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Editorial

Pregnancy at high altitude

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INTRODUCTION

An estimated 140 million people world-wide are permanent residents at altitudes greater than 2500 m, making the hypobaric hypoxia of pregnancy at high altitude the most common cause for maternofetal hypoxia[1]. Babies born at high altitude are known to be small, and the degree of smallness is inversely correlated with the number of generations of ancestors of high-altitude residence. Accordingly, women in populations with high-altitude ancestry, such as the Aymaras or Quechuas in South America and Tibetans, give birth to heavier babies than women from European ancestry in South America or Han women in China living at high altitude[2]. Jensen and Moore[3] have shown that in Colorado altitude acts as an independent factor in determining birth weight, with a reduction in birth weight of 100 g per 1000 m elevation gain. The low birth weight at high altitude is not due to the lower socioeconomic status[4,5]; the question is whether it reflects hypoxia-induced intrauterine growth restriction or genetic adaptation. The latter implies a strong fetomaternal interaction involving adaptation to hypoxia on several levels, and the importance of the interaction between the mother and the fetus is stressed by the fact that better maternal ventilatory response to hypoxic stress at high altitude correlates positively with birth weight[6].

People living at altitudes of 4000 m and above have an arterial partial pressure of oxygen of 50 mmHg and an arterial oxygen saturation of just above 80%[7]. Populations that have been living in high-altitude regions for many generations, such as Quechuas and Tibetans, have been studied extensively and they display a number of functional and structural adaptations allowing them to at least partially circumvent the main metabolic problem they are facing: to maintain an acceptably high scope for sustained aerobic metabolism despite reduced availability of oxygen in the inspired air. Aerobic capacity, which reflects maximum work performance, has been used as a measure of functional adaptation to high altitude because it reflects the success of the individual's biological oxygen transport system. In non-pregnant subjects, maximum oxygen uptake values at altitudes of around 4200 m are reduced only modestly, to 89–95% of normoxic values[8].

FETAL GROWTH RESTRICTION OR PHYSIOLOGICAL ADAPTATION

Fifty years ago, low birth weight used to be interpreted as prematurity, and therefore the incidence of preterm delivery was thought to be higher at high altitude than at sea level[9]. It was then proved that the length of gestation is similar at high altitude compared with at sea level[10] and therefore intrauterine growth must be impaired at high altitude. This has changed the paradigm that low birth weight is necessarily due to prematurity.

The obvious question was, from what stage of pregnancy does the difference in size become statistically significant? We have performed fetal biometry and Doppler measurements by ultrasound for the first time in a Peruvian population that has been living at an altitude of over 4000 m for at least three generations[4]. In this population, all fetal biometry measurements follow a lower trajectory than in an ethnically similar population in Lima, which is at sea level, and, when gestational bands were compared, a significant difference in size

was present from 25–29 weeks onwards. The measurements at high altitude were normally distributed and were not skewed towards smaller measurements.

The fetus at sea level experiences a degree of hypoxemia, which is similar to that in adults at 4000–5000 m altitude, with an umbilical venous partial pressure of oxygen (pO_2) of about 50 mmHg[11]. Even so, there is indirect evidence that the fetus at high altitude is more hypoxic than that at sea level; cord blood samples taken after delivery in a Bolivian population living at 3600 m have a higher hematocrit and fetal hemoglobin level compared with those taken in Santa Cruz (400 m)[12].

Doppler measurements of the fetal arterial circulation performed at 4300 m in our study population have shown that there is no arterial redistribution[13] as there would be in intrauterine growth restriction due to placental insufficiency at sea level[14]. However, blood flow velocities in all vessels studied were lower at high altitude compared with those at sea level. This effect was particularly evident in the umbilical artery flow. The most likely explanation for this is the higher fetal blood viscosity due to the higher hematocrit[12]. At low shear rates (such as in venules and small veins) red cell aggregation occurs; the placental circulation has low-pressure gradients and low shear rate, being thus potentially more vulnerable in situations of increased hematocrit[15].

Moore *et al.*[16] reported an increased prevalence of intrauterine growth restriction and hypertensive disorders in pregnancy in high-altitude residents in Colorado. This may be an appropriate interpretation for a population with short-term acclimatization to high altitude. In contrast, the neonatal and infant mortality rates in low birth-weight infants in high altitude populations have been shown to be lower compared with those in low-altitude populations both in Peru[17] and in Mexico[18]. Our data also suggest that the low birth weight in a population that has been living at high altitude for many generations is due to physiological adaptation rather than to a higher number of pathologically growth-restricted babies. Therefore, it is appropriate to use altitude-specific ultrasound biometry charts to assess fetal size at high altitude after 25 weeks' gestation in order to avoid the overdiagnosis of intrauterine growth restriction.

What are the mechanisms that constrain fetal growth at altitude? There is no doubt that maternal hypoxia predisposes to small fetal size. In humans at high altitude, maternal arterial oxygenation[19] and ventilatory response to additional acute hypoxic stress are correlated with birth weight[6]. The growth restriction may be mediated by hypoxia-induced up-regulation of insulin-like growth factor binding proteins (IGFBPs)[20] and by a limitation of maternal fuels, in particular glucose, which have an impact on fetal growth[21].

DOES THE SYSTEM FAIL TO GET ENOUGH OXYGEN TO THE BABY?

In high-altitude native people, the shortfall in the pO_2 of ambient air is compensated for by a much less steep oxygen cascade. This means that the oxygen gradients are much smaller between the different compartments transporting oxygen from the inspired air to the tissue. Thus, although the pO_2 in the ambient air at high altitude is much less than that at sea level, the final pO_2 achieved in the mixed venous blood of subjects at high altitude is not greatly diminished[7].

In pregnancy, maternal adaptation is targeted towards increasing blood flow, nutrient and oxygen transport to the uterus. At sea level, from the early stages of gestation, oxygen intake increases because of a higher respiratory rate and a larger tidal volume and throughout gestation maternal arterial pO_2 increases and pCO_2 deceases. Blood volume and cardiac output increase, although the overall oxygen carrying capacity decreases due to hemodilution[22].

Similar changes in the respiratory response are seen during pregnancy at high altitude. The difference is that at an altitude of 4300 m, the atmospheric oxygen pressure is only half of that at sea level. Despite a higher tidal volume and minute ventilation, pregnant women start off with almost 50% lower arterial pO_2 and pCO_2 values, and the increase in pO_2 is not as marked as that at sea level[23]. Hypoxia is known to induce the erythropoietin gene[24] and, owing to the higher hemoglobin levels, the arterial oxygen content is actually higher at high altitude than it is at sea level[23]. High hemoglobin concentrations increase the oxygen transport capacity, but also the blood viscosity[25]. There is some concern that high blood viscosity impairs tissue perfusion at the capillary level. In pregnancies at sea level, increased hematocrit[26] and increased blood viscosity[27] are associated with complications such as intrauterine growth restriction and pre-eclampsia, which is in agreement with the hypothesis that higher blood viscosity is a risk factor for suboptimal perfusion of the placenta. In addition, the increased blood viscosity at high altitude will increase the peripheral resistance and may therefore be the cause of the lower baseline flow in the maternal brachial artery[28] and of the reduced cardiac output (N. Kametas, personal communication) which again reduces oxygen transport to the tissue. Overall, the hypoxia-induced maternal ventilatory and circulatory changes may well be at a limit, where the balance between beneficial and unfavorable components is tilted towards reduced oxygen delivery to the baby.

THE PLACENTA DOES ITS BEST

Maternal hypoxemic hypoxia results in intervillus blood hypoxia. At high altitudes the placenta is larger and the compensatory morphological changes in placental villi include increased branching of the capillaries[29] with a decreased diffusion distance and alterations in villus capillary diameter, although there is some disagreement as to whether villus capillary diameter increases or decreases in this situation[30–35]. Our group[36] has also studied morphological features in term pregnancies and has demonstrated that the difference between placental terminal villi from term pregnancies at high altitude compared to those at sea level is primarily related to maternal pO_2. At high altitude, in agreement with most previous studies, we observed a trend towards an increasing number of capillary cross-sections per villus cross-section, but the predominant morphological alteration was an increase in villus capillary diameter and therefore in the

proportion of villus cross-sectional area occupied by capillary lumens[36]. A common response to chronic hypoxia is neovascularization, with a predominant increase in number, rather than size, of tissue capillaries[37]. It is therefore possible that the placental response to maternal hypoxia observed at high altitude may not simply be mediated by the local release of angiogenic growth factors, but may be secondary to an adaptive increase in blood flow to the placenta.

In accordance with these findings, Doppler assessment of the uterine arteries showed lower uteroplacental impedance at high altitude than at sea level[38]. This may reflect a compensatory mechanism of uteroplacental development to lower oxygen tension associated with high altitude. Doppler ultrasound velocimetry of the uterine arteries has been used at sea level to assess impedance to blood flow in the uteroplacental circulation[39] and to predict adverse pregnancy outcome, such as pre-eclampsia and intrauterine growth restriction[40,41]. Prior to pregnancy, and in early gestation, uterine artery Doppler waveforms are characterized by high impedance and early diastolic notching. These Doppler waveforms evolve throughout the second trimester into a lower impedance flow with a loss of uterine artery notching. This is brought about by trophoblast invasion of the muscular spiral arteries during the first and second trimesters of pregnancy, which leads to a loss of reactive musculoelastic vascular tissue in the uteroplacental arteries, converting them into dilated, tortuous channels. Inadequate trophoblast invasion is associated with high-impedance uteroplacental flow and with intrauterine growth restriction and pre-eclampsia[42]. Our finding of lower impedance to flow at high altitude suggests that the smallness of such fetuses is not due to impaired placentation; on the contrary, trophoblast invasion may be improved and may be part of the compensatory mechanism to optimize oxygen transport to the fetus. The factors mediating this potentially include locally derived vasoactive factors that may have an effect on spiral artery dilatation, thus modulating impedance. Nitric oxide has potent smooth muscle relaxant properties and is responsible for both arterial and venous dilatation. Endothelial nitric oxide synthase transcription in cytotrophoblastic cell lines is elevated at low oxygen tension[43]. Indeed, this hypothesis is strengthened by animal studies which demonstrate higher levels of plasma nitrate, a stable metabolite of nitric oxide, in pregnant ewes maintained at an altitude of 3800 m throughout their pregnancy compared to the sea-level controls[44].

Reduced uterine artery volume flow measured by Doppler ultrasound has been reported in the third trimester of pregnancy at high altitude. In a study of five women living at an altitude of 3100 m in Colorado for more than 4 years, compared with seven controls resident at 1600 m, uterine artery velocity was found to be higher, whereas vessel diameters were smaller[45]. This is a potentially interesting finding, but volume flow does not necessarily correlate with impedance to blood flow, which we found to be similar at high altitude and sea level in the second half of pregnancy. Volume flow methodology using sonography is prone to error[46]. In particular the small vessel diameters are difficult to measure and affect the volume flow calculation to the power of 2.

GROWTH FACTORS

At sea level, hypoxia at the maternal–fetal interface in intrauterine growth restriction and pre-eclampsia is associated with higher maternal serum concentrations of IGFBP-1, and *in vitro* studies[47] show that an excess of IGFBP-1 has the potential to inhibit trophoblast invasion. However, in our study population[48], there was no significant difference in IGFBP-1 before 25 weeks of pregnancy between pregnant women living under hypobaric hypoxia at high altitude and those living at sea level. Similar to our findings of improved uterine artery flow, this makes it unlikely that, inadequate trophoblast invasion and placental insufficiency cause the reduced fetal growth at high altitude.

In the second half of pregnancy, maternal serum IGFBP-1 concentrations are increased at high altitude. This may be due to the increase in maternal and fetal demands. Low atmospheric oxygen with resulting maternal systemic hypoxemic hypoxia may cause placental hypoxia, which stimulates increased production of IGFBP-1. This in turn restricts the IGF-mediated fetal growth as an adaptive mechanism to prevent worsening of the fetoplacental hypoxia[48].

FOOD FOR THE FETUS

The most important maternal fuel for the growth of the fetus is glucose. Glucose crosses the placenta by facilitated diffusion, which results in a high correlation between fetal and maternal plasma glucose concentrations[49]. The frequently seen clinical example is maternal hyperglycemia associated with fetal macrosomia[50]. The opposite is also true: in fetal growth restriction, maternal plasma glucose is decreased[51]. During normal pregnancy, the increased insulin resistance leads to lower fasting insulin concentrations, but to a substantial postprandial increase in glucose and insulin, particularly in the second half of pregnancy[52]. These higher maternal postprandial glucose levels render more of the ingested glucose available to the fetus.

At high altitude in non-pregnant native women, fasting plasma glucose is decreased[53]. We found that in pregnancy, fasting concentrations of glucose are even lower than in non-pregnant controls, and therefore are considerably lower than those at sea level. This is associated with lower fasting concentrations of insulin and higher insulin sensitivity, whereas C-peptide concentrations and β-cell function remain the same. The body mass index or socioeconomic status, as assessed by the level of education, could not explain these differences[54]. They are therefore unlikely to reflect differences in nutrition or levels of activity between the two groups. The cause of this increased glucose uptake by the maternal tissue in the absence of higher insulin concentrations may be due to an insulin-independent increase in glucose utilization. It is recognized that any given exercise task at high altitude is accomplished at a relatively greater effort than it is at sea level and it is thus conceivable that pregnancy has greater energy requirements at high altitude than at sea level. Because of the lower maximum aerobic capacity at high altitude the relative increase in metabolic rate during pregnancy may be greater than that at sea level. Therefore, carbohydrate

oxidation would be the preferred metabolic pathway for aerobic exercise because it provides the highest ATP yield per mole oxygen[8].

There is an association between birth weight and maternal glucose metabolism at sea level, where a negative correlation between insulin sensitivity and birth weight has been described[55]. Therefore, the low maternal fasting plasma glucose associated with high peripheral insulin sensitivity at high altitude may partly explain the lower birth weights at high altitude.

CONCLUSION

The hypobaric hypoxia of pregnancy at high altitude is a complex situation, which makes it obvious that mother and fetus interact on many levels. Maternal adaptation includes changes in ventilation, oxygen transport capacity and cardiovascular function. The placental function is optimized, with improved trophoblast invasion and reduced oxygen diffusion distances. This still results in reduced oxygen delivery to the fetus, but the fetus does not show signs of severe hypoxia or acidemia. Maternal metabolism appears to 'instruct' the fetus to constrain its growth in order to cope with the limited oxygen availability.

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