Oxygen for intrauterine resuscitation: of unproved benefit and potentially harmful

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Maternal oxygen is often given to laboring women to improve fetal metabolic status or in an attempt to alleviate nonreassuring fetal heart rate patterns. However, the only 2 randomized trials investigating the use of maternal oxygen supplementation in laboring women do not support that such supplementation is likely to be of benefit to the fetus. And by increasing free radical activity, maternal oxygen supplementation may even be harmful. Based on a review of the available literature, we conclude that until it is studied properly in a randomized clinical trial, maternal oxygen supplementation in labor should be reserved for maternal hypoxia, and should not be considered an indicated intervention for nonreassuring fetal status.

Key words: fetal resuscitation, labor, maternal oxygen

Every day, on most labor and delivery units in the United States, laboring women receive inhaled oxygen in the hope that it will improve the metabolic condition of their fetuses, or at least alleviate nonreassuring fetal heart rate patterns. In fact, administration of oxygen for this purpose is sanctioned by the American Congress of Obstetricians and Gynecologists; the Association of Women's Health, Obstetric, and Neonatal Nurses; and the American College of Nurse-Midwives.[1] Although population-based data on the frequency of this practice are not available, in 1 randomized trial of fetal pulse oximetry,[2] two-thirds of patients received oxygen at some point during their labor for a nonreassuring fetal heart rate tracing (written personal communication Steven Weiner, MS, April 8, 2013). Despite its frequent use, data to support that maternal oxygen supplementation benefits the fetus are limited. Fawole and Hofmeyr,[3] in their Cochrane Review, conclude that there is insufficient evidence to support the notion that use of oxygen for prophylaxis in labor or for treatment of fetal distress is beneficial to the fetus. Indeed, it may even be harmful. Herein we review the physiology pertinent to maternal oxygen supplementation, and the available relevant animal and human data to summarize the potential benefits and risks of maternal oxygen administration during labor.

To inform our review, we conducted a search of the electronic databases MEDLINE, PubMed, and the Cochrane Database of Systematic Reviews through September 2013 using the phrases or key words: "fetal resuscitation," "maternal oxygen administration," "maternal oxygen therapy," "nonreassuring fetal heart tracing/patterns," and "lipid peroxidation in labor." Additionally, we reviewed the reference lists of the articles identified in our electronic search for pertinent studies.

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Background

Our understanding of maternal-fetal gas exchange comes primarily from animal experiments, specifically with sheep, and, to a lesser extent, from human observational data.[4] At baseline, Po_2 (oxygen dissolved in blood and unbound to hemoglobin) in maternal arterial blood is around 100 mm Hg, while the umbilical venous Po_2 in the near term fetus is estimated to be approximately 28 mm Hg.[4] Despite lower partial pressures within the umbilical vein, the fetus is able to adequately oxygenate its tissues. Oxygen saturation is the percentage of oxygen-binding sites on hemoglobin that are bound by oxygen. Normal oxygen saturation in healthy women is 99-100% while in the near term fetus it is usually 60-70%.[4]

The fetus survives in this relatively hypoxic state because fetal hemoglobin more avidly binds oxygen than maternal hemoglobin, and the fetal hemoglobin concentration is higher than the maternal: 16.5 g/dL (range, 15−18.6 g/dL)[5] vs 12.5 g/dL (range, 11.0−14.0 g/dL).[6,7] Oxygen content in blood is the combination of dissolved oxygen and oxygen bound to hemoglobin. Despite lower partial pressure, because of increased binding capacity and higher hemoglobin, when compared with maternal arterial blood, umbilical venous blood has similar total oxygen content.[4]

Why give oxygen?

Under normal physiologic conditions, oxygen supply to the fetus exceeds demand; fetal oxygen uptake is not affected until oxygen delivery is reduced by more than half.[8] Work in nonhuman primates by James et al[9] in 1972 indicates that fetal hypoxia is the principle cause of late decelerations and can be resolved by increasing fetal Po_2. Additional primate work by Murata et al[10] suggests that late decelerations are early signs of hypoxia that, without intervention, will be followed by the absence of accelerations, and, if the hypoxia is sustained, fetal acidemia. Thus, administration of supplemental maternal oxygen would appear to be a logical intervention in response to an abnormal fetal heart rate pattern.

Will maternal oxygen supplementation alleviate abnormal fetal heart rate patterns?

In fact, there is a significant body of animal and human data demonstrating that maternal oxygen administration increases fetal oxygen levels and can remediate abnormal fetal heart rate patterns. As early as 1967, Althabe et al[11] reported human data showing that 100% oxygen via face mask corrected fetal tachycardia and reduced the frequency of late decelerations, or eliminated them altogether. The fetal heart rate effects correlated with changes in fetal muscle Po_2 levels. Four years later, in 1971, Khazin et al[12] also found that just a few minutes of giving oxygen to laboring women alleviated late decelerations.

Does the alleviation of abnormal fetal heart rate patterns with oxygen translate into improved fetal metabolic status?

Human observational data by Kubli et al[13] demonstrate a relationship between late decelerations and abnormal fetal acid-base status. However, data on the relationship between maternal oxygen administration and fetal acid-base status are mixed, and limited for the most part to nonrandomized trials, or trials that do not exclusively involve laboring women. Newman et al[14] administered either 50% or 100% oxygen to women during the first stage of labor and measured fetal scalp blood pH. During maternal hyperoxia, no significant change in fetal scalp pH was observed ([mean ± SD] baseline value 7.28 ± 0.013 vs hyperoxia 7.30 ± 0.01, *P* value not stated). In addition to alleviating late decelerations, Khazin et al[12] also reported that maternal hyperoxia during labor was associated with an increase in fetal Po_2 without concomitant acidosis; however, mean pH and *P* values were not reported. In a randomized trial by Ramanathan et al[15] in 1982, 40 women undergoing elective cesarean delivery under epidural anesthesia were assigned to breathe 1 of 4 different concentrations of oxygen via face mask. Mean duration of oxygen exposure was 36 ± 4 minutes and fetal umbilical cord pH was measured at delivery. Fraction of inspired oxygen (Fio_2) ranged from 0.21−1.00 and no differences in fetal pH were found between normoxic (Fio_2 0.21, 7.33 ± 0.09) and hyperoxic (Fio_2 0.47, 7.33 ± 0.01; Fio_2 0.74, 7.34 ± 0.07; Fio_2 1.00, 7.32 ± 0.005) groups.

To date there have been only 2 randomized trials investigating the use of maternal oxygen supplementation in exclusively laboring women. Both were trials of oxygen as prophylaxis in labor and enrolled <200 patients.

In 1995, Thorp et al[16] investigated the effects of maternal oxygen on fetal cord pH. In all, 86 women with reassuring fetal heart tracings were randomly allocated during the second stage of labor to breathe oxygen at 10 L/min via face mask or to breathe room air. While there was no difference in mean umbilical artery pH between the 2 groups (7.258 ± 0.069 vs 7.285 ± 0.058, oxygen and control, respectively, $P = .06$), neonates born to women in the oxygen group were significantly more likely to have umbilical artery pH values <7.20 (9/41 vs 2/44, $P = .02$, Fisher exact test).

In 1997, Sirimai et al[17] randomized 160 women at term to breathe oxygen or room air throughout the entirety of the second stage of labor. As in the trial of Thorp et al,[16] more neonates born to mothers in the oxygen group had umbilical artery cord pH values <7.2 (8/80 vs 3/80 in the room air group). However, this difference was not statistically significant ($P = .12$). Information from this trial is quite limited as it is available only in abstract form.[17]

Animal trials have allowed researchers to simulate and observe fetal compromise in scenarios that would be impossible to study in human beings by allowing oxygen to be studied as a single intervention. As previously mentioned, James et al[9] conducted observational research monitoring the cardiovascular and acid-base status of laboring nonhuman primates. As labor progressed, a group of fetuses was noted to become hypoxic, hypotensive, and acidotic. The initial response to fetal hypoxia was fetal tachycardia and then, as hypoxia worsened, late decelerations appeared. While 100% maternal oxygen was successful at improving or even resolving late decelerations, it had no effect on acid-base status or fetal hypotension.[9] In additional work with primates, Morishima et al[18] administered 100% oxygen for 30 minutes during labor (spontaneous or induced) to mothers of fetuses with and without signs of "fetal distress" (which they defined as late decelerations). In the 40 primates with signs of fetal distress they found that while maternal oxygen raised both fetal and maternal oxygen levels and reduced the frequency of late decelerations, it did not improve mean fetal pH (7.10 ± 0.029 vs 7.07 ± 0.034). In the 15 subjects for whom maternal oxygen had no beneficial effect on the frequency of decelerations, pH worsened significantly (6.97 ± 0.035 vs baseline 7.11 ± 0.028, $P < .01$).[18]

Therefore, the available human and animal data, which admittedly are not robust, suggest that at best, maternal oxygenation supplementation can alleviate abnormal fetal heart rate patterns but not improve fetal acid-base status. At worst, such oxygen supplementation may actually lower fetal pH. And while it might be postulated that the alleviation of abnormal fetal heart rate tracings by maternal oxygen supplementation will reduce the number of operative deliveries for that indication, in our review of the literature (described earlier), we found no human trials that directly address this issue.

Other than possibly lowering fetal pH, how else might oxygen be detrimental?

Maternal oxygen supplementation readily induces maternal hyperoxia. Polvi et al[19] found that just 5 minutes of breathing 50% oxygen via face mask increased maternal Pao_2 to >200 mm Hg, and an additional 5 minutes of 100% oxygen increased it to >300 mm Hg.

Maternal hyperoxia, in turn, may lead to increased free radical activity in both mothers and neonates. In 2002, in a double-blinded trial, Khaw et al[20] randomized women undergoing elective cesarean delivery under spinal anesthesia to breath room air or 60% oxygen via face mask prior to delivery and then measured 3 markers of free radical activity in maternal and umbilical cord blood: malondialdehyde (MDA), isoprostane,