Placental oxygen transfer reduces hypoxia/reoxygenation swings in fetal blood in a sheep model of gestational sleep apnea

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ABSTRACT

AIM: Obstructive sleep apnea (OSA), characterized by events of hypoxia-reoxygenation, is highly prevalent in pregnancy, negatively affecting the gestation process and particularly the fetus. Whether the consequences of OSA on the fetus and offspring are mainly caused by systemic alterations in the mother or by direct effect of intermittent hypoxia in the fetus is unknown. In fact, how apnea-induced hypoxemic swings in OSA are transmitted across the placenta remains to be investigated. The aim of this study was to test the hypothesis, based on a theoretical background on the dampening effect of oxygen transfer in the placenta, that oxygen partial pressure (PO_2) swings resulting from obstructive apneas mimicking OSA are mitigated in the fetal circulation. METHODS: To this end, 4 anesthetized ewes close to term pregnancy were subjected to obstructive apneas consisting of 25-s airway obstructions. Real time PO_2 was measured in the maternal carotid artery and in the umbilical vein using fast-response fiberoptic oxygen sensors. RESULTS: The amplitude of PO_2 swings in the umbilical vein were considerably smaller (3.1 ± 1.0 vs. 21.0 ± 6.1 mmHg ($m \pm SE$); $p < 0.05$). Corresponding estimated swings in fetal and maternal oxyhemoglobin saturation tracked PO_2 swings. CONCLUSION: This study provides novel insights into fetal oxygenation in a model of gestational OSA, and highlights the importance of further understanding the impact of sleep-disordered-breathing on fetal and offspring development.

NEWS & NOTEWORTHY:

This study in an airway-obstruction sheep model of gestational sleep apnea provides novel data on how swings in oxygen partial pressure (PO_2) translate from maternal to fetal blood. Real-time simultaneous measurement of PO_2 in maternal artery and in umbilical

vein shows that placenta transfer attenuates the magnitude of oxygenation swings. These data prompts to further investigate to what extent maternal apneas could induce similar direct oxidative stress in fetal and in maternal tissues.

Keywords: fetal oxygenation, intermittent hypoxia, pregnancy apnea.

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent syndrome in the general population (54) and has been recently identified as particularly frequent among pregnant women, affecting 8% - 45% in mid/late pregnancy (46,52). OSA affects pregnant women either because the patient already suffered the syndrome prior to pregnancy or because gestational changes promote OSA incidence (24,52). Given that the major risk factor for OSA is obesity (65) — a current worldwide pandemic (50) particularly affecting young individuals approaching reproductive age (34) —, it is expected that the prevalence of OSA in pregnancy will further increase in the upcoming years. Besides the well-known long-term consequences of OSA (e.g. increase in morbidity and mortality by cardiocirculatory, metabolic, neurocognitive and malignant diseases (25,28,33,38,61), OSA poses a specific challenge during pregnancy. Indeed, both clinical and animal studies have shown that OSA imposes significant risk accrual for the emergence diabetes and pre-eclampsia in pregnant women, while increased risk for metabolic syndrome is apparent in offspring both short-term and long-term, and even transmitted across generations (3,13,35,37,40,52,69).

Although our understanding of the pathological mechanisms playing a role in the deleterious effects of OSA in pregnancy is scarce, current data available from systemic and end-organ research in children and adults suggest that gestational OSA may negatively impact on the fetus via two different ways: (i) the fetus is exposed to the systemic alterations induced by OSA in the mother. Indeed, as any other patient with OSA, a pregnant woman suffering from this sleep breathing disorder will be subjected to intermittent hypoxemia and hypercapnia, sleep fragmentation, and increased negative swings in intrathoracic pressures, resulting in a variety of systemic effects that could

potentially affect the fetus. For instance, increased sympathetic activation (48,51) and subsequent blood pressure alterations, or maternal circulating cytokines and exosomes (released as a result of oxidative stress and inflammation (2,36,41,42,59) could influence fetal homeostasis via their transfer through the placental barrier (22,29,66). (ii) OSA may induce fetal alterations via intermittent hypoxia developing in the fetus. Indeed, during the process of gas exchange in the placenta, fetal blood is directly exposed to the maternal intermittent hypoxemia induced by OSA, and hence all fetal tissues are potentially exposed to hypoxia/reoxygenation events. Noteworthy, there is existing evidence of hypoxia in the human placenta in OSA (57). However, how intermittent hypoxemia is translated from the mother to the fetus in OSA has not been explored to date.

From the fetal viewpoint, the placenta plays a similar role to the lungs after birth, i.e., the organ in which blood gases are interchanged with the environment, Figure 1 (17,67). Specifically, fetal blood extracts oxygen from maternal blood, similar blood extracting oxygen from alveolar gas. In both cases, oxygen transfer is passively driven by a gradient of oxygen concentration through a thin and high-surface barrier. There are, however, important differences between the alveolo-capillary barrier and the placental barrier. For instance, O₂ diffusing capacity and O₂ transfer rate are one order of magnitude higher in the lungs than in the placenta, O₂ tissue consumption and acid transfer are significant in the placenta and insignificant in the lungs, and Bohr and Haldane effects are double in the placenta and single in the lungs (45). Moreover, in the alveolo-capillary barrier, oxygen transfer takes place through the wall of a short and thin capillary with a blood transit time of slightly less than 1 s, facilitating fast equilibration between oxygen partial pressures (PO₂) in the alveolus and the blood. In contrast, oxygen transfer through the human placental barrier (Figure 1.A) is achieved as fetal blood circulates from the

umbilical arteries to the capillaries inside the placental villi, and returns to the umbilical vein, whereas maternal blood percolates through a relatively high volume intervillous compartment outside this arboreous structure (67). As a result, PO_2 in the fetal blood leaving the placenta through the umbilical vein is considerably lower than PO_2 in the maternal artery (6,8,32). Remarkably, maternal blood circulation through the human intervillous space is a process with a washout time of ≈ 30 s (9). Such relatively high circulation time does not pose a problem under normal stationary conditions of oxygenation, but can hinder gas exchange during events such as those that characterize OSA, in light of the fast-rate oxygen desaturation/re-oxygenation times, which can last as short as 10 seconds or longer (44). Accordingly, it would be anticipated that placental oxygen transfer would also reduce the amplitude of hypoxia/reoxygenation swings in fetal blood.

Therefore, the aim of this work was to test the hypothesis that PO_2 swings resulting from obstructive apneas mimicking OSA are reduced in fetal blood compared to maternal blood because of the dampening effect of oxygen transfer in the placenta. To this end, we carried out first ever real-time measurements of PO_2 in maternal arterial blood, and in umbilical venous fetal blood during application of obstructive apneas realistically mimicking OSA in a sheep model.

METHODS

The study was carried out on 4 near-term pregnant ewes (140 ± 0.8 days of gestation; ~95% of the total length of sheep pregnancy), aged 4-6 years-old and with mean weight of 61.5 ± 8.5 kg, from a commercial meat crossbreed. The experimental protocol was assessed and approved by the CEU Cardenal Herrera University Committee of Ethics in Animal Research and by the relevant regional authorities (report 2019/VSC/PEA/0007) according to the Spanish Policy for Animal Protection (RD53/2013), which meets the European Union Directive 2010/63/UE.

Animals were fasted from food but not from water 12 hours before surgery. Ewes were sedated with intravenous administration of midazolam ($0.5 \text{ mg}\cdot\text{kg}^{-1}$; Midazolam Normon $15 \text{ mg}\cdot\text{ml}^{-1}$, Normon, Spain). Oxygen ($3 \text{ liters}\cdot\text{min}^{-1}$) was administered using a facemask for 10 minutes. Afterwards, anesthesia was induced with intravenous propofol (Propofol Lipuro $10 \text{ mg}\cdot\text{ml}^{-1}$, B. Braun Melsungen AG, Germany) to proceed with endotracheal intubation. Anesthesia was maintained with Sevoflurane (room air). Ewes were then placed in sternal recumbency and epidural bupivacaine 0.5% (7.5 ml; Bupivacaina, B. Braun, Spain) was administered for intraoperative analgesia (5 ml). In case of intraoperative sign of nociception, rescue analgesia was administered with intravenous fentanyl ($3 \text{ }\mu\text{gr}\cdot\text{kg}^{-1}$; Fentadon $50 \text{ }\mu\text{gr}\cdot\text{ml}^{-1}$, Dechra Veterinary Products, Spain). Neuromuscular blockage was induced with cisatracurium ($0.5 \text{ mg}\cdot\text{kg}^{-1}$; Cisatracurio $2 \text{ mg}\cdot\text{ml}^{-1}$ EFG, Pfizer, Spain). All animals were mechanically ventilated with room air during the procedure with a tidal volume and respiratory rate suitable to maintain end-tidal CO_2 (35-45 mmHg).

An electronically driven 3-way valve connected at the entrance of the endotracheal tube was used for allowing application of a minimum of 12 obstructive apneas (25 s duration; 1 apnea each 2 min) by diverting mechanical ventilation to a ventilator test lung connected to the 3-way valve. The ewe carotid artery was exposed for measurement of maternal blood oxygenation and a caesarean section was carried out to expose the umbilical vein for measuring fetal blood oxygenation. After completing the whole experimental procedure, which lasted ≈ 90 min per ewe, the animals were immediately euthanized with an overdose of intravenous sodium pentobarbital ($150 \text{ mg}\cdot\text{kg}^{-1}$, Dolethal; Vtoquinol, Madrid, Spain).

To measure blood PO_2 at the input (maternal artery) and output (umbilical vein) of the placental system, we used fiber-optic O_2 sensors similar to those previously employed to measure real-time in vivo blood PO_2 (26). Two identical 0.5 mm-diameter needles incorporating a retractable, miniaturized ($\sim 50 \text{ }\mu\text{m}$ tip diameter; nominal accuracy: $\pm 0.2\%\text{O}_2$ at $20\%\text{O}_2$) and fast (nominal response time in liquid $< 2 \text{ s}$) sensor (OXR50, PyroScience, Aachen, Germany) were introduced into the blood vessels. PO_2 signals from both oxygen sensors were recorded simultaneously by a dual oxygen meter (FireStingO2, PyroScience, Aachen, Germany) and digitally stored for subsequent analysis. This meter also carried out automatic temperature compensation by using the reference signal from a shielded submersible temperature sensor (TSUB36, PyroScience, Aachen, Germany) placed into the ewe's esophagus. Immediately before and after use in each animal, the calibration and response time of both oxygen sensors was checked by subsequent fast submersion into water at room air equilibrium ($21\% \text{ O}_2$) and into an anoxic solution of 0.1 M sodium ascorbate and NaOH ($0\% \text{ O}_2$). In each experiment, the mean of maximum, minimum and

oxygen swings from at least 4 of the last apneic events in each ewe were computed. The data are presented as mean $\pm$ SE and the differences in these variables were compared by paired t-tests. Differences were considered statistically significant when p values were <0.05 .

The oxygen dissociation curves for fetal and adult ovine blood were used to determine the oxygen saturation (SaO₂) corresponding to each measured value of PO₂ in the umbilical vein of the fetus and in the ewe carotid artery. To this end, we used the relationship $\log(\text{PO}_2) = K_1 - K_2 \cdot \text{pH} + K_3 \cdot \log(\text{SaO}_2 / (100 - \text{SaO}_2))$ with $K_1 = 4.522$, $K_2 = 0.404$, $K_3 = 0.362$ for the adult sheep blood and $K_1 = 4.849$, $K_2 = 0.492$, $K_3 = 0.384$ for the fetal sheep blood, corresponding to 38 °C (47), for pH=7.4.

RESULTS

Obstructive apneic events imposed to the pregnant ewe for 25 s induced reductions in blood oxygenation in the mother and in the fetus as indicated by PO_2 levels measured in the maternal artery blood and in the umbilical vein, respectively (Figure 2). Figure 3A shows the mean ($\pm$ SE) of baseline and nadir PO_2 values in maternal and fetal blood. In both instances, the changes observed in PO_2 values during the imposed obstructive apneic events were significant (paired t-test; $p < 0.05$). As shown in Figure 3B, maternal PO_2 values swing amplitudes were considerably and significantly smaller in the fetus: from 21.0 mmHg to 3.1 mmHg, respectively ($p < 0.05$).

Figure 4 shows how the swings in blood PO_2 during obstructive apneas translate into swings in SaO_2 . The dissociation curves of oxygen in adult (black) and fetal (red) ovine blood illustrate the well-known higher fetal blood affinity for oxygen. Vertical dashed lines indicate the range of PO_2 values measured during imposed apnea events (from Figure 3A) in the maternal (black) and fetal (red) blood and horizontal dashed lines correspond to the ranges of SaO_2 in both sets. As expected from the monotonous increase in PO_2 - SO_2 relationship and despite the known differences in slopes, swings in oxyhemoglobin saturation were clearly smaller in the fetus when compared to the mother (8.5% vs 14.0%).

DISCUSSION

This study confirms the hypothesis that the placenta behaves as an oxygen transfer system that dampens the amplitude of blood hypoxia-reoxygenation events caused by obstructive apneas mimicking gestational OSA. As a result, oxygen swings in the umbilical vein are considerably smaller than concomitant changes in maternal arterial blood.

The present study was carried out in a sheep model rather than the most commonly used rodent models which have previously explored the effects of maternal OSA on the fetus and offspring (3,13,35,37,40). A minor, but certainly not negligible advantage of the ovine model is that the size of both mother and fetus (usually single-gestation) are very close to those in humans, thereby facilitating local measurements and tissue biopsy at different fetal organs and most importantly, allowing for implantation of telemetric sensors to monitor physiological signals in the developing fetus subjected to maternal OSA from mid to late gestation. Notwithstanding, the most important advantage of the ovine model is the fact that the preponderance of data and conclusions derived from the pregnant sheep is immediately applicable to human placental physiology (4,12,49), in particular when studying how different interventions in the mother alter fetal oxygenation (27,30,43,53,60,68). Besides the widely accepted suitability of the sheep gestation model, the structures of the human and sheep placentas (Figure 1) present differences that could impact on the dynamics of oxygen transfer during the fast, intermittent hypoxic events caused by apneas mimicking OSA. One main difference is in the number of layers in the barrier separating fetal and maternal blood. Whereas the human placenta is hemomonochorial -only one layer of syncytiotrophoblasts separates the maternal blood space from the fetal capillaries-, the sheep placenta is epitheliochorial -one layer of uterine

epithelium cells and one layer of trophoblast cells separate maternal and fetal capillaries- (21). Thus, the thicker placenta barrier in the sheep could result in more buffering or blunting of the dynamics of oxygen transfer from mother to fetus. By contrast, another main structural difference, specifically concerning the villous structure could attenuate oxygen swings in the human discoid placenta as compared to sheep placenta. Such difference is not in the fetal villous tree since in both species there are stem, intermediate and terminal villi which consist of stem arteries and veins, intermediate arterioles and venules, and terminal capillaries (4). The main difference is that in the sheep placenta maternal villi interdigitate fetal villi, whereas in the human placenta there are no villi but an intervillous space (Figure 1). Therefore, potential differences in the values of oxygen swing attenuation through the placenta in sheep and humans cannot be ruled out.

A valve placed at the entrance of the ewe airway was used to realistically mimic the events of upper airway collapse that characterize OSA. A 25-s valve occlusion elicited hypoxia and reoxygenation with timing characteristics similar to those recorded in OSA patients (44). However, it could be possible that different amplitudes in the hypoxemic swings were induced in case that 25-s occlusions were applied chronically (as obstructions are experienced by OSA patients) instead of acutely as in this study. Mechanical ventilation was applied with room air and not with oxygen-enriched air to induce hypoxic events under the atmospheric normal conditions as occurs in OSA patients. In fact, the baseline values of PO_2 in maternal artery and umbilical vein (71.5 mmHg and 23.2 mmHg, respectively; Figure 3A) were virtually the same as those previously reported in anesthetized pregnant sheep (71). It should be mentioned, however, that our sheep were not obese, in contrast with most pregnant OSA patients in whom it has been reported that obesity modulates

umbilical cord oxygen values (58). Moreover, potential effects of anesthesia on sympathetic activity, hormones, uteroplacental blood flow and umbilical blood could not be ruled out. Although the baseline maternal PO_2 was lower than in non-anesthetized animals, we should remark that arterial PO_2 in pregnant women in the supine position is considerably lower during pregnancy (90.1 mmHg) when compared to paired postpartum control (99.2 mmHg) (70). Moreover, although a conventional baseline arterial PO_2 of ~ 100 mmHg is applicable to most humans, $\approx 7.5\%$ of the world population (≈ 580 million people) inhabits areas at an altitude higher than 1,400 m (16) presenting a baseline arterial PO_2 below 80 mmHg (20). Interestingly, the prevalence and severity of sleep disordered breathing is substantially higher in highlanders compared with lowlanders (55). However, the most relevant variable for the present study, which focused on the short-time dynamics of placental oxygen transmission, was realistic, since the maternal arterial swings produced in our model (21.0 mmHg, Figure 3) were similar to the ones observed in pregnant women with severe OSA (24).

The main blood oxygenation variable measured in this study was PO_2 since, according to Fick's law, this is the primary variable determining oxygen transfer by diffusion through the placental barrier. Moreover, PO_2 can currently be directly measured in real time by fast-response fiber-optical sensors which do not require that blood is pulsating for properly functioning. Hence, PO_2 measurements were preferred despite the fact that SaO_2 is the variable used to non-invasively monitor hypoxemia in OSA patients in a clinical setting. Indeed, whereas arterial SaO_2 in the ewe could be measured by pulse oximetry, this technique could not be used for real time measuring oxygenation in the umbilical vein since this vessel is not pulsatile, a basic and essential requirement of pulse

oximetry. However, given that blood oxygen content is mainly determined by SaO_2 since the amount of dissolved oxygen transported by blood is very low as compared with the oxygen carried by hemoglobin, we computed the values of SaO_2 corresponding to the measured PO_2 values. To this end, we used available data describing the dissociation curves of oxygen in the maternal and fetal blood of the sheep (47) to describe the changes in SaO_2 induced by the obstructive apneas (Figure 4). This figure, derived for $T=38^\circ\text{C}$ and $\text{pH}=7$, illustrates that the higher O_2 reserve in fetal blood contributes to attenuate the transient hypoxic events effects induced by obstructive apneas. However, it should be mentioned that *in vivo* the maternal and fetal dissociation curves tend to be closer since maternal arterial blood is slightly alkalotic and hypocarbic, while fetal blood is slightly acidotic and hypercarbic, while fetal temperature is slightly higher than mother temperature (45).

The hypothesis that the placenta attenuates the amplitude of hypoxia-reoxygenation swings when oxygen is transferred from maternal to fetal blood is based on the anatomical structure of this temporary organ (Figure 1). Although oxygen transport through the placenta has been theoretically investigated with complex placental models, all studies to date have focused on the physiological conditions of steady state oxygen transport (10,14,15,62,64), and fast transient conditions in placental oxygen transfer, such as those occurring in OSA have not been addressed. Figure 5A depicts a simplified scheme of the maternal section of the human placenta (Figure 1.A) from a circulatory viewpoint. Blood flow (V') enters the system from the maternal artery, is mixed with the blood volume (V_0) of the intervillous space and leaves the placenta through the maternal vein. As PO_2 of blood in the intervillous space is higher than in the fetal blood, which circulates along the villi, and given that both blood compartments are separated by a membrane permeable to oxygen, there is a passive diffusion process of oxygen proportional to the PO_2 gradient

across the membrane (Figure 1). This process finally determines the PO_2 of blood leaving the fetal portion of the placenta through the umbilical vein. However, given that oxygen transfer in the placenta does not follow a model of concurrent vessels, but rather reflects flow in a mixed-pool model (Figure 5A) (6), there is no full equilibration of the PO_2 between maternal and fetal blood. In fact, in both human and ovine pregnancy there is an almost constant baseline shift, with PO_2 in the umbilical vein registering 10-20 mmHg lower than in the uterine vein (6,32) despite their different models (pool vs. concurrent vessels). Whereas PO_2 closely equilibrates at the "end capillary" of the placenta, measured differences in venous PO_2 reflect vascular shunts, perfusion-perfusion inequalities, and placental O_2 consumption, which are factors present in both the pool and concurrent models (32,45). Therefore, although oxygen transfer across the placenta is mainly determined by maternal arterial PO_2 , any reduction in maternal arterial PO_2 is always translated into a smaller decrease in umbilical vein PO_2 (8).

Another phenomenon that could reduce the amplitude of oxygenation swings across the human placenta is illustrated in Figure 5.B. In the event of a transient decrease in maternal arterial PO_2 (for instance caused by an obstructive apnea), PO_2 in the blood within the intervillous space will not change immediately, since there is a mixing process between the entering blood (V') and the blood (V_0) in the intervillous space. In fact, simply as a result of mixing, if maternal PO_2 experiences a decreasing step, PO_2 in the intervillous space would decrease exponentially with a time constant $\tau = V_0/V'$ (Figure 5B). For the sake of simplicity this mixing model neglects the amount of oxygen flowing to fetal blood. Another limitation of this simplified model is that the washout time may not exactly reflect the effective intervillous transit time for gas exchange at the villous interface, since blood

321 flow within the intervillous space is heterogeneous and includes both fast and slow
 322 components. Despite the model limitations, it can be assumed that the intervillous space
 323 behaves as a first order dampening system effectively slowing the changes in PO₂ in
 324 maternal arterial blood. For the human placenta, τ can be estimated from published data for
 325 V' and V_0 . De-Paula *et al.* (23) reported that near term of gestation the volume of maternal
 326 blood in the placenta is 428-644 ml (50%-90% percentile). Taking into account that the
 327 intervillous space is $\approx 56\%$ of the placental volume (7), and that the fraction of uterine
 328 artery that flows to the intervillous space is $\approx 450 \text{ ml} \cdot \text{min}^{-1}$ (5,63), it can be estimated that τ
 329 $\approx 30\text{-}50 \text{ s}$. Interestingly, these τ values from data near gestation term should not be different
 330 at mid-gestation since, according to de-Paula *et al.* (23) and Browne *et al.* (8), V' and V_0
 331 change in a similar proportion (by 2-2.5 fold) from gestation week 20 to term. Given that
 332 this time constant τ is similar or even longer than the rate of change of PO₂ in maternal
 333 arterial blood during obstructive apneas, its dampening effect in PO₂ swings must be
 334 considerable. Indeed, Figure 5.C shows one of the recordings of arterial PO₂ in an ewe
 335 during obstructive apneas mimicking OSA -which could be an example of the ones
 336 experienced by pregnant OSA patients (24)- and the result of applying a first order filter
 337 with τ of 30 s and 50 s to estimate the time course of PO₂ at the intervillous space. To this
 338 end, and following a conventional discrete-time realization of a first order filter, the output
 339 signal at time-point i (y_i) was computed from a combination of the input signal value at
 340 time-point i (x_i) and the previous output value (y_{i-1}) according to $y_i = \alpha \cdot x_i + (1 - \alpha) \cdot y_{i-1}$,
 341 where $\alpha = \Delta/(\tau + \Delta)$, being Δ the data sampling time interval and τ the filter time constant
 342 (V_0/V'). The original swing amplitude of 30 mmHg is considerably reduced to 13 mmHg
 343 and 9 mmHg, respectively (Figure 5.C). Given that intervillous PO₂ is the main driver of

oxygen transfer across the human placenta, the swing attenuation induced by τ must contribute to reduce the swings in fetal blood oxygenation within the umbilical vein.

It should be mentioned, that this study was focused on measuring and comparing the real time measurements of umbilical venous and maternal arterial PO₂ to document the attenuations occurring in the fetus during apneas simulating OSA, and that studying the complex different mechanisms determining oxygen dynamics in the placenta and the fetus —explained in detail by Longo (45) and more recently reviewed by Carter (12) — was beyond the scope of the present study. This experimental work in a sheep model has several limitations, some of which have already been discussed, and these limitations must be considered when trying to translate the results to pregnant women with sleep apnea. Besides the obvious differences between human and sheep physiology in pregnancy, we should point out that apneas were applied acutely and not chronically, and the potential effects of apneas of different duration was not explored. Fetal variables such as temperature, heart rate and arterial pressure were not measured. In addition, the transit times used in the simplified simulation were estimated rather than measured. Moreover, blood oxygen content was not measured but estimated from measured PO₂ values. Notwithstanding its limitations, this study highlights a relevant question on the potential impact of direct intermittent hypoxia on the fetus in gestational OSA. On the one hand, since the severity of hypoxemic swings is attenuated in the fetus, it could be anticipated that hypoxia-reoxygenation, and thus the oxidative stress induced in the various fetal organs and tissues would be lower than those experienced by adult tissues (1). Whereas this hypothesis seems plausible, we do not know how sensitive the fetus is to transient hypoxemic insults. It is well known that beyond maternal-fetal adaptation mechanisms for chronic hypoxia

such as living at high altitude (12), the fetus has adaptive mechanisms to tolerate acute hypoxia, such as that originating from umbilical cord compression (12,30). For instance, during acute hypoxia the fetus can counter a 50% reduction in oxygen delivery by increasing fractional extraction (12). However, these mechanisms have been observed during events lasting from several minutes to hours, a period much longer than those associated with transient OSA events. Whether such fetal protective mechanisms are activated and effective during much shorter hypoxemic events is unknown. It is also possible that the sensitivity and tolerance of fetal tissues to very short intermittent hypoxia, which has so far not been studied, is different than in adults (56). Moreover, the impact of intermittent hypoxemia, even of low amplitude, could be different in the fetus and in adults, since fetal mechanisms to regulate the distribution of blood flow among organs is markedly different from adults (11,12,30,31). These potential differences could modulate the epigenetic changes observed in the offspring following gestational intermittent hypoxia (18,19,39,40).

In conclusion, this study reveals that the oxygenated blood perfusing fetal tissues experiences attenuated hypoxic swings than those registered in maternal blood during obstructive apneas similar to the ones occurring in pregnant OSA patients, and highlights the importance of furthering our understanding on how obstructive apneas modulate the response of the fetal cardiovascular system and how relevant are the resulting hypoxia-reoxygenation events in fetal tissues. This information will be useful to better characterize the impact of gestational intermittent hypoxia in fetus development, and to clarify the mechanisms underlying the effects of intermittent hypoxia during gestation on long-term and transgenerational alterations in the offspring.

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596

FIGURE LEGENDS

Figure 1. (A). Schematic representation of blood flow through the placenta and surrounding tissues. Blue and red arrows show the flow directions of oxygenated (red) and deoxygenated (blue) fetal blood through the placental vasculature. Dashed white arrows show idealized flow lines through intervillous space for maternal blood. Relative oxygenation states shown by the red to blue color gradient. Maternal septa divide vascular spaces into the placental cotyledons. Reproduced from reference (67) under the terms of the Creative Commons Attribution License. (B) Schematic diagram of placental vascular circuit in higher ruminants (sheep and cow). The yellow and gray areas represent the fetus and mother membranes, respectively; the localized areas of formation of the feto-maternal villous units, the placentomes, are indicated (left). The maternal (red) and fetal (blue) vessels are schematized. Detailed scheme of a bovine placentome (right) showing that the placental fetal villi are intimately enmeshed with preformed maternal endometrial crypts. Of note, the placentome organization in the cow and sheep is identical, except that on the fetal side it is convex in the cow and concave in the sheep. Reproduced from reference (17) with permission granted.

Figure 2. Illustrative example of oxygen partial pressure (PO_2) measured in maternal artery blood and in the umbilical venous fetal blood during application of an obstructive apnea mimicking OSA in a pregnant ewe.

Figure 3. (A) Mean ($\pm$ SE; $n=4$) of baseline and nadir of oxygen partial pressure (PO_2) measured in maternal and fetal blood during application of obstructive apneas mimicking OSA. (B) Corresponding PO_2 swings in the maternal and fetal blood. *: $p<0.05$.

Figure 4. Dissociation curves of oxygen in adult (black) and fetal (red) ovine blood derived for $T=38\text{ }^{\circ}\text{C}$ and $\text{pH}=7$. Dashed lines indicate how the swings in oxygen partial pressure (PO_2) experienced by both types of circulation during obstructive apneas (Figure 3) translate into swings in oxygen saturation. *In vivo*, these two curves tend to be closer because of the differences of fetal and maternal pH and temperature. See text for further details.

Figure 5. Simplified model of blood hypoxia-reoxygenation dampening in the human placenta. (A). Diagram of the maternal section of the human placenta from a circulatory viewpoint. V' is blood flow entering the intervillous space and V_0 is intervillous space volume. Oxygen diffuses from maternal to fetal blood across the villous membrane (dotted line). (B) In case of a sudden reduction in the oxygen partial pressure (PO_2) of the maternal artery blood, PO_2 in the intervillous space blood decreases exponentially with a time constant $\tau = V_0/V'$. (C) Black line: example of arterial blood PO_2 recorded in an ewe during obstructive apneas. Blue and red lines: result of filtering the original (black) signal with a first order system with a time constant τ of 30 s and 50 s, respectively. See text for detailed explanations.

(A)

(B)