OBSTETRICS

Hyperoxygenation in pregnancy exerts a more profound effect on cardiovascular hemodynamics than is observed in the nonpregnant state

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BACKGROUND: Supplemental oxygen is administered to pregnant women in many different clinical scenarios in obstetric practice. Despite the accepted uses for maternal hyperoxygenation, the impact of hyperoxia on maternal hemodynamic indices has not been evaluated. As a result, there is a paucity of data in the literature in relation to the physiological changes to the maternal circulation in response to supplemental oxygen.
OBJECTIVE: The hemodynamic effects of oxygen therapy are underrecognized and the impact of hyperoxygenation on maternal hemodynamics is currently unknown. Using noninvasive cardiac output monitoring which employs transthoracic bioreactance, we examined the effect of brief hyperoxygenation on cardiac index, systemic vascular resistance, blood pressure, stroke volume, and heart rate in pregnant mothers during the third trimester, compared with those effects observed in a nonpregnant population subjected to the same period of hyperoxygenation.
STUDY DESIGN: Hemodynamic monitoring was performed in a continuous manner over a 30-minute period using noninvasive cardiac output monitoring. Hyperoxygenation (O_2 100% v/v inhalational gas) was carried out at a rate of 12 L/min via a partial non-rebreather mask for 10-minutes. Cardiac index, systemic vascular resistance, stroke volume, heart rate, and blood pressure were recorded before hyperoxygenation, at completion of hyperoxygenation, and 10 minutes after the cessation of hyperoxygenation. Two-way analysis of variance with repeated measures was used to assess the change in hemodynamic indices over time and the differences between the 2 groups.
RESULTS: Forty-six pregnant and 20 nonpregnant women with a median age of 33 years (interquartile range, 26—38 years) and 32 years (interquartile range, 28-37 years) were recruited prospectively, respectively (P=.82). The median gestational age was 35 weeks (33—37 weeks). In the pregnant group, there was a fall in cardiac index during the hyperoxygenation exposure period (P=.009) coupled with a rise in systemic vascular resistance with no recovery at 10 minutes after cessation of hyperoxygenation (P=.02). Heart rate decreased after hyperoxygenation exposure and returned to baseline by 10 minutes after cessation of therapy. There was a decrease in stroke volume over the exposure period, with no change in systolic or diastolic blood pressure. In the nonpregnant group, there was no significant change in the cardiac index, systemic vascular resistance, stroke volume, heart rate, or systolic or diastolic blood pressure during the course of exposure to hyperoxygenation.
CONCLUSION: Hyperoxygenation during the third trimester is associated with a fall in maternal cardiac index and a rise in systemic vascular resistance without recovery to baseline levels at 10 minutes after cessation of hyperoxygenation. The hemodynamic changes that were observed in this study in response to hyperoxygenation therapy during pregnancy could counteract any intended increase in oxygen delivery. The observed maternal effects of hyperoxygenation call for a reevaluation of the role of hyperoxygenation treatment in the nonhypoxemic pregnant patient.

Key words: hemodynamic, hyperoxygenation

Supplemental oxygen is administered to pregnant women in many different clinical scenarios in obstetric practice. It is often administered empirically, without any prior knowledge of maternal oxygen saturation. Maternal oxygen administration is used commonly in an attempt to improve fetal oxygenation.[1—3] It is administered frequently in labor, in the setting of obstetric emergencies, and in an attempt to conserve fetal oxygenation in the operating room before cesarean delivery.[4] Hyperoxygenation is used more chronically in an attempt to improve fetal oxygenation in intrauterine growth-restricted fetuses[5] and has been used as a diagnostic tool when a fetus is affected by a congenital cardiac abnormality.[6—8]

Every year, >3 million laboring women in the United States receive supplemental oxygen with the intention of improving the fetal metabolic milieu, but in the absence of evidence of maternal hypoxemia.[9] Studies have shown that maternal oxygen administration does improve fetal oxygen levels and ameliorates fetal heart rate (HR) patterns that are indicative of hypoxia.[10—14] However, there is no evidence that maternal hyperoxygenation (MH) improves maternal or neonatal outcomes. Despite the widespread use of oxygen in intrauterine resuscitation, there is no clear guidance regarding an indication for oxygen therapy, appropriate dose range, duration, and curative effect.[15]

The effects of hyperoxia have been well-documented in the fetus[6—8,16,17]; however, there is a paucity of data that describe changes in maternal hemodynamic indices to hyperoxygenation. A Cochrane review in 2003 of 3 studies that included 94 women concluded that there is not enough data to estimate the benefits and risks of MH and that further trials of MH are warranted.[5]

The ability to conduct noninvasive hemodynamic monitoring of pregnant patients has evolved in recent years.[18—21]

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AJOG at a Glance

Why was this study conducted?

The hemodynamic effects of oxygen therapy are underrecognized, particularly in a pregnant population. This study was conducted to establish the response of the maternal cardiac hemodynamics to hyperoxia.

Key findings

Our key findings are that hyperoxia leads to a significant decrease in cardiac index and a rise in systemic vascular resistance that does not return to baseline levels after the cessation of therapy. This effect was not demonstrated in a nonpregnant cohort.

What does this add to what is known?

Hyperoxia is performed in many different clinical scenarios in obstetric practice. Our findings, which demonstrate specific changes in maternal hemodynamics in response to hyperoxia, have not been documented previously. These changes could counteract any intended increase in oxygen delivery. The observed maternal effects call for a reevaluation of the role of hyperoxygenation treatment in the nonhypoxemic pregnant patient.

The noninvasive cardiac output monitor (NICOM; Cheetah Medical, Maidenhead, Berkshire, United Kingdom) uses a new technique of transthoracic bioreactance technology. Clinical validation for the use of NICOM in an obstetric population has been studied.[22,23] NICOM has demonstrated repeatable measurements of stroke volume (SV) and cardiac output (CO) in pregnant women.[22] CO measurements achieved through NICOM have been shown to correlate with other noninvasive devices in both normotensive and hypertensive pregnant patients.[24] Recent studies have demonstrated good agreement between NICOM and 2-dimensional transthoracic echocardiography in the estimation of CO and SV, specifically in the third trimester of pregnancy.[25,26]

Therefore, the objective of this study was to assess the effect of hyperoxygenation on cardiac index (CI), systemic vascular resistance (SVR), blood pressure (BP), SV, and HR in pregnant women during the third trimester by noninvasive means and to compare the hemodynamic effects to those observed in a nonpregnant cohort of women.

Materials and Methods

Study design and setting

This prospective cohort study was undertaken in the Department of Obstetrics and Gynecology in the Rotunda Hospital Dublin, Ireland, between January 2017 and July 2018. The Rotunda Hospital is a tertiary-level, stand-alone maternity hospital in Dublin, Ireland, with >8500 deliveries per year. There is a large Maternal Fetal Medicine and Neonatology Department that accepts national referrals, with >1500 admissions to the neonatal unit per year. The study was approved by the National Research Ethics Committee of the National Maternity Hospital and by the Health Products Regulatory Authority in Ireland.

Patient population

Pregnant women who had attained a minimum gestational age of 31 weeks and up to 40 weeks were recruited to the study. The patients were recruited through the Ultrasound Department and the Prenatal Ward in the hospital. If deemed eligible, subjects were approached by the lead study investigator and invited to take part in the study. Nonpregnant women were recruited as a comparison group. Nonpregnant subjects were recruited through Gynecology Departments and included research and clinical staff members who were interested in enrolling in the study. Control subjects were matched for age and body mass index (relating to the pregnant patients booking body mass index) to allow for comparison.

Inclusion criteria for both the pregnant and nonpregnant groups were age >18 years old, no significant medical history, and a nonsmoking status. Singleton pregnancies with a normally grown fetus (estimated fetal weight >5th percentile and <95th percentile for gestational age) at ≥31 weeks gestation were included.

Exclusion criteria included known non-Down fetal chromosomal abnormality, chronic respiratory disease, maternal congenital heart disease, uncontrolled diabetes mellitus, use of bleomycin or amiodarone, current use of nitrofurantoin or use within the last 7 days (because interactions can occur between these drugs and oxygen), and the use of any preexisting vasoactive medication that could affect cardiac function or those women who were unable to provide written informed consent.

Clinical data collection

Baseline characteristics of all women that were recorded included maternal age, gestational age, gravidity, body mass index, and antepartum hemoglobin level.

Study procedures

Oxygen (80−100%), at a rate of 12 L/min for a duration of 10 minutes via a non-rebreather mask, was administered to the women while they were in a semirecumbent position in the hospital Ultrasound Department. The NICOM machine was used to obtain and record the hemodynamic variables.

The following patient details were recorded in the NICOM device: patient age, gender, height, current weight, and study number. Hemodynamic monitoring was performed with the patient lying in a semirecumbent position. Four emitting and receiving double NICOM electrodes were attached: 2 below the clavicle in the mid-clavicular line and 2 at the costal margin in the mid-clavicular line. A noninvasive BP cuff was placed on the patient's upper arm to measure brachial artery pressure at 5-minute in-

tervals. The NICOM was allowed to calibrate, then hemodynamic monitoring was continued for 30 minutes. Readings of CO, CI, SV, and HR were measured every minute. SVR was derived by the system when noninvasive BP was measured at 5-minute intervals. Transthoracic bioreactance is a new technique of noninvasive continuous CO monitoring based on analysis of relative phase shifts of oscillating currents that occur when current traverses the thoracic cavity.[27] It analyzes the variations in frequency spectra (relative phase shifts) after delivering a transthoracic alternating current. Measurements of CI, SV, HR, BP, and SVR were taken at baseline (Time 1), at 10 minutes of MH (Time 2), and at 10 minutes after the cessation of MH (Time 3).

Statistical analysis

Data were tested for normality with the use of the Shapiro-Wilk test and a histogram representation of data. Continuous variables were presented as means±standard deviation (or medians (interquartile range), as appropriate. Two group comparisons were performed with the Student *t* test or the Mann Whitney *U* test, as appropriate. Two-way analysis of variance with repeated measures was used to assess the change in the hemodynamic measurements over time and between the 2 groups. Pairwise comparisons were performed to assess the difference between timepoints 1 and 2 and timepoints 1 and 3. SPSS software (version 24.0; IBM Corporation, Armonk, NY) was used for analysis. A post-hoc power calculation to judge the appropriateness of our sample size was performed (based on the lower number of 20 subjects in the nonpregnant group). Power analysis based on a total peripheral resistance difference of 300 dynes/sec/cm^{-5} between the groups with a standard deviation of 350 dynes/sec/cm^{-5} provides a power of 0.793 and an error probability that was associated with this test of this null hypothesis of 0.05.

Results

Forty-six pregnant and 20 nonpregnant women were recruited with a median age of 33 years (range, 26−38 years) and 32 years (range, 28−37 years). respectively (P=.82). The median gestation was 35 weeks (range, 33−37 weeks). The body mass index in the pregnant group that was measured at the booking visit was 26.4±4.1 kg/m^2 and, in the third trimester, it was 29.9±5.4 kg/m^2; in the nonpregnant group, it was 24.5±3.6 kg/m^2 (P=.08 and .002, respectively). All pregnant patients had a normal hemoglobin level documented in the third trimester, with a median level of 11.7 g/dL (range, 11.1−12.7 g/dL). Baseline hemodynamic measurements in the pregnant and nonpregnant groups are given in the Table. In the pregnant group, there was a fall in CO and CI over the course of the HO exposure time that was coupled with a rise in SVR with no recovery by 10 minutes after cessation of HO therapy (Figure 1). Maternal HR decreased during hyperoxygenation and returned to baseline levels by 10 minutes after the cessation of MH. There was a decrease in SV during HO therapy in the pregnant group (P=.003), with no accompanying change in systolic or diastolic BP level. In the nonpregnant group, there was no significant change in the CI, SVR, SV, systolic BP, or diastolic BP in response to hyperoxygenation. In the nonpregnant group, the decrease in HR did not reach statistical significance. Serial changes in CO, CI, HR, and SV are given in Figure 2.

TABLE
Baseline hemodynamic measurements in pregnant vs nonpregnant subjects

Baseline measurements	Pregnant (n=46), mean±standard deviation	Not pregnant (n=20), mean±standard deviation	*P* value
Cardiac output (L/min)	6.3±1.1	4.9±1.1	.001
Cardiac index (L/min/m^2)	3.3±0.5	2.8±0.6	.004
Systemic vascular resistance (dynes/sec/cm^{-5})	1236±286	1509±312	.002
Stroke volume (mL)	73±13	68±13	.16
Heart rate (beats per minute)	87±10	72±9	.001
Systolic blood pressure (mm Hg)	121±17	114±8	.083
Diastolic blood pressure (mm Hg)	78±10	76±7	.14

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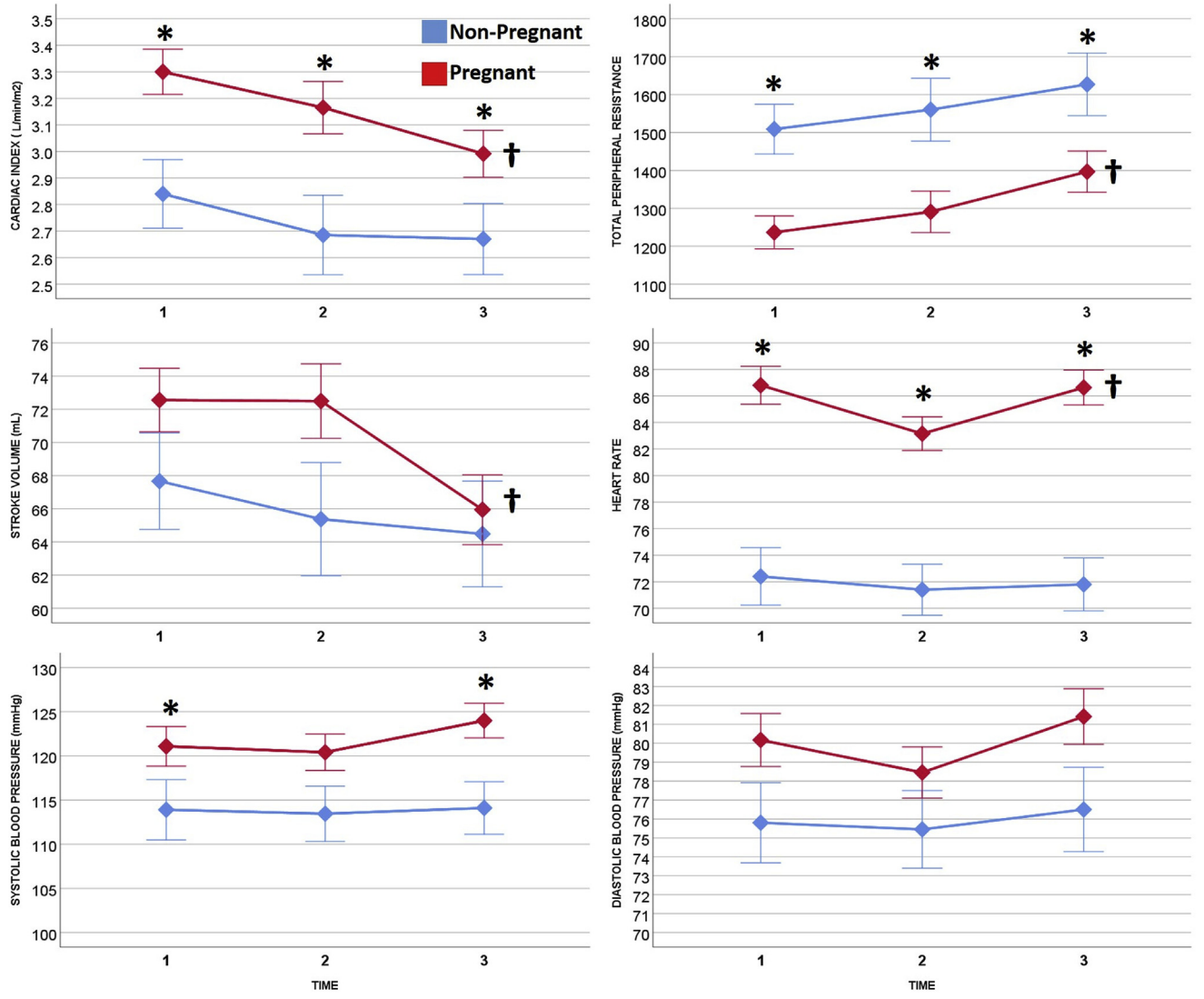
Comment

The literature to date has concentrated on either the response of the fetus to MH or the response of nonpregnant subjects to hyperoxia. Despite the accepted uses for MH, the impact of hyperoxia on maternal hemodynamic indices has not been evaluated. As a result, there is a paucity of data in the literature in relation to the physiologic changes to the maternal circulation in response to supplemental oxygen.

We have demonstrated that MH during the third trimester is associated with significant changes in maternal hemodynamic indices that are characterized by a fall in CI and a rise in SVR without recovery to baseline levels at 10 minutes after cessation of MH. In our study, oxygen administration lead to an increase in SVR that coincided with an acute reduction in resting HR and CI. The observed changes in HR were reversed rapidly after a return to room air concentrations. The decrease in CI and SV continued beyond the cessation of MH. The observed increase in SVR also persisted. There was no baseline difference demonstrated in SV between the 2 groups, which is likely due to the fact that SV declines towards term and all pregnant patients in this study were at >35 weeks gestational age. An increased

FIGURE 1
Changes in hemodynamics



Changes in hemodynamics over time in pregnant vs nonpregnant subjects are shown. The *asterisk* indicates a probability value of <.05 between groups at each timepoint; the *cross* indicates a probability value of <.05 within groups at Time 3 vs Time 1.

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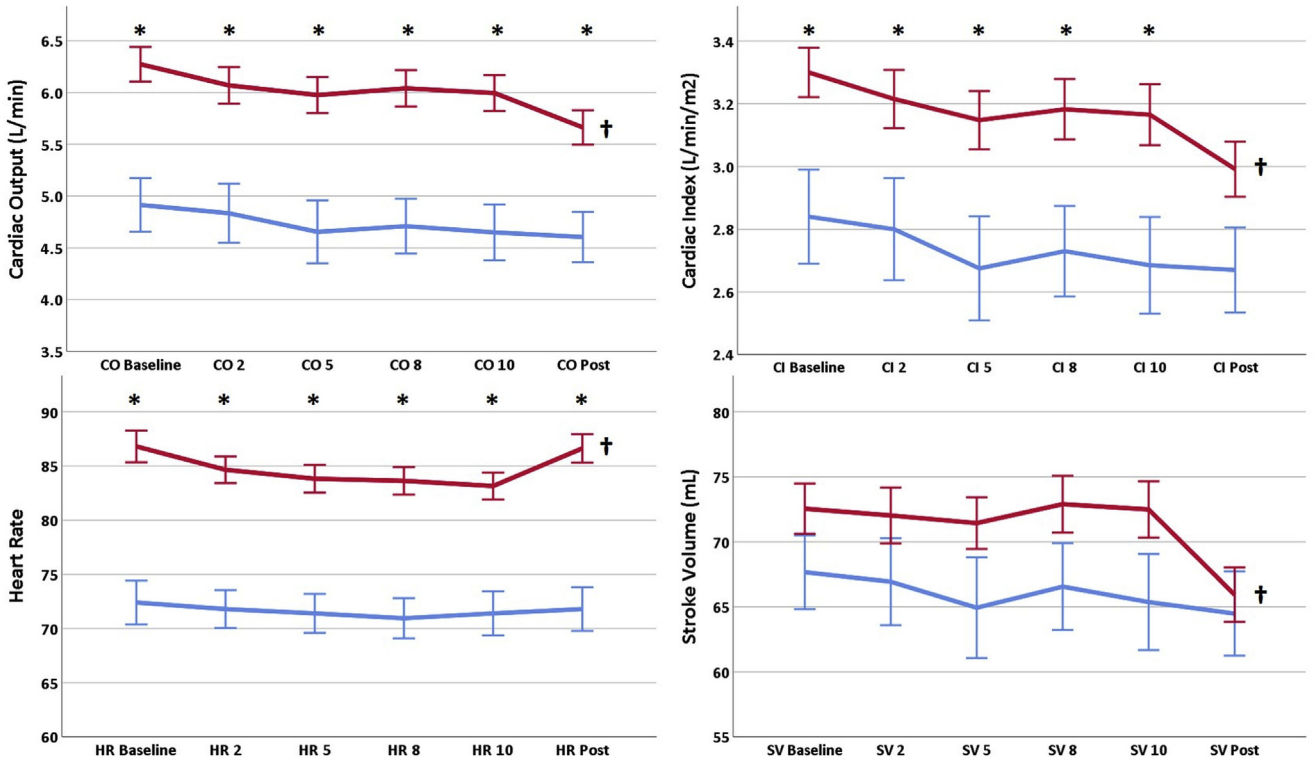
HR is maintained in the third trimester, thus maintaining the increase in CO in the pregnant group at baseline.

During pregnancy, there is a significant increase in the demand for oxygen because of the increased metabolic rate and a 20% increased consumption of oxygen. Resting minute ventilation and tidal volume increase, as does arterial pO2. A mild fully compensated respiratory alkalosis is normal in pregnancy.[28] Simchem et al[29] have shown that 100% oxygen administration to pregnant women is associated with significant hypocapnia and hyperventilation. End tidal pCO_2 levels decreased by 12% during HO, with 100% oxygen at a rate of 5 L/min in the third trimester of pregnancy. Other studies that have explored the maternal response to HO have concluded that they did not observe any adverse maternal side-effects or maternal complications during or after HO;[30,31] however, these studies did not monitor maternal hemodynamic indices (such as CO, SV, or SVR) objectively. Our study recorded the hemodynamic response after a 10-minute exposure to HO; this time interval was chosen because many of the studies that assess the fetal response to hyperoxia use a 10-minute duration of oxygen exposure.[7,30,32,33] In literature about nonpregnant patients, hemodynamic changes have been observed after a short duration of hyperoxygenation.[34,35]

FIGURE 2
Serial changes



Serial changes in cardiac output, cardiac index, heart rate, and stroke volume in pregnant vs nonpregnant subjects are shown. *Red* indicates pregnant patients; *blue* indicates nonpregnant patients. The *asterisk* indicates a significant difference between groups at that timepoint; the *cross* indicates a significant change over time within the group.

CI, cardiac index; *CO*, cardiac output; *HR*, heart rate; *SV*, stroke volume.

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Our study demonstrates that MH leads to an increase in cardiac parasympathetic activity, which is consistent with observations that have been reported in previous studies of healthy nonpregnant volunteers.[36] The reduction in HR therefore is likely to reflect increased vagal activity. Parasympathetic activation appears to be unrelated to changes in BP because there was no significant change in BP during HO treatment in either group. The mechanism by which oxygen administration leads to a reduction in CO and an increase in SVR is poorly understood. One possible hypothesis is that hyperoxia leads to the generation of reactive oxygen species,[37] which in turn decrease the bioavailability of local nitric oxide[38] that impairs nitric oxide–dependent vasodilatation and increases basal vascular tone.[39] Another plausible mechanism is that hyperoxia can induce vasoconstriction by acting directly on long-lasting calcium channels.[40] It has been shown in animal studies that oxygen sensitive long-lasting calcium channels are present on vascular smooth muscle and are involved in the local circulatory control during hyperoxia.[41]

In healthy nonpregnant subjects, the effect of acute oxygen administration has been examined in a series of studies that used validated, noninvasive techniques.[42-44] In fact, the effects of hyperoxia on cardiovascular function in nonpregnant subjects was investigated extensively from 1940–1970. These studies demonstrated a reduction in HR and CI and a reduction in cardiac oxygen consumption and coronary blood flow.[45-47] They also highlighted the increase in BP and SVR in response to hyperoxia in healthy subjects. However, there remain inconsistent data in the literature in relation to the effects of HO in different patient populations, and there exists significant heterogeneity in the methods, particularly in the method of hemodynamic monitoring that is used. A unique aspect of this study is the insight offered by NICOM technology for both the pregnant and nonpregnant groups.

Accurate monitoring of hemodynamic outputs has been performed traditionally with the use of invasive methods, such as pulmonary artery catheterization, or minimally invasive methods, such as an arterial catheter for pulse contour analysis, intratracheal tube for partial carbon dioxide rebreathing, or continuous Doppler

velocity flow assessment via a suprasternal transthoracic ultrasound beam or an esophageal probe.[48,49] Methods to monitor maternal hemodynamics noninvasively have been evaluated and gained recent interest.[50-52] Recent studies have demonstrated good agreement between NICOM and 2-dimensional transthoracic echocardiography in estimating CO and SV, specifically in the third trimester of pregnancy.[26] NICOM recently has been validated against transthoracic echocardiography in the obstetric population.[22] Measurements derived from bioreactance-based noninvasive CO monitor (NICOM) assessment correlate well with results that are derived from pulmonary artery catheterization. The machine is entirely operator independent and therefore is not subject to any interobserver variation. The NICOM system has demonstrated acceptable accuracy, precision, and responsiveness for CO monitoring in patients in a wide range of circulatory situations.[53]

MH is undertaken commonly in obstetric practice. Many of the therapeutic and diagnostic practices that use hyperoxia use a rate of oxygen delivery that ranges from 5−12 L/min.[2,11,29-33,54,55] A rate of 12 L/min was chosen for this study to cover the wide variation in rate of oxygen delivery and the many applications for HO use in an obstetric population. MH is used during cesarean delivery with regional anesthesia in many centers worldwide. Oxygen inhalation of 60−100% during elective cesarean delivery has been shown to increase arterial oxygen and oxygen free radicals in both the mother and fetus.[56,57] A recent study concluded that among patients with a category II fetal HR tracing in active labor, intrauterine resuscitation with room air is not inferior to oxygen in improving umbilical artery lactate.[58] A Cochrane review in 2012 established that there is limited evidence to support the use of oxygen in the management of intrapartum fetal distress.[3] Notwithstanding this evidence, there are now data that link hyperoxygenation in infants with increased respiratory and neurologic morbidity, which has prompted the American Academy of Pediatrics to review its recommendations on neonatal resuscitation and oxygen administration.[58,59] Further investigation into the benefits and risks of HO in an obstetric population is required urgently.

To our knowledge, this is the first study to use direct maternal hemodynamic measurements to evaluate the effects of hyperoxygenation in pregnancy. The NICOM system that was used is entirely operator-independent and therefore is not subject to any interobserver variation or bias.

We acknowledge the small sample size in our study. Measurements of circulating antioxidants or markers of oxidative damage were not obtained.

The routine monitoring methods that were used on labor wards in the assessment of the pregnant women include BP monitoring with a manual or automated BP cuff and measurement of the HR. Based on these proxy measures, we gain very little insight into the true circulatory response to any treatment or measure aimed at increasing the CO or oxygen delivery to the fetus. The NICOM system offers the capability to reflect such circulatory changes accurately beyond the analysis of vital signs alone.

In light of the observed pregnancy-specific reaction to hyperoxygenation that is not reflected in BP and HR measurements, maternal administration of high oxygen concentrations should be undertaken judiciously and with appropriate monitoring. The findings of this study that indicate that HO therapy in the nonhypoxemic pregnant woman may have unintended and potentially detrimental hemodynamic effects warrant further exploration in a larger cohort. Importantly, these changes need further evaluation in disease states such as preeclampsia, because the changes in that population may be more profound and with potentially deleterious consequences. Oxygen supplementation in the setting of hypoxia clearly is justified. However, we must caution its use in normoxic pregnant women until randomized controlled trial evidence is available to support its use. These studies are imperative because hyperoxia confers a theoretic potential to cause harm. The precise role of hyperoxygenation therapy in an obstetric population should be evaluated carefully. ■

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