consensus on whether or not prolonged oxygen during labor (more than 2 to 3 hours) was harmful. The only reference at the time was one (99 participants) of these four RCTs conducted by Raghuraman et al.. In the oxygen group, the median duration of oxygen exposure was 96 minutes and a quarter of the participants received oxygen for more than 176 minutes, and there were no differences between the two groups in the umbilical arterial lactate or pH.

In our country, therapeutic or prophylactic oxygen is widely used with few people realize the potentially harmful. In the real world, the duration of oxygen exposure ranged from a few minutes to several hours, depending on clinical experience with no guideline or consensus. To avoid pulmonary oxygen toxicity, supplemental high fraction of inspired oxygen cannot exceed 12 hours in our study, and the total duration of oxygen exposure is generally expected to be between 3 to 7 hours; To reduce the incidence of adverse events, we include very low risk participants rather than high-risk participants; To expeditiously resolve abnormal fetal heart rate tracings, we can perform operative vaginal delivery or cesarean section in the labor room. All three centers have standard operating rooms in the labor rooms and have departments of NICU.

5. Potentially benefit

In addition, some animal and clinical studies have shown that maternal oxygen inhalation can increase the blood oxygen content of the mother, thereby increasing the blood oxygen content of the fetus, preventing or reducing fetal hypoxia. Our empirical, not evidence-based, opinion is that prophylactic oxygen can reduce the incidence of non-reassuring fetal status. Although your fetal heart rate monitoring at the start of the study is normal, absolutely normal fetal heart rate monitoring is rare. Only a small number of women (16%) had monitor strips with category I fetal heart rate tracings exclusively, most women (84%) would develop category II fetal heart rate tracings at some point during labor. Assuming you do not take part in this study, there is still about a 50% probability of being given oxygen therapy during labor (ranged from a few minutes to several hours). The use of oxygen for intrauterine resuscitation is widely used, but again it is empirical rather than evidence-based.

You will not receive direct financial compensation from this study, but you may receive a partial waiver of medical expenses. We provide you with free epidural anesthesia (8:00 am to 5:30 pm) and 10 times free pelvic floor rehabilitation. At present, the two items are not included in the Beijing maternity insurance.

Because the research results are currently unknown, it is highly likely that you will not receive any medical benefit from the research results. But the results of research may suggest new treatment theories for you and other women, which may benefit you and others.

6. Refusal and withdrawal of consent

You have the right to refuse to sign this informed consent. Your refusal to sign this informed consent will not affect any of your rights and interests, and you will not be discriminated against or treated differently, nor will it affect your normal medical treatment. You may withdraw your consent at any time without giving any reason. We will immediately destroy the remaining samples and information according to your request, and will not continue to use.

7. Personal privacy protection

We will protect your privacy to the extent prescribed by law. Samples and information donated by you will be

TABLE 1
Randomized controlled trials of prophylactic or therapeutic use of oxygen during labor

Study	Participants	Interventions	Outcomes
Thorp 1995	N = 85, Category I FHR, normal labor at the onset of second stage	80% O_2 vs room air	umbilical arterial pH 7.285 vs 7.258, $p = 0.06$ umbilical arterial pH less than 7.2 9/41 vs 2/44, statistical difference
Sirimai 1997	N = 160, Category I FHR, normal labor at the onset of second stage	O_2 vs room air	umbilical arterial pH less than 7.2 8/80 vs 3/80, no statistical difference
Qian 2017	N = 443, Category I FHR, normal labor at the onset of second stage	30% O_2 vs room air	umbilical arterial pH 7.261 vs 7.266, $p = 0.64$
Raghuraman 2018	N = 99, Category II FHR, normal labor at any point in the active phase of labor	80% O_2 vs room air	umbilical arterial pH 7.25 vs 7.26, no statistical difference umbilical arterial lactate 30.6 vs 31.5 mg/dL, $p = 0.69$

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anonymized, and users will not be able to obtain personal information that can identify you. The data may be published publicly, but your name or identifiable personal information will not be published.

You can keep abreast of the information and progress of this study. If you have any questions related to this study, or have any discomfort or injury during the study, or have questions about the rights and interests of participants in this study, you can contact _____ (investigator) at _____ (telephone number).

If you have any questions about this study before and after the experiment, please contact the Medical Ethics Committee Office of the Sixth Medical Center of PLA General Hospital at 010-66957608.

Subject Statement

1. I have read and understood the entire contents of this informed consent form.
2. I had the opportunity to ask questions and all questions were answered.
3. I understand that participation in this study is entirely voluntary. I can also choose to withdraw from the study at any time, and my medical treatment and benefits will not be affected.
4. I know that signing my name does not imply a waiver of any expenses or obligations.
5. I hope I don't want to know about any research results that have a major impact on my health.
6. I agree to donate umbilical cord blood samples for future teaching and scientific research in this project.

Subject Signature: Date: YYMMDD

Investigator Statement

I have accurately informed the subject of the informed consent form and answered the subject's questions, and the subject voluntarily participated in this clinical study.

Investigator Signature: Date: YYMMDD

References

8. Thorp JA, Trobough T, Evans R, Hedrick J, Yeast JD. The effect of maternal oxygen administration during the second stage of labor on umbilical cord blood gas values: a randomized controlled prospective trial. Am J Obstet Gynecol 1995;172:465–74.

9. Sirimai K, Atisook R, Boriboonhirunsarn D. The correlation of intrapartum maternal oxygen administration and umbilical cord blood gas values. Acta Obstet Gynecol Scand Suppl 1997;76:90.

10. Qian G, Xu X, Chen L, et al. The effect of maternal low flow oxygen administration during the second stage of labour on umbilical cord artery pH: a randomised controlled trial. BJOG 2017;124:678–85.

11. Raghuraman N, Wan L, Temming LA, et al. Effect of oxygen vs room air on intrauterine fetal resuscitation: A randomized noninferiority clinical trial. JAMA Pediatr 2018;172:818–23.

Further reading

Thorp JA, Trobough T, Evans R, Hedrick J, Yeast JD. The effect of maternal oxygen administration during the second stage of labor on umbilical cord blood gas values: a randomized controlled prospective trial. Am J Obstet Gynecol 1995;172:465–74.

Sirimai K, Atisook R, Boriboonhirunsarn D. The correlation of intrapartum maternal oxygen administration and umbilical cord blood gas values. Acta Obstet Gynecol Scand Suppl 1997;76:90.

Qian G, Xu X, Chen L, et al. The effect of maternal low flow oxygen administration during the second stage of labour on umbilical cord artery pH: a randomised controlled trial. BJOG 2017;124:678–85.

Raghuraman N, Wan L, Temming LA, et al. Effect of oxygen vs room air on intrauterine fetal resuscitation: A randomized noninferiority clinical trial. JAMA Pediatr 2018;172:818–23.

Maternal Oxygen Administration for Fetal Distress II (Protocol)

ClinicalTrials.gov Identifier: NCT03764696

Recruitment Status: Completed
First Posted: December, 2018
Last Update Posted: December, 2021

Sponsor:

Sixth Medical Center (Former Navy General Hospital), Chinese PLA General Hospital, Beijing, China.

Principle Investigators:

Yunhai Chuai and Yuanqing Yao, Chinese PLA General Hospital, Medical School of Chinese PLA, Fuxing Road No. 28, Beijing 100853, China.

Study Description

Nowadays, maternal oxygen (O_2) administration was the most common intervention for intrapartum resuscitation, it was estimated that more than half of women received O_2 at some point during labor, although they were not hypoxic.[1,2] Obstetricians and midwives hoped that the additional O_2 can improve the fetal acid-base metabolism status and relieve suspicious or abnormal fetal heart rate (FHR) tracings.[1,2] However, there was much controversy about the effects of therapeutic or prophylactic maternal O_2 inhalation therapy during labor on neonatal outcomes.[3,4] Systematic reviews found low or very low-certainty evidence of hyperoxia-induced vasoconstriction in animal models and in healthy volunteers and patients.[5,6] The effects of hyperoxia on pregnant hemodynamics was studied in a cohort study, which found supplemental 80 to 100% fraction of inspired O_2 (FiO_2) for 10 minutes decreased cardiac index and increased systemic vascular resistance.[7] At present, there were only five randomized clinical trials (RCTs) of prophylactic or therapeutic O_2 inhalation during labor showed that supplemental O_2 did not improve fetal acid-base status or other neonatal outcomes, of these trials, women received prophylactic O_2 during the second stage of labor (30 to 80% FiO_2); or therapeutic O_2 (80% FiO_2) when they developed category II or III tracings at any point in the active phase or the second stage of labor until delivery.[8–12]

An unproven hypothesis of O_2 for intrauterine resuscitation is that the supra-physiological O_2 can be transferred across the placenta to fetal circulation.[13,14] Fetal oxygenation was often tested by fetal pulse oximetry ($FSpO_2$), blood O_2 level-dependent magnetic resonance imaging (BOLD-MRI), and umbilical cord venous (Uv) partial pressure of O_2 (PO_2): for $FSpO_2$, Dildy *et al.*[15] showed that supplemental 40% FiO_2 (20 or 45 mins) resulted in no significant change

in fetal O_2 saturation, but other studies showed that 40 to 100% FiO_2 (15 to 30 mins) increased fetal O_2 saturation[16–18]; for BOLD-MRI, studies showed that a short time breathing 100% FiO_2 (6 mins) increased cerebral blood oxygenation in fetuses with single ventricle or aortic obstruction, but 100% FiO_2 did not affect fetal brain oxygenation (6 and 40 mins) or fetal liver oxygenation (15 mins) in healthy fetuses[19–21]; for Uv PO_2, Thorp *et al.*[8] found no significant change in Uv PO_2 with maternal 80% FiO_2 for mean 45 minutes during the second stage of labor, but Watkins *et al.*[14] showed a significant decrease in Uv PO_2 (median 25.5 versus 32.5 mmHg) with maternal 80% FiO_2 over 176 minutes during the partial active phase and the second stage of labor.

In the real world, the duration of O_2 exposure ranged from a few minutes to several hours, depending on clinical experience with no consensus.[14] We perform this trial to assess the effect of maternal long-duration high FiO_2 exposure during labor on Uv PO_2. The long-duration high FiO_2 is defined as supplemental 60 to 80% FiO_2 during the major part of labor (i.e. late latent phase, whole active phase and second stage of labor), and this duration is usually more than 3 hours.

To avoid pulmonary O_2 toxicity, supplemental high FiO_2 cannot exceed 24 hours,[22] and the total duration of O_2 exposure is not allowed to exceed 12 hours in our study.

Study Design

The study is a 3-site (based in Beijing, China), randomized, open-label, parallel-group trial of women in the latent phase of labor who had category I FHR tracings.

The study was approved by the human research ethics committees at Sixth Medical Center and Seventh Medical Center of Chinese PLA General Hospital, and PLA Strategic Support Force Characteristic Medical Center.

The trial was registered on ClinicalTrials.gov with the identifier NCT03764696 before its commencement.

Women will complete informed consent at the time of their presentation to the labor units.

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment:	140 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open Label)
Primary Purpose:	Prevention
Official Title:	The Effect of Maternal Long Term High Flow Oxygen Administration During Labor on Umbilical Cord Blood Gases
Actual Study Start Date:	January 1, 2021
Estimated Primary Completion Date:	October 31, 2021
Estimated Study Completion Date:	December 31, 2021

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Contacts and Locations

Contact: Yunhai Chuai, Dr +86-18810892004 wangyh85@foxmail.com

Locations

Department of Obstetrics and Gynecology, Sixth Medical Center, Chinese PLA General Hospital, Beijing, China
Contact: Yunhai Chuai
Principal Investigator: Yunhai Chuai, Dr
Sub-Investigator: Lei Chen, Dr

Department of Obstetrics and Gynecology, Seventh Medical Center, Chinese PLA General Hospital, Beijing, China
Contact: Wen Jiang
Sub-Investigator: Wen Jiang
Sub-Investigator: Yuanqing Yao

Department of Obstetrics and Gynecology, PLA Strategic Support Force Characteristic Medical Center, Beijing, China
Contact: Lanmei Zhang
Sub-Investigator: Lanmei Zhang
Sub-Investigator: Kefei Peng

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Eligibility Criteria

Ages Eligible for Study:	18 Years to 40 Years (Adult)
Sexes Eligible for Study:	Female
Accepts Healthy Volunteers:	Yes

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Criteria

Inclusion Criteria:

at term (>37 weeks, <42 weeks), singleton, cephalic presentation, spontaneous or induced labor, normal labor, category I FHR tracings, 2 to 3 cm of cervical dilation in nulliparity, 1 to 2 cm of cervical dilation in multipara, informed consent.

Exclusion Criteria:

respiratory or cardiovascular disease, diabetes mellitus or insulin-treated gestational diabetes mellitus, hypertension or preeclampsia, oligohydramnios, fetal growth restriction, placental abruption, cephalopelvic disproportion, meconium-stained amniotic fluid, tachysystole, having received O_2, uterine incision (myomectomy or perforation), anemia, fever, chorioamnionitis, tobacco or alcohol use, disorders in oxygen saturations, hypotension, uncomfortable with facemask.

Randomization

Obstetricians assess women for eligibility. Consented women are randomized at 2 to 3 cm of cervical dilation in nulliparity and 1 to 2 cm of cervical dilation in multipara in the latent phase of labor. Participants are randomly assigned to a computer-generated random sequence that use balanced variable blocks within each site in a ratio of 1:1. Random sequence is generated by one investigator at each site who take no further part in this study. Randomization is performed by the sequential opening of sealed numbered envelopes by one research nurse at each site.

Arms and Interventions

Arm	Intervention/ treatment
No Intervention: air, the first and second stage of labor Patients randomized to the group will receive room air. The therapy will continue until after delivery	
Experimental: oxygen, the first and second stage of labor Patients randomized to the group will receive oxygen administered by high flow facemask oxygen at 10 L/min oxygen. The therapy will continue until after delivery	Device: tight-fitting simple facemask Oxygen will be administered by facemask at 10 L/ min oxygen. The therapy will continue until after delivery

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Women are assigned to receive either O_2 via the tight-fitting simple facemask at a flow rate of 10 L per minute (FiO_2 was about 60 to 80%[8,11,12]) until delivery, or room air only without a facemask. The facemask is administered by one research nurse to ensure that it is worn properly to cover the nose and mouth. Supplemental O_2 can be interrupted for some reasons such as eating, drinking, and etc., but the total duration cannot exceed 15 minutes. To avoid O_2 toxicity, the total duration of O_2 exposure is not allowed to exceed 12 hours, otherwise the intervention will be terminated. All participants will receive standard intrapartum care and give birth in a supine position. Electronic fetal monitoring is tested every 15 to 30 minutes in the first stage of labor and continuously during the second stage. A three-tiered interpretation recommended by the American College of Obstetricians and Gynecologists (ACOG) is used to manage category II or III FHR tracings,[23] and the techniques of intrauterine resuscitation for both groups including changing maternal position, discontinuation of oxytocin, intravenous fluid bolus, and tocolytic agents. Amnioinfusion will not be used in this study.

Data Collection

Baseline characteristics of study participants are collected, including maternal age, gestational age, nulliparity or multipara, body mass index (BMI), antepartum hematocrit, spontaneous or induced labor, pain management, augmentation of labor.

Outcome Measures

Primary Outcome Measures:

The primary outcome is the Uv PO_2. The paired Uv and umbilical cord arterial (Ua) blood samples will be collected as recommended by ACOG.[24] A segment of umbilical cord (20 cm) is double-clamped, divided, and blood samples were obtained by trained technicians immediately after delivery, and these samples are analyzed in the delivery units using the Gem Premier 4000 benchtop blood gas analyzer (Werfen America).

Cord arterial pH values [Time Frame: within 30 to 60 seconds of birth]
Immediately after delivery (within 30-60 seconds of birth), blood gas sample will be obtained.

Cord arterial partial pressure of oxygen [Time Frame: within 30 to 60 seconds of birth]
Immediately after delivery (within 30-60 seconds of birth), blood gas sample will be obtained.

Cord arterial partial pressure of carbon dioxide [Time Frame: within 30 to 60 seconds of birth]
Immediately after delivery (within 30-60 seconds of birth), blood gas sample will be obtained.

Cord venous pH values [Time Frame: within 30 to 60 seconds of birth]
Immediately after delivery (within 30-60 seconds of birth), blood gas sample will be obtained.

Cord venous partial pressure of oxygen [Time Frame: within 30 to 60 seconds of birth]
Immediately after delivery (within 30-60 seconds of birth), blood gas sample will be obtained.

Cord venous partial pressure of carbon dioxide [Time Frame: within 30 to 60 seconds of birth]
Immediately after delivery (within 30-60 seconds of birth), blood gas sample will be obtained.

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We validate the umbilical cord blood gases according to the criteria of Monneret et al.,[25] who established three exclusion criteria: an Uv - Ua pH difference < 0.02, an Ua - Uv partial pressure of carbon dioxide (PCO_2) < 5.25 mmHg, and an Uv $PCO_2 < 21.75$ mmHg.

Secondary Outcome Measures:

Rate of abnormal fetal heart tracing [Time Frame: at 1 minute after birth]

Secondary outcomes are women who develop category II or III FHR tracings in labor. Two trained research nurses, unaware of randomization assignments, assess FHR tracings in the storage computer independently, and resolve disagreements by discussion with a third nurse. Details of II or III FHR tracings are recorded, including baseline, variability, and deceleration.

Three-Tiered Fetal Heart Rate Interpretation System

Category I

- Bradycardia not accompanied by absent baseline variability
- Tachycardia

Baseline FHR variability

- Minimal baseline variability
- Absent baseline variability with no recurrent decelerations
- Marked baseline variability

Accelerations

- Absence of induced accelerations after fetal stimulation

Periodic or episodic decelerations

- Recurrent variable decelerations accompanied by minimal or moderate baseline variability
- Prolonged deceleration more than 2 minutes but less than10 minutes
- Recurrent late decelerations with moderate baseline variability
- Variable decelerations with other characteristics such as slow return to baseline, overshoots, or "shoulders"

Category III

Category III FHR tracings include either

- Absent baseline FHR variability and any of the following:
  —Recurrent late decelerations
  —Recurrent variable decelerations
  —Bradycardia
- Sinusoidal pattern

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Other Outcome Measures:

Rate of cesarean delivery [Time Frame: at 1 minute after birth]
Rate of assisted vaginal delivery [Time Frame: at 1 minute after birth]
Apgar score less than 7 [Time Frame: at 1 and 5 minutes after birth] The Apgar scale is determined by evaluating the newborn baby on five simple criteria on a scale from 0 to 2, then summing up the five values thus obtained. The resulting Apgar score ranges from 0 to 10. The five criteria are summarized using words chosen (Appearance, Pulse, Grimace, Activity, Respiration). The infant is given a score of 0, 1 or 2. The scores are added up and the total sum is their Apgar score. The test is generally done at one and five minutes after birth, and may be repeated later if the score is and remains low. Scores 7 and above are generally normal, 4 to 6 fairly low, and 3 and below are generally regarded as critically low.
Rate of serious neonatal morbidity or death [Time Frame: within 28 days of birth]
Cord arterial plasma liquid chromatography mass spectrometry analysis [Time Frame: within 30 to 60 seconds of birth] The systematic identification and quantitation of all the metabolic products (mainly endogenous small molecule compounds with relative molecular weight within 1000 Da) of cord arterial plasma under oxygen and room air conditions. Immediately after delivery (within 30-60 seconds of birth), blood plasma sample will be obtained and the analysis will be performed by the Novogene Co., Ltd.

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Sample size

Sample size is calculated based on the Uv PO_2. According to our institutional data and literature, we estimate a baseline Uv PO_2 mean ± standard deviation of 27 ± 6 mmHg in term infants without pathologic pregnancies or complicated deliveries during labor.[25] The Cochrane review (including 10 RCTs, 683 participants) showed the short-duration supplementary O_2 could significantly increase Uv PO_2 (FiO_2 at least 60%, MD 8.19 mmHg, and FiO_2 less than 60%, MD 3.95 mmHg) during caesarean section, however, it was a very low-certainty evidence due to small sample studies and high heterogeneity.[26] The findings from two RCTs (2 RCTs, 200 participants) reported the short-duration 80% FiO_2 did not affect Uv/Ua PO_2 during labor,[8,14] and the secondary analysis of one trial (12 non-random samples) found that prolonged O_2 exposure (over 176 mins) was associated with lower Uv PO_2 (median 25.5 versus 32.5 mmHg).[14] In the present trial, a clinically significant change of Uv PO_2 is assumed to be 3 mmHg units. To detect the 3 mmHg difference in Uv PO_2 with 80% power and a 2-sided test of 0.05, we estimate that 64 women were needed in each group. We anticipate a 10% loss to unattainable paired cord gases, resulting in our plan to enroll 140 participants.

Statistical Analysis

Data analysis for the primary outcomes will be performed using the modified intention-to-treat principle, participants with unvalidate paired cord blood gases will be excluded. The paired cord blood gases samples will be collected as recommended by ACOG.[24] The blood samples are obtained by trained technicians, and the rate of loss to follow-up is expected to be is less than 5%. According to our experience, of those who will be enrolled, the cesarean delivery rate is less than 5%, and their duration of labor will be recorded based on the results of the last observation.

Per protocol analyses will be performed if randomized women receive their assigned interventions with interruption or crossover.

The distribution of continuous variables will be analyzed using the Kolmogorov-Smirnov test.

Student's *t* test or Mann-Whitney *U* test will be used as appropriate.

Categorical variables will be analyzed using Chi-square test or Fisher exact test.

Data will be expressed as mean (standard deviation), median (IQR), or number (%).

All statistical analyses will be performed using SPSS version 19 (IBM SPSS Statistics).

References

1. Hamel MS, Anderson BL, Rouse DJ. Oxygen for intrauterine resuscitation: of unproved benefit and potentially harmful. Am J Obstet Gynecol 2014;211:124–7.
2. Reddy UM, Weiner SJ, Saade GR, et al. Intrapartum resuscitation interventions for Category II fetal heart rate tracings and improvement to Category I. Obstet Gynecol 2021;138:409–16.
3. Fawole B, Hofmeyr GJ. Maternal oxygen administration for fetal distress. Cochrane Database Syst Rev 2012;12:CD000136.
4. Raghuraman N, Temming LA, Doering MM, et al. Maternal oxygen supplementation compared With room air for intrauterine resuscitation: A systematic review and meta-analysis. JAMA Pediatr 2021;175:368–76.
5. Smit B, Smulders YM, Eringa EC, et al. Effects of hyperoxia on vascular tone in animal models: systematic review and meta-analysis. Crit Care 2018;22:189.
6. Smit B, Smulders YM, van der Wouden JC, Oudemans-van Straaten HM, Spoelstra-de Man AME. Hemodynamic effects of acute hyperoxia: systematic review and meta-analysis. Crit Care 2018;22:45.
7. McHugh A, El-Khuffash A, Bussmann N, Doherty A, Franklin O, Breathnach F. Hyperoxygenation in pregnancy exerts a more profound effect on cardiovascular hemodynamics than is observed in the nonpregnant state. Am J Obstet Gynecol 2019;220:397.e1–8.
8. Thorp JA, Trobough T, Evans R, Hedrick J, Yeast JD. The effect of maternal oxygen administration during the second stage of labor on umbilical cord blood gas values: a randomized controlled prospective trial. Am J Obstet Gynecol 1995;172:465–74.
9. Sirimai K, Atisook R, Boriboonhirunsarn D. The correlation of intrapartum maternal oxygen administration and umbilical cord blood gas values. Acta Obstet Gynecol Scand Suppl 1997;76:90.
10. Qian G, Xu X, Chen L, et al. The effect of maternal low flow oxygen administration during the second stage of labour on umbilical cord artery pH: a randomised controlled trial. BJOG 2017;124:678–85.
11. Raghuraman N, Wan L, Temming LA, et al. Effect of oxygen vs room air on intrauterine fetal resuscitation: A randomized noninferiority clinical trial. JAMA Pediatr 2018;172:818–23.

12. Moors S, Bullens LM, van Runnard Heimel PJ, et al. The effect of intrauterine resuscitation by maternal hyperoxygenation on perinatal and maternal outcome: a randomized controlled trial. Am J Obstet Gynecol MFM 2020;2:100102.
13. Raghuraman N, López JD, Carter EB, et al. The effect of intrapartum oxygen supplementation on category II fetal monitoring. Am J Obstet Gynecol 2020;223:905.e1–7.
14. Watkins VY, Martin S, Macones GA, Tuuli MG, Cahill AG, Raghuraman N. The duration of intrapartum supplemental oxygen administration and umbilical cord oxygen content. Am J Obstet Gynecol 2020;223:440.e1–7.
15. Dildy GA, Clark SL, Loucks CA. Intrapartum fetal pulse oximetry: the effects of maternal hyperoxia on fetal arterial oxygen saturation. Am J Obstet Gynecol 1994;171:1120–4.
16. Simpson KR, James DC. Efficacy of intrauterine resuscitation techniques in improving fetal oxygen status during labor. Obstet Gynecol 2005;105:1362–8.
17. Haydon ML, Gorenberg DM, Nageotte MP, et al. The effect of maternal oxygen administration on fetal pulse oximetry during labor in fetuses with nonreassuring fetal heart rate patterns. Am J Obstet Gynecol 2006;195:735–8.
18. Aldrich CJ, Wyatt JS, Spencer JA, Reynolds EO, Delpy DT. The effect of maternal oxygen administration on human fetal cerebral oxygenation measured during labour by near infrared spectroscopy. Br J Obstet Gynaecol 1994;101:509–13.
19. Huen I, Morris DM, Wright C, Sibley CP, Naish JH, Johnstone ED. Absence of PO_2 change in fetal brain despite PO_2 increase in placenta in response to maternal oxygen challenge. BJOG 2014;121:1588–94.
20. You W, Andescavage NN, Kapse K, Donofrio MT, Jacobs M, Limperopoulos C. Hemodynamic responses of the placenta and brain to maternal hyperoxia in fetuses with congenital heart disease by using blood oxygen-level dependent MRI. Radiology 2020;294:141–8.
21. Morris DM, Ross JA, McVicar A, et al. Changes in foetal liver T2* measurements by MRI in response to maternal oxygen breathing: application to diagnosing foetal growth restriction. Physiol Meas 2010;31:1137–46.
22. Wang C, Gao Z. Internal medicine: respiratory and critical care medicine. Beijing, People's Republic of China. People's Health Publishing House; 2016.
23. ACOG Practice Bulletin No. 106. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol 2009;114:192–202.
24. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 348, November 2006: umbilical cord blood gas and acid-base analysis. Obstet Gynecol 2006;108:1319–22.
25. Monneret D, Desmurs L, Zaepfel S, Chardon L, Doret-Dion M, Cartier R. Reference percentiles for paired arterial and venous umbilical cord blood gases: an indirect nonparametric approach. Clin Biochem 2019;67:40–7.
26. Chatmongkolchart S, Prathep S. Supplemental oxygen for caesarean section during regional anaesthesia. Cochrane Database Syst Rev 2016;2016:CD006161.