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How hypoxia slows fetal growth: Insights from high altitude

Lorna G. Moore, Ph.D. [Professor]

Department of Obstetrics and Gynecology, University of Colorado Denver School of Medicine, MS 8613, 12700 E 19th Avenue, Room 3004, Aurora, CO 80045 USA

Abstract

A continuous oxygen supply is vital for fueling fetal growth, yet we know surprisingly little as to the precise mechanisms by which hypoxia reduces fetal growth. Animal models, while important, are limited by the enormous variability in mammalian physiologic responses to pregnancy. One of the earliest models for understanding hypoxia-induced reductions in fetal growth came from studies at high altitude that showed high altitude to have one of the strongest depressant effects on fetal growth. But all populations are not equally affected. Dolma et al., have added valuable information now showing that that Ladakhis, like Tibetans and Andeans, have a lower-than-expected frequency of small-for-gestational age (SGA) infants. Consistent with previous reports, these authors also found that uterine artery diameters at mid pregnancy (week 26–28) were larger in women giving birth to appropriate-for-gestational-age (AGA) than SGA infants at high but, interestingly, not at low altitude. Much remains to be learned about the physiologic pathways by which hypoxia impairs fetal growth. The variability among high-altitude populations and increasing sophistication of tools for investigating causal mechanisms have the potential to expand our presently limited means for identifying new treatments for hypoxia-related complications of pregnancy and fetal life.

Together with their Indian colleagues, this University College London team headed by Hugh Montgomery and Sara Hillman have added valuable information for persons interested in mechanisms underlying hypoxia-associated fetal growth restriction. Consistent with previous studies in multigenerational Himalayan residents, their results show that residents of high altitude (conventionally defined as >2500 m) in Leh, Ladakh (3524 m, n=316) give birth to heavier than expected babies (3.15 kg), especially when of Tibetan ancestry (3.62 kg), and correspondingly have fewer small-for-gestational age (SGA) infants than residents of Delhi (216 m, n=101) (14% *vs.* 19%, respectively). Maternal risk factors (*e.g.*, age, BMI, socioeconomic indicators) were similar in the two groups as were gestational age at delivery and baby sex, thus implicating protection from fetal growth restriction in the Ladakhi residents as the cause of the birth weight differences. Associated with such protection were greater, but still within the normal range, maternal age and BMI, and greater

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Corresponding author and mailing address: Department of Obstetrics and Gynecology, University of Colorado Denver School of Medicine, MS 8613, 12700 E 19th Avenue, Room 3004, Aurora, CO 80045 USA, Lorna.Moore@cuanschutz.edu, Phone number: 303-724-7474.

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uterine artery diameter at weeks 26–28. Interestingly, while similar relationships with birth weight were seen for maternal age and BMI at low altitude, there were no differences in uterine artery diameter between the mothers of SGA *vs.* AGA infants at high altitude.

Birth weights have long been observed to fall at high altitude, decreasing on average 100 gm per 1000 m altitude gain[1]. The effect of high altitude is independent of other known risk factors (*e.g.*, maternal age, weight gain, access to prenatal care, smoking) and has the greatest effect on birth weight next to gestational age. While the consensus is that reduced oxygen availability ("hypoxia") rather than some other attribute of the high-altitude environment is responsible, the precise mechanisms by which hypoxia slows fetal growth remain unknown. Nor are all women or populations are equally affected. As noted in the present report, multigenerational high-altitude residents are protected relative to women of low-altitude, European, Han, or as now shown here, Indo-Aryan ancestry. This protective effect is seen even when the persons of low-altitude ancestry were themselves born and raised at high altitude, thereby implicating genetic rather than developmental factors[2]. Ladakhi's, like Tibetans, are descended from Mongolian populations but also have ancestral roots among the Dards, a group living in the Hindu Kush mountains of northern Pakistan. The women in the present report had more than 5 generations of high-altitude residence but perhaps less than the >15,000-to-25,000-year duration estimated for Andeans or Tibetans, respectively. If so, the comparatively short time frame (in evolutionary terms) would be consistent with the likelihood that uterine vascular responses to pregnancy were subject to strong selective pressure and/or involved relatively few genes.

These authors' observation of lower uterine artery diameters at weeks 26–28 in high-altitude residents giving birth to SGA *vs.* AGA babies is consistent with reports of less pregnancy-associated increase in uterine artery diameter or blood flow at week 20–36 in 3100 *vs.* 1600 m Colorado women of European ancestry, and greater uterine artery diameters and blood flow in multigenerational Andean or Tibetan residents of ~3600 m than in women of European or Han ancestry, respectively, living at the same altitude[3–5]. Dolma et al.'s observation that such differences in uterine artery diameter at week 26–28 is important because this is before growth begins to measurably slow at high altitude[6] and, in turn, suggests that greater blood flow enables the maintenance of normal fetal growth under conditions of hypoxia. But exactly how hypoxia acts to slow fetal growth remains unclear. Experimental animal and isolated human myometrial artery vasoreactivity studies indicate that hypoxia, whether due to altitude or the pregnancy complications of fetal growth restriction or preeclampsia[7], impairs normal maternal uterine vasodilator and/or growth responses to pregnancy. Pregnancy profoundly vasodilates the entire maternal systemic (and pulmonary) circulation but has even greater vasodilator effects in the utero-placental vasculature, which thereby directs the majority of the ~30% rise in cardiac output to that vascular bed by term. Uterine vasodilation is due to trophoblast remodeling of the end (spiral) arteries but also to upstream effects as demonstrated by the enhanced vasodilator response and/or marked growth seen during pregnancy in uterine, arcuate, basal, and myometrial arteries[8,9].

As remarked by the authors, the availability of multiple populations with and without genetic adaptations to high altitude makes high altitude a unique natural laboratory for

investigating hypoxia-associated fetal as well as maternal complications of pregnancy. There are presently no treatments for such disorders, apart from early delivery which is costly and can itself have unfavorable effects. As noted, promising results have been reported by our group using adenosine monophosphate kinase (AMPK) or peroxisome proliferator-activated receptor gamma activators *in vitro* in resistance-sized human uterine vessels and *in vivo* in experimental animals. Noteworthy was that the enhanced vasodilation in response to AMPK activation was selective for the maternal uteroplacental circulation, unlike the body-wide vasodilation seen using sildenafil whose clinical trial as a preeclampsia therapy was stopped due to adverse fetal effects[10,11].

Additional studies are needed for identifying the ways in which uterine blood flow can be raised selectively as well as for defining the mechanisms by which hypoxia influences fetal growth. Future studies at high altitudes can be valuable given that the increased frequency of fetal growth restriction (and preeclampsia, another pregnancy disorder associated with uteroplacental ischemia) reduces the number needed to treat[12] but also because most high-altitude residents live in low- to middle-income countries where 98–99% of maternal and perinatal deaths occur[13]

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