Simulated airplane flight increases plasma lactate in fetal rabbits

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Schumacher B, Olson GL, Saade GR, Ou C-N, Sutton TE, Moise KJ Jr, Fife CE. Simulated airplane flight increases plasma lactate in fetal rabbits. Undersea Hyper Med 1999; 26(2):67–73.—We studied the effect of 9 h of simulated airplane cabin conditions at cruising altitude (8,000 feet; inspired oxygen equivalent to 15% O_2 at sea level) on fetal plasma lactate in near-term pregnant rabbits. Controls (n = 19) spent 9 h at sea level (21% O_2). Study group I (n = 21) experienced airplane cabin conditions. Study group II (n = 17) was studied at 8,000 feet with the inspired O_2 concentration normalized to sea level. Study group III (n = 19) remained at sea level breathing 15% O_2. Before ending each exposure, fetal blood sampling for lactate was performed under ultrasound guidance. Maternal lactates were obtained before and after sampling fetuses. Wilcoxon signed rank test, analysis of variance, and Bonferroni's method were used as appropriate. $P < 0.05$ denoted statistical significance. Study group I (altitude/hypoxia) had higher fetal lactates than controls (sea level/normoxia) and study group II (altitude/normoxia). Fetal lactates in study group I (altitude/hypoxia) were higher than in study group III (sea level/hypoxia). Maternal lactates were lower after fetal sampling. Fetal lactic acidemia was observed after 9 h of airplane cabin conditions. This was attributed to the combined effect of the lowered oxygen concentration and the decrease in atmospheric pressure.

rabbit, fetus, altitude, lactate, hypoxia

As we approach the twenty-first century, jet air travel has become a common mode of transportation. Millions of individuals travel by air daily, and more of them are women, many of whom are pregnant. Currently, most commercial airlines allow passengers and crew members to travel up to the final month of their pregnancies, and airplane travel during pregnancy is generally considered safe (1). However, there is still concern regarding in-flight fetal hypoxia, as neurohumoral and metabolic responses may be adequate for the normal fetus but may not protect the compromised fetus (2).

Commonly, commercial aircraft maintain cruising altitudes of 20,000–40,000 feet, while the passenger cabin is pressurized to approximately an equivalent altitude as high as 8,000 feet above sea level. This results in a decreased inspired partial pressure of oxygen (P_{O_2}) of 116 mmHg, which is equivalent to 15% O_2 when compared to sea level (21% O_2) (3). A normal fetus at sea level has an umbilical arterial P_{O_2} of 32 mmHg, whereas its mother's arterial P_{O_2} will be approximately 100 mmHg. At a "passenger cabin altitude" of 8,000 feet, the mother's P_{O_2} will be only 64 mmHg with an arterial O_2 saturation of approximately 90%, whereas the fetal umbilical arterial P_{O_2} decreases from 32 mmHg to an estimated 26 mmHg (4).

Many aspects of chronic high-altitude exposure during pregnancy and the resulting maternal-fetal physiologic adaptive responses, such as increased maternal ventilation and hemoglobin concentration, decreased birth weight, and reduced thickness of the villous gas exchange membrane have been extensively studied (5–7). Little is known, however, about the effects of *acute* altitude decompression on the fetus.

The current investigation was designed to expose a pregnant animal model to similar acute altitude decompression as experienced aboard commercial aircraft during a 9-h flight. We used a rabbit model and simulated flight conditions to test the hypothesis that airplane travel results in fetal lactic acidemia.

MATERIALS AND METHODS

The study was approved by the Animal Protocol Review Committee of Baylor College of Medicine, the Animal Welfare Committee of the University of Texas Health Science Center, and the Hermann Hospital Infection Control Committee. Also, established safety standards and procedures for the use of the altitude chamber research facility at the Hermann Center for Environmental, Aerospace, and Industrial Medicine of the University of Texas Health Science Center were observed at all times.

Seventy-six healthy, adult New Zealand White rabbits

with carefully timed pregnancies were entered into our study on Day 25 of gestation (term = 32 days). After arrival from a local breeder, does were maintained in our facility for approximately 4 days before the experiment. On arrival at Baylor College of Medicine, all animals were examined by the veterinary staff and confirmed to be in good health. They were maintained at the vivarium in stainless steel cages with open mesh floors in a fully climatized environment with access to ample food (Purina Laboratory Chow, Purina Mills, Inc., St. Louis, MO) and water. Animal housing conditions included a temperature of 21° ± 2°C, relative humidity between 40 and 60%, a 12/12-h light/dark cycle, and similar cages to reduce the level of anxiety in the animals. The altitude chamber used in this study was a 3.35 × 1.83 m diameter pressure vessel converted for high-altitude research applications (Hyperbaric Oxygen Treatment Systems, Inc., San Diego, CA; altitude conversion Mechidyne Systems, Inc., Houston, TX; rate of ventilation approximately 10 liter · min^{-1}). Details of the hyperbaric chamber conversion for use in altitude studies have been described (8). Evacuation of the altitude chamber was accomplished using two vacuum pumps (PIAB USA, Inc., Hingham, MA).

On Day 29 of gestation, the abdomen of each doe was shaved, and the pregnant rabbits were transported by air-conditioned van across the short distance between Baylor College of Medicine and the altitude chamber at the Hermann Center for Environmental, Aerospace, and Industrial Medicine of the University of Texas Health Science Center. Also, while in the chamber, does were maintained in stainless steel cages with open mesh floors in a fully climatized environment with access to ample food and water. All does underwent a 9-h environmental exposure. Using an air lock, the time of entry into the chamber for each doe was staggered at 30-min intervals to later allow adequate procedure time for the investigators. During the final hour of each environmental exposure, the does were sedated by intramuscular injection in a hindlimb of 3 ml of a combination anesthetic solution of ketamine 42.8 mg · ml^{-1}, xylazine 8.6 mg · ml^{-1}, and acepromazine 1.4 mg · ml^{-1}. The does were then secured in the dorsal supine position, and cardiac blood was aspirated from multiple fetuses using ultrasound guidance (Aloka 680, Corometrics Medical Systems, Inc., Wallingford, CT; 7.5 MHZ curvilinear transducer). These sampling techniques have been previously reported (9,10). Briefly, an 18-gauge, 1.5-inch introducer needle (Becton Dickinson & Co., Franklin Lakes, NJ) was introduced through the abdominal wall of the doe into one of its two uterine horns. A second 22-gauge, 3.5-inch Quincke-type point spinal needle (Becton Dickinson & Co.) was directed through the 18-gauge needle into the fetal heart. Approximately 0.2– 0.4 ml of fetal blood was aspirated into a 1.0-ml tuberculin syringe. Air was injected into the fetal heart afterwards; this allowed for ultrasound identification of those fetuses that had already undergone sampling. In the majority of cases, this also resulted in fetal cardiac asystole. The fetal blood was then transferred to specialized microcentrifuge tubes containing 1 mg sodium fluoride and 15 IU heparin · ml^{-1} blood to ensure anticoagulation (Microvette CB 300 tubes; Sarstedt GmbH, Nuembrecht, Germany). The tubes were then centrifuged at 5,000 rpm for 5 min (Eppendorf Microcentrifuge 3200; Brinkmann Instruments, Westbury, NY). The plasma was separated and immediately transported on ice to the laboratory. The plasma lactate concentration for each fetus sampled was measured using a commercially available spectrophotometric clinical chemistry slide (Kodak Ektachem Clinical Chemistry Slide (LAC); Eastman Kodak Co., Rochester, NY). Blood was also aspirated from the auricular artery of each doe, and maternal plasma lactate concentrations were measured immediately before and after the fetal cardiac blood sampling procedures. All rabbits in this study were randomly assigned to a control or one of three study groups.

Controls (n = *19; chamber O_2 concentration 21%*): On Day 29 of gestation, the does in this group spent 9 h in the altitude chamber at sea level breathing room air (barometric pressure of 760 mmHg; ambient P_{O_2} of 159 mmHg; equivalent to 21% O_2). Does were sedated during the final hour of this environmental exposure, and fetal cardiac as well as maternal blood sampling for lactate measurements were immediately performed as described above.

Study group I (n = *21; chamber O_2 concentration 15% when compared at sea level*): On Day 29 of gestation, the does in this group experienced 9 h of in-flight airplane cabin conditions at a simulated altitude of 8,000 feet (barometric pressure of 558 mmHg; ambient P_{O_2} of 116 mmHg; equivalent to approximately 15% O_2 when compared to sea level). This "cruising altitude" was reached in the altitude chamber using approximately 15 min of ascent time, similar to that in commercial aircraft (1). The O_2 concentration in the chamber was continuously monitored using an oxygen analyzer calibrated at sea level (MiniOxI; Catalyst Research Corp., Owings Mills, MD). A stable altitude of 8,000 feet was ensured with a digital pressure gauge (model 370; Setra Systems, Inc., Acton, MA). Again, does were sedated during the final hour of exposure, and fetal cardiac as well as maternal blood sampling for lactate measurements were immediately performed as described above.

Study group II (n = *17; chamber O_2 concentration 28.5%, which is equivalent to approximately 21% O_2*

when compared at sea level): This arm of the study was designed to isolate the effect of decreased atmospheric pressure alone on the plasma lactate concentration in the near-term fetal rabbit. On Day 29 of gestation, the does in this group spent 9 h at a simulated altitude of 8,000 feet, but with the inspired O_2 concentration normalized to sea level by providing 28.5% O_2 (barometric pressure of 558 mmHg; ambient P_{O_2} of 159 mmHg; equivalent to approximately 21% O_2 when compared to sea level). Using an air-oxygen mixer (model 3500 HL; Sechrist Industries, Medical Products Division, Anaheim, CA), a mixture of hospital wall air and oxygen was added to the chamber to effect this O_2 correction once the chamber had equilibrated at 8,000 feet altitude. The composition of the cabin air was kept constant. Again, does were sedated during the final hour of exposure, and fetal cardiac as well as maternal blood sampling for lactate measurements were immediately performed as described above.

Study group III (n = *19; chamber O_2 concentration 15%)*: This final arm of our study was designed to isolate the effect of the decreased O_2 tension alone on the plasma lactate concentration in the near-term fetal rabbit. On Day 29 of gestation, the does in this group spent 9 h at sea level but were confined to the altitude chamber breathing 15% O_2 (barometric pressure of 760 mmHg; ambient P_{O_2} of 116 mmHg). This low O_2 concentration was maintained by continuously adding nitrogen to the chamber at a pressure of approximately 10 psi. Hospital wall O_2 was also added to the chamber at a rate of approximately 10 liter $\cdot$ min^{-1} using a flow meter (model 2MFA1001; Precision Medical Inc., Northampton, PA) to ensure a constant O_2 concentration of 15% O_2. Does were sedated during the final hour of exposure, and fetal cardiac as well as maternal blood sampling for lactate measurements were immediately performed as described above.

Statistical analysis: Using the ovine hypoxia literature as background (11), a sample size calculation was performed before the study. It was estimated that at least 16 does would be required in each group to detect an approximately 30% increase in fetal plasma lactate levels related to altitude and hypoxia with an alpha error of 5% and a power of 80%. The mean plasma lactate concentration of the fetuses of each litter was determined and used for that doe in the final analysis. Samples with insufficient plasma for accurate lactate determination were excluded. Sigma Stat Statistical Software was used for all computations (Jandel Scientific Software, San Rafael, CA). The Kolmogorov-Smirnoff test was used to check the data for normality of distribution. Our data passed this test for normality with the following Kolmogorov-Smirnoff Distances: 0.147 (controls; $P = 0.362$), 0.108 (study group I; $P = 0.674$), 0.133 (study group II; $P = 0.567$), and 0.122 (study group III; $P = 0.588$). Paired *t* test, Wilcoxon signed rank test, analysis of variance, pairwise multiple comparison (Bonferroni's method), and multiple linear regression were applied as appropriate, using $P < 0.05$ to denote statistical significance.

RESULTS

Maternal plasma lactate concentrations decreased significantly when measured before (median: 2.3; range: 1.1–10.7 mmol $\cdot$ liter^{-1}) and after (median: 1.9; range: 1.0–7.0 mmol $\cdot$ liter^{-1}) the fetal blood sampling process ($P < 0.0001$, *see* Table I). To demonstrate that the mean fetal plasma lactate level measured is independent of this statistically significant decrease in the maternal plasma lactate concentration, multiple linear regression analysis was performed. Multiple linear regression analysis comparing the change in maternal lactate before and after fetal sampling with the mean fetal plasma lactate concentration for each doe failed to show a significant correlation ($r = 0.149$; P value of non-significance = 0.2075).

During the present study a median of five fetuses (range 1–8) from each doe were sampled. Of the 404 fetuses sampled, 374 (93%) were included in the final analysis. Two-way analysis of variance using the general linear model was performed. Our data passed the tests for normality ($P = 0.5638$) and equal variance among study groups ($P = 0.1146$). The differences in the mean values among the different levels of P_{O_2} are greater than would be expected by chance alone after allowing for effects of differences in altitude. This represents statistically significant differences ($P = 0.0000119$). The effect of different levels of altitude depends on what level of

Table 1: Maternal Plasma Lactate Concentrations Before and After Fetal Sampling, Presented as Median (Range) in Millimoles per Liter

Study Group	*n*	Before	After	*P*
Controls (sea level/normoxia)	19	2.4 (1.2–8.0)	2.0 (1.2–7.0)	0.37
I. (altitude/hypoxia)	21	3.0 (1.5–7.6)	2.3 (1.6–6.7)	0.051
II. (altitude/normoxia)	17	1.7 (1.1–7.3)	1.5 (1.0–2.4)	0.01
III. (sea level/hypoxia)	19	2.5 (1.3–10.7	2.1 (1.2–5.4)	0.04
For all does studied	76	2.3 (1.1–10.7)	1.9 (1.0–7.0)	<0.0001

P_{O_2} is present. Thus, there is a statistically significant interaction between altitude and P_{O_2} ($P = 0.00268$). Next, using Bonferroni's method, multiple comparisons between study groups were drawn. Study group I (altitude/hypoxia) had significantly higher fetal plasma lactate concentrations than controls (sea level/normoxia) and study group II (altitude/normoxia) (8.19 ± 0.98 vs. 6.37 ± 1.10 vs. 5.34 ± 1.37 mmol · liter^{-1}). This represents a 28.6% and 53.4% increase in fetal plasma lactate, respectively. Fetal plasma lactate concentrations in study group I (altitude/hypoxia) were significantly higher than in study group III (sea level/hypoxia) (8.19 ± 0.98 vs. 6.92 ± 1.73 mmol · liter^{-1}), constituting an 18.4% increase in lactate from the effect of altitude alone. Mean fetal plasma lactate concentrations and all pairwise comparisons of study groups are summarized in Table 2 and Fig. 1, respectively.

DISCUSSION

Reports from the literature emphasize the safety of air travel during pregnancy (1,12). However, these non-invasive studies examined fetal well-being during short flights with durations of 90 min or less. Huch et al. (1) studied only a total of 10 volunteers at 32–38 weeks gestation and reported the mean fetal heart rate to be within normal limits. No fetal bradycardia, tachycardia, or significant loss of heart rate variability was observed (1). There are also little animal data discussing acute altitude exposure during the third trimester of pregnancy. Makowski et al. (13), however, acutely exposed six near-term pregnant ewes to high altitude (14,260 feet) after fetal umbilical vessel cannulation. These investigators showed that O_2 content in the umbilical vein decreased significantly during the first 48 h of high altitude exposure. Matsuda et al. (11) exposed near-term ovine fetuses to sustained severe hypoxic insults (approximately 10% O_2 for up to 8 h). Significant fetal lactic acidemia developed after 60 min and reached 6 times baseline values after 6 h of exposure.

Similarly, Jones et al. (14,15) exposed ewes to severe acute hypoxia and documented fetal lactic acidemia within less than 60 min from the start of the environmental exposure. It thus becomes evident that severe hypobaric hypoxia can lead to a sustained rise in the fetal plasma lactate concentration, which is a reflection of its reduced utilization for oxidative metabolism (16). The increased fetal plasma lactate levels after exposure to hypobaric hypoxia are the result of a cellular shift from aerobic to anaerobic metabolism (17–19).

The present study also used plasma lactate as a sensitive indicator of fetal acidosis and compromise (11,20–24). Mammalian fetuses produce lactic acid during a significant in utero hypoxic insult. Such an insult leads to decreased fetal O_2 delivery and incomplete combustion of carbohydrates and fatty acids. Anaerobic metabolism and fetal metabolic acidosis result (25). The severity of the fetal hypoxia can be related to the decrease in maternal oxygenation, utero-placental blood flow, oxygen transfer across the placenta, fetal tissue oxygenation, and thus increased fetal plasma lactate production (22,25).

In this model, New Zealand White rabbits were chosen for their short, predictable mean gestation of only 32 days, large litter size, and human-like hemochorial placentation (26). Because of the small volume of fetal blood obtained, our ability to use different tests to detect fetal hypoxia was limited. Fetal plasma lactate is a simple, sensitive indicator of acute fetal hypoxia (20).

Hypoxia leads to a steep and immediate rise in fetal plasma lactate, which is even more pronounced in the fetus with intra-uterine growth restriction (27). Fetuses can sense even small decreases in uterine blood flow, which are not sufficient to affect the umbilical arterial or venous blood gases, but are expressed as an increase in the fetal plasma lactate concentration. Fetal plasma lactate rises within minutes of the onset of even mild hypoxia caused by a decrease in uterine blood flow (28). Studying the effects of ischemia on lung tissue in fetal rabbits at 25–28 days gestation by interrupting uterine blood flow through inflation of an aortic balloon, Das et al. (29) showed that the lactate content of the fetal lung doubled after only 20 min with essentially no change in pyruvate.

From human cordocentesis data it is known that fetal plasma lactate levels rise during an in utero hypoxic insult before any abnormalities appearing on the fetal heart rate

Table 2: Mean Fetal Plasma Lactate Concentrations by Study Group (millimoles per liter)

Study Group	*n*	Fetuses Sampled	Fetuses Included (%)	Mean Fetal Lactate	Standard Deviation
Controls (sea level/normoxia)	19	92	86 (93)	6.37	±1.10
I. (altitude/hypoxia)	21	113	101 (89)	8.19	±0.98
II. (altitude/normoxia)	17	97	86 (89)	5.34	±1.37
III. (sea level/hypoxia)	19	102	101 (99)	6.92	±1.73
Total	76	404	374 (93)		

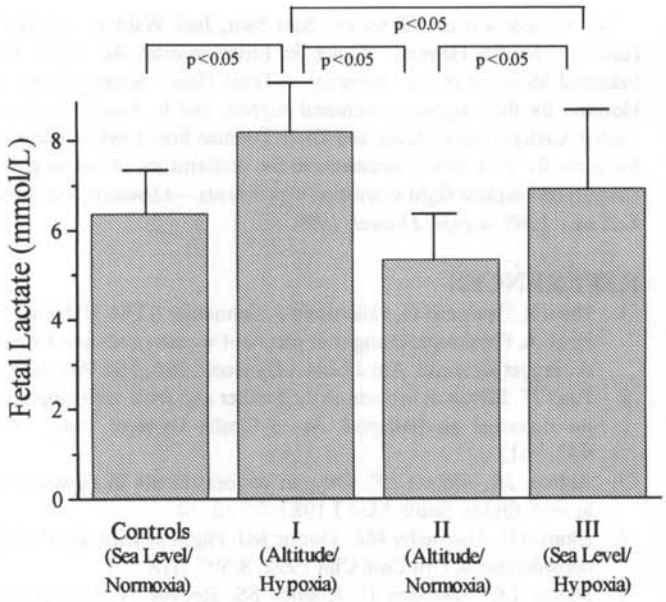

FIG. 1—Comparison among study group mean fetal plasma lactate concentrations. *Vertical confidence bars* indicate standard deviations.

monitor tracing (21). Arterial blood gases may have been equally informative or superior to plasma lactate in the present study, but would not be valid due to the technical difficulties of sampling the fetal heart in the rabbit model. It was not possible to determine during the ultrasonographic examination whether the fetal blood in this study was obtained from the right- or the left-sided cardiac chambers. If fetal blood gases were used in this study, this information would be important, as there are significant differences in oxygenation between the blood in the right and left side of the fetal heart (25,30). During a normal pregnancy, however, fetal plasma lactate levels remain constant with advancing gestational age (23), and arterial and venous lactates do not differ significantly (24). We believe, therefore, that fetal cardiac blood containing a mixture from the arterial and venous circulations accurately represents the true overall fetal plasma lactate level. Furthermore, even though our baseline fetal plasma lactate levels (controls 6.37 ± 1.10 mmol · liter^{-1}) may appear high, they actually compare favorably with the literature. Mims (31) shows that the mean lactate concentration of term rabbit pups at delivery is 5.7 mmol · liter^{-1}.

The decrease in the maternal plasma lactate concentration after fetal cardiac blood sampling may be explained by the loss of the metabolically active fetuses that produce lactate and contribute to the total lactate pool. Conversely, altitude-induced hyperventilation in the does and the resultant respiratory alkalosis could have stimulated an overall increase in the rate of maternal and fetal lactate production. The fetuses themselves do not have the ability to metabolize lactate, once accumulated, even in the presence of sufficient oxygen (25,31). To demonstrate, though, that this decrease in the maternal plasma lactate concentration is independent of the mean fetal plasma lactate concentration for each doe, multiple linear regression analysis was performed, which failed to demonstrate a significant correlation when comparing the change in maternal lactate before and after fetal sampling with the mean fetal plasma lactate concentration of each litter.

Separate assessment of the decreased oxygen tension and atmospheric pressure on fetal acid hypoxia was undertaken. In the current study, fetal plasma lactate levels were higher in the simulated airplane flight group, study group I (altitude/hypoxia), even after controlling for the lower O_2 concentration in study group III (sea level/hypoxia).

Although in our present study exposure to both altitude *and* hypoxia leads to a 29% increase in fetal plasma lactate (controls: 6.37 ± 1.10 mmol · liter^{-1} vs. study group I: 8.19 ± 0.98 mmol · liter^{-1}), altitude alone leads to an 18% increase in lactate (study group III: 6.92 ± 1.73 mmol · liter^{-1} vs. study group I: 8.19 ± 0.98 mmol · liter^{-1}). These two comparisons reach statistical significance with $P < 0.05$. On the other hand, even though not statistically significant, hypoxia alone leads to a 9% increase in the fetal plasma lactate concentration (controls: 6.37 ± 1.10 mmol · liter^{-1} vs. study group III: 6.92 ± 1.73 mmol · liter^{-1}).

Significant fetal lactic acidemia was noted at the end of a 9-h exposure to in-flight airplane passenger cabin conditions. It is quite noteworthy that 10 of the 21 samples (that is 47.6%) taken from study group I (altitude/hypoxia) were clearly abnormal, i.e., larger than the mean normal lactate concentration *plus* two standard deviations. The observed increase in the fetal plasma lactate concentration seems to be secondary to the combination of the decreased inspired oxygen concentration and decreased atmospheric pressure at 8,000 feet. The decision was made to study one point in time to standardize and compare all variables in this study. As noted in other studies, the duration of the exposure may also be important, as a direct correlation exists between the length and severity of the hypoxic insult and the degree of fetal lactic acidemia (11,32). Future studies are needed to assess the effect of the duration of the exposure to acute altitude decompression on the fetus.

Nonetheless, our present study constitutes an important step toward showing that third-trimester fetal exposure to hypobaric hypoxia at 8,000 feet ("cruising altitude") results in lactic acidemia, which represents a very sensitive fetal stress response. While maybe not in and of itself detrimental to the fetus, clinically this lactic acidemia has significance as a marker for impending fetal stress or even distress, particularly in the face of a growth-restricted gestation.

While control and study groups were treated in an identical fashion in our study, important limitations still remain. It is conceivable that the experimentally induced hypoxia in the study animals was exacerbated by the use of sedation during the fetal blood sampling process. In particular, the anesthetic mixture may have caused hypotension in the animals. Still, as control and study animals underwent identical anesthetic procedures, even if the anesthesia itself had artifactually elevated baseline fetal plasma lactate values in all animals, this would affect all animals to an equal degree and thus not distract from the statistically significant differences between control and study group fetal plasma lactate levels.

Our study also leaves ample room for further investigation. Future studies should clearly attempt to incorporate the use of arterial blood gas data to better assess the degree and the physiologic consequences of maternal and fetal hypoxia in the animals. Blood gas data would, for example, help clarify the issue of whether hyperventilation induced by the altitude exposure alone may have led to respiratory alkalosis with a decreased P_{CO_2} in the animals, which may then have induced a reciprocal increase in placental and fetal lactate production. As our present study does not include Pa_{CO_2} measurements, respiratory alkalosis from hyperventilation cannot be excluded as a possible stimulant for placental and fetal lactate production.

In addition, the exact cause of how altitude leads to an increase in the fetal plasma lactate concentration independently of hypoxia remains to be elucidated. Stress, the noise level in the chamber, hypocapnia, and barotrauma variation between the different study groups may be contributing factors. Measuring serum corticosteroids and catecholamines as well as assessing changes in the cardiac output of the experimental animals may help answer this question in the future.

Recent reports regarding aeromedical evacuations involving pregnant women at 34 weeks gestation or beyond and with air travel times up to 12 h describe the use of maternal in-flight O_2 in all high-risk patients (33). Our data support that in-flight maternal O_2 administration should be considered for pregnant women having to travel a significant distance by air, particularly if their pregnancy is known to be complicated by a condition that may compromise uteroplacental blood flow, such as intrauterine growth restriction. Short flights in healthy pregnant women carrying an uncomplicated pregnancy, on the other hand, are generally thought to be well tolerated.

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