HYPOXIA AND REPRODUCTIVE HEALTH

Reproductive challenges at high altitude: fertility, pregnancy and neonatal well-being

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Abstract

High altitude offers a natural laboratory for studying the effects of chronic hypoxia on reproductive health. Counter to early accounts, fertility (the number of livebirths) appears little affected although stillbirths are more common. Birth weights are lower due to fetal growth restriction, not shortened gestation. Multigenerational (Andean or Tibetan) compared with newcomer residents appear relatively protected from pregnancy loss as well as altitude-associated fetal growth restriction, perhaps due in part to preservation of the normal rise in uterine artery blood flow. Myometrial artery vasodilator response, a key determinant of uterine blood flow, is blunted in healthy Colorado high-altitude residents, similar to what occurs in intrauterine growth restriction or preeclampsia at low altitude. The high-altitude vessels are also more sensitive to the vasodilatory actions of AMP kinase (AMPK) activation. The gene region containing *PRKAA1* (coding for AMPK's alpha-1 catalytic subunit) has been acted upon by natural selection in Andeans and is related to preservation of normal blood flow and fetal growth at high altitude, suggesting one mechanism by which high-altitude adaptation may have been achieved. Preeclampsia is more common at high altitudes but unknown is whether multigenerational residents are protected relative to newcomers. Postnatal loss is diminished in Tibetans vs Han with equal access to health care, perhaps due in part to better maintained arterial O₂ saturation during infancy. Finally, pregnancy and intrauterine development not only affect immediate survival but also susceptibility to the later-in-life cardiovascular disease, chronic mountain sickness.

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Introduction

Studies at high altitude have long been of interest for the study of reproduction given the vital nature of O₂ supply for the conceptus and the reduction in O₂ availability at high altitudes. Reports from the Spanish Conquistadors fueled these interests with reports of the inability of imported domesticated animals or of the Spaniards themselves to reproduce, prompting successive moves of the capital from high-altitude locales to Lima at near sea level (Monge 1948). While these early accounts are subject to the uncertainties of historical reporting, they are supported by more recent observations that, even though Han populations live above 3800 m in the Tibet autonomous region, there were no deliveries to Han women over a 2-year period because, as we were told, the Han women descended to locations near sea level elsewhere in China to give birth Moore (Moore *et al.* 2001a).

Mammalian reproduction is highly complex but, as judged from the proliferation of the 19 mammalian orders following the demise of the dinosaurs approximately 65 million years ago, appears to have been highly successful. The first mammals appeared some 160 million years ago (Ji *et al.* 2002) and were placental (eutherian), rather than like the egg-laying prototherian (e.g. platypuses and spiny anteaters) and/or early-delivering metatherian (e.g. marsupials) mammals of today. Placental mammals today, and likely also in the past, require extensive maternal as well as fetoplacental adaptations given that the placenta, a product of the developing embryo/fetus, must negotiate between maternal and paternal genomes, and both mother and baby must protect themselves from immunologic rejection by the 50% genetically-related 'other'.

There are many important mechanisms by which the placenta as well as the ovaries, uterus, and fetus meet hypoxic challenges. Here I will address those facing

human populations residing at high altitude. The over 140 million persons living at high altitude, conventionally defined as >2500 m, provide an instructive natural laboratory for understanding the problems and solutions for ensuring reproductive health under conditions of chronic hypoxia. The hypoxic stress at high altitudes is due to the obligatory fall in barometric pressure with increasing elevation, which results from the diminishing weight of the atmosphere and consequently lower partial pressure of O₂ in the inspired air (Fig. 1). The 'thin air' also has the effect of increasing diurnal temperature variation, reducing humidity, and raising the level of UV radiation.

Human populations live at high altitude in four major world regions: the Rocky Mountains of North America, Andean Altiplano of South America, Himalayan Plateau of central Asia, and Ethiopian Highlands of eastern Africa. The highest year-round communities are located at ~5100 m in southern Peru/northern Bolivia, at nearly that high in Tibet, at 3100 m in North America, and 2833 m in Ethiopia.

Genome scans using gene-chip microarrays have permitted identifying gene regions acted upon by natural selection in Andean, Himalayan and East African populations. Statistical tests are then used to detect natural selection producing, for example, increased variation, decreased variation, or increased linkage disequilibrium (i.e. the nonrandom association of alleles usually due to being situated on the same chromosome). Such statistical tests derive from the observation made nearly 50 years ago that only two of the four forces driving evolution (gene flow, or the movement of genes across populations, and natural selection) have directional effects. Since gene flow affects all loci the same way, natural selection can be measured as the heterogeneity between gene loci (Lewontin & Krakauer 1973). With such scans and, more recently, whole genome sequencing, there has been an exponential rise in the number of studies of genetic adaptation to high altitude with over 300 publications appearing in the past 20 years.

Figure 1 The hypoxia of high altitudes is due to the progressive fall in barometric pressure (Pb) with increasing elevation. As a result, there is a concomitant fall in the partial pressure of O₂ (pO₂) in the atmosphere, which can also be expressed in terms of the percent of O₂ relative to that present at sea level.

The largest number of studies has been conducted in Tibetan, Sherpa and other Himalayan populations; a considerable number in Andeans and fewer but nonetheless important ones in Ethiopian highlanders. Many genetic variants or single nucleotide polymorphisms (SNPs), but by no means all or even a disproportionate number, reside in the hypoxia-inducible factor (HIF) pathway (Bigham *et al.* 2009), which is a key mechanism by which hypoxia activates more than 100 genes. Among them are some involved in the formation of blood vessels (*VEGF*, *PDGF*, *FLT*), red cell production (*EPO*), cell death (*TGFA*, *TNF*, *MMP*), inflammation (*IL6*), vasodilation or constriction (*EDN*, *NOS*, *PRKAA1*), glucose metabolism (*IGFBP*, *PRKAA1*) and others affecting the O₂ transport system (see Beall 2014, Julian 2019, Witt & Huerta-Sanchez 2019, Simonson & Malhotra 2020 for review). With the exception of a missense mutation in the *EGLN1* gene (Lorenzo *et al.* 2014), all the other gene regions identified thus far are not unique to high-altitude populations but rather present in different frequencies than seen in low altitude groups, indicating that natural selection has principally acted upon standing variation rather than new alleles resulting from mutations.

Residence at high altitude poses many adaptive challenges. These are summarized in Fig. 2 and, as can be seen, many cluster in the perinatal period. While much has been learned about the physiological responses to high altitude in long-resident populations (see Beall 2014, Moore 2017, Julian 2019, Simonson & Malhotra 2020 for review), much remains to be learned as to whether and, if so, how the selected- genes influence the ability to confront these adaptive challenges. Therefore, the plan for this article is to review prior studies addressing factors directly affecting reproduction at high altitude – fertility, pregnancy, and infant survival – and the evidence for physiological adaptation during these periods in human populations.

ADAPTIVE CHALLENGES OF HIGH ALTITUDE

Figure 2 There are multiple challenges to reproductive success at high altitude, with several clustering in the reproductive period and early postnatal life. Such effects are likely subject to natural selection given their importance for producing offspring who survive through the completion of the reproductive period. Adapted from Moore (2017).

Fertility

Fertility is generally defined as the ability to produce offspring, whereas fecundity refers to the processes involved in the production of viable sperm and eggs, fertilization, and carrying a pregnancy to term. The early Spaniard's descriptions of the inability of domesticated animals as well as human beings to successfully reproduce made it unclear as to whether it was fecundity, fertility, or neonatal/infant survival that was impaired. The nature of mammalian reproduction makes it hard to distinguish between these processes since early pregnancy loss is difficult to detect. Here fertility is used to refer to the processes affecting the ability to produce live offspring and, more specifically, as to how residence at high altitude affects the age of menarche, menopause and the production of viable eggs and sperm.

Age of menarche and menopause

Early studies of postnatal growth in Peruvian high-altitude Quechua indicated a slow and prolonged period of adolescent growth, and an approximately 1-year delay in the age of menarche (Frisancho 1970). While later studies indicated that poor nutrition was also a contributor to the slowed growth, a somewhat delayed age of menarche continues to be seen in Andean as well as Nepalese highland populations, but the age of menopause appears little affected (Crognier *et al.* 2002, Vitzthum 2013).

Ovarian and testicular function

Ovarian cycle length and the proportion of ovulatory cycles seem within the normal range in reports from the Bolivian Andes. Salivary progesterone and testosterone levels, while seasonally variable, are also within the normal range (Vitzthum 2013). Spermatogenesis is decreased following days to months of hypoxic exposure in mountaineers at extreme altitudes (Okumura *et al.* 2003), but to the best of our knowledge unknown for lifelong residents.

Conception and pregnancy rates

The age of first birth is somewhat delayed in rural or urban Bolivians in comparison with low altitude populations (Crognier *et al.* 2002). However, completed fertilities in Andean as well as Himalayan populations are either similar or greater than those of comparable low altitude groups (Vitzthum 2013). Pregnancy rates, as judged by elevated human chorionic gonadotropin levels in women seeking to conceive, also appear to be similar in high-altitude Andeans and sea-level United States of America residents (Vitzthum 2013).

Pregnancy

Historical interest

There has been a long history of studies of pregnancy at high altitude. Interest was sparked by the early fetal physiologist Joseph Barcroft, who likened the environment in which the fetus develops to 'Mt Everest in utero' (Barcroft 1946). Donald Barron and his distinguished team took this concept to the Peruvian Andes where, in sheep native to 4900 m in, they showed that 'despite a reduction of approximately one-half in the O₂ pressure gradient between the maternal and fetal bloods, the sheep fetus at altitude lives in an internal environment in which the O₂ pressure and the quantity available to it are not significantly different from that of a fetus at sea level' (Barron *et al.* 1964). Interestingly these sheep fetuses were not growth-restricted (Metcalfe *et al.* 1967).

About the same time, human high-altitude studies were being done in Colorado by Dr John Lichty, a pediatrician at the University of Colorado. He showed that in Leadville (3100 m), North America's highest city, birth weights were markedly lower than at sea level, with intermediate values being present in Denver (1600 m). Careful analysis of other factors influencing birth weight such as gestational age, maternal nutrition, Hispanic ethnicity, lead and other environmental contaminants, and obstetrical practices (e.g. induction of labor, frequency of Cesarean sections) led the authors to conclude that it was chronic hypoxia and not some other attribute of the high-altitude environment that was responsible (Lichty *et al.* 1957). Importantly this study demonstrated that the birth-weight decline was due principally to slowed fetal growth, not shortened gestation, and was thus the first to demonstrate the existence of fetal growth restriction on a population scale (Moore 2001).

Pregnancy loss

Spontaneous abortion or miscarriage is common, with about half being thought due to genetic anomalies, endocrine infections or other issues but half remains unexplained. Very low levels of pO₂ are present in the uterine environment prior to the rise in uterine artery blood flow (Jauniaux *et al.* 2006) but whether uterine pO₂ levels are affected by residence at high altitude is unknown. From 6–10 to after 10 weeks of gestation, decidual PaO₂ gradually rises and is negatively correlated with the TGFβ family proteins (i.e. inhibin, activin, VEGF, PlGF, sFlt-1 and endoglin) that are closely involved in vessel formation and placentation (Muttukrishna *et al.* 2008). Given the vital role of these proteins in establishing pregnancy, their dysregulation could contribute to early pregnancy loss. Consistent with such a possibility, VEGF and sFlt-1 levels were higher in women with vs without subsequent miscarriages

and suggested to have been the result of exaggerated hypoxia and/or compromised endothelial function (Pang *et al.* 2013).

A large study of 22,662 consecutive births in Peru found higher rates of stillbirths at high compared to low altitudes (Gonzales *et al.* 2008), but another report, based on a literature review of nine studies in indigenous Andean or Himalayan residents, showed lower levels of pregnancy loss than in United States of America sea-level populations (Vitzthum 2013). Compared to high-altitude newcomers, several lines of evidence suggest that indigenous Andean as well as Himalayan residents have lower rates of pregnancy loss. Based on the difference between the numbers of pregnancies and livebirths, we found that prenatal mortality rates were one-third lower in Tibetan than Han high-altitude residents (Moore *et al.* 2001a). Well controlled analyses in a large series of birth records in Bolivia showed a similar degree of protection in Andean compared to European high-altitude residents (Grant *et al.* 2020). A Peruvian report found that birth weights were greater (more normal) in the southern than northern highland regions, which the authors attributed to the longer altitude residence of the Aymara groups in southern Peru (Gonzales 2007) but perhaps also due to the Incan domination in the north which was achieved, in part, by moving population centers to disrupt political opposition (Monge 1948).

Pregnancy complications fetal growth restriction

As noted above, the first observation on a population scale that slowed fetal growth, as well as preterm delivery, could lower birth weight came from high altitude. Since then studies have been conducted in over 7 million babies on three continents – North America, South America and Asia – that demonstrate an approximately 100 g birth-weight reduction for every 1000 m elevation gain (Jensen & Moore 1997, Mortola *et al.* 2000, Hartinger *et al.* 2006, Bailey *et al.* 2020). While multiple factors can reduce fetal growth and most of these studies had only birth weights and gestational age estimates available (and not, e.g., fetal biometry showing progressive reductions in estimated fetal weight or Doppler indices of brain sparing), the consistency among these reports implicate a slowing of fetal growth as the primary cause.

The effect of high-altitude residence on fetal growth is strongly population dependent. Across a sea level to 3600 m altitude gradient, the greatest reductions are seen in North America (352 g), intermediate declines in South America (270 and 282 in Peru and Bolivia respectively), and the least effect in Tibetans (72 g) (Niermeyer 2001). This order approximates the differing durations of human occupation; paleontological or archeological evidence shows that there has been human occupation of the Tibetan Plateau for as long as 25,000 years and of the Andean

altiplano for ~14,000 years. There are no cities in Europe at an elevation above 2500 m so European-derived population residence at high altitude is limited to ~400 years in South America and only ~150 years in North America (Native American residents of high altitude were not considered since their occupation of high-altitude regions in the Rocky Mountains was seasonal). The duration of human residence at high altitudes in Ethiopia is unclear and, to our knowledge, no birth weight studies in relation to altitude have been conducted there.

To better assess the influence of duration of high-altitude residence on fetal growth, we considered those studies in which samples were collected by the same investigative team in residents living at ~3600 m (conveniently, the altitude at which both La Paz, Bolivia and Lhasa, Tibet Autonomous Region, China are located) and sea level, and for which ancestry was assessed by self-report, surnames, or gene markers. Shown in Fig. 3 is the mean birth weights for the 305,935 babies born to these Andean, Tibetan, European or Han women. Of interest, the average birth-weight reduction in the Andeans and Tibetans is similar, averaging 167 g, and approximately half that seen in Europeans or Han. In a follow-up study in Bolivia, we considered whether one or several generations of high-altitude residence conferred protection. Using gene markers to confirm population ancestry, lifelong or up to four generations of high-altitude residence conferred little benefit as the birth weights of babies born to such women were similar to those of newcomers, suggesting that genetic rather than developmental factors were responsible (Julian *et al.* 2011).

The rise in uterine artery blood flow during pregnancy exerts an important influence on fetal growth (Palmer *et al.* 1992, Konje *et al.* 2003). In a series of reports, we have shown that there is less pregnancy-associated rise in uterine artery blood flow at high compared to low altitude, which is due principally to a lesser increase in uterine artery diameter (Zamudio *et al.* 1995, Julian *et al.* 2008, 2009).

Figure 3 Mean birth weights are shown for infants born to multigenerational (Andean or Tibetan) mothers or shorter-term (European or Han 'Chinese') women who reside either at high (~3600 m) or low altitude (~sea level). Represented are birth weights from a total of 305,935 infants and 15 studies. Adapted from Niermeyer and Moore (2015).

The importance of uterine artery diameter is often overlooked in studies of pregnancy complications where, often, only uterine artery resistance indices are measured. Such indices are derived from systolic and end-diastolic flow velocities and while easily obtained, neither measure volumetric blood flow nor vascular resistance since, by definition, resistance is blood pressure divided by flow. Trophoblast-induced remodeling of the end spiral arterioles into dilated, flaccid vessels does indeed reduce uteroplacental vascular resistance, but changes in the more upstream vessels are also important contributors for several reasons (Clark *et al.* 2018). First, the spiral artery remodeling effectively moves the primary site of vascular resistance upstream to the myometrial arteries, which undergo remodeling and vasoreactivity that are primarily due to maternal factors, not simply trophoblast invasion. Secondly, alterations in the growth, remodeling and/or vasoreactivity of the uterine and other upstream arteries begin prior to the completion of trophoblast invasion, and are responsible for the major portion of the uterine artery blood flow rise up to week 16 (Dickey & Hower 1995, Osol & Moore 2014).

Given the importance of myometrial arteries for the determination of uteroplacental vascular resistance, Dr Ramón Lorca from our group has performed myometrial artery vasoreactivity studies in vessels isolated from biopsies obtained at unlabored cesarean section from Colorado low- and high-altitude residents. Similar to what has been reported from IUGR or preeclamptic pregnancies at sea level (Cockell & Poston 1997, Kublickiene *et al.* 1997, Ong *et al.* 2003, Kublickiene *et al.* 2000, Luksha *et al.* 2010), myometrial artery vasodilator response was blunted in the vessels from the high- (2902 m) compared to the low- (1600 m) altitude women (Lorca *et al.* 2019). The blunted response was due to impaired nitric oxide signaling, similar to what has been seen in high-altitude exposed guinea pigs or rats (White *et al.* 2000, Aljunaidy *et al.* 2016). Greater myogenic tone in resistance vessels in the uterine circulation of pregnant sheep exposed to high altitude has also been reported, and attributed to less potassium-channel vasodilation (Hu *et al.* 2012). Other factors may also be involved since, for example, pregnant Andeans vs European high-altitude residents had higher activity levels for the anti-oxidants, catalase and superoxide dismutase, and possibly therefore greater protection from oxidative stress (Julian *et al.* 2012). Thus, existing data provide compelling evidence that chronic hypoxia can interfere with the normal maternal, uterine vasodilator responses to pregnancy so as to reduce uteroplacental blood flow and thereby contributes to the reduction in fetal growth.

To determine the genetic factors involved in Andean protection from altitude-associated fetal growth restriction, we conducted genome scans to identify gene regions showing evidence of having been acted

upon by natural selection (Bigham *et al.* 2009), and then carried out association studies to identify those related to protection from altitude-associated reductions in birth weight and uterine artery blood flow. We found that gene regions containing *PRKAA1*, which codes for the alpha-1 catalytic subunit of AMP kinase (AMPK) and *EDNRA*, which controls the expression of the vascular smooth muscle cell endothelin receptor A, were related to heavier (more normal) birth weights at high altitude. However, only the selected-for *PRKAA1* genotype was positively related to both birth weight and uterine artery diameter at high altitude. Suggesting a functional link, the *PRKAA1* SNPs were also associated with the expression patterns of mTOR pathway genes implicated in fetal growth restriction (Bigham *et al.* 2014).

Currently, we are examining the effects of AMPK activation *in vitro* in women and, in mice, *in vivo*. Addition of the AMPK agonist, A769662, has potent vasodilator effects in isolated mouse main uterine arteries and human myometrial arteries; these are partially due to stimulation of nitric oxide production but largely to vascular smooth muscle actions (Skeffington *et al.* 2016, Lane *et al.* 2019, Lorca *et al.* 2019). Mice treated at mid-gestation with the AMPK activator AICAR and then exposed to hypoxia until term have increased uterine artery diameters, greater uterine artery blood flow (either absolutely or expressed as a percent of cardiac output), and only half the altitude-associated reduction in fetal growth compared with their hypoxia-exposed, vehicle-treated counterparts (Lane *et al.* 2020). Further, we have recently published studies showing that AMPK activation not only dilates myometrial arteries but that its effects are greater in vessels from appropriate for gestational age (AGA) vs IUGR pregnancies (Lorca *et al.* 2020). While much remains to be learned, given that drugs such as metformin activate AMPK and have been safely used in pregnancy, such studies offer the possibility of yielding new therapies for treating or preventing pregnancy disorders characterized by uteroplacental ischemia and hypoxia.

Other oxygen-transport related variables have also been associated with preserved fetal growth or reproductive outcomes. At high altitudes in Colorado, Peru and Tibet, greater pregnancy-associated increases in hypoxic ventilatory sensitivity, ventilation, and arterial oxygenation are positively related to infant birth weight (Moore *et al.* 1982, 1986, 2001b). Ethnically Tibetan women living at high altitudes in Nepal with lower hemoglobin levels and higher SaO₂ also had better pregnancy outcomes (Cho *et al.* 2017). Consistent with this, high (>14.5 g/dL) as well as very low (<7 g/dL) hemoglobin levels are associated with poor pregnancy outcomes at high or low altitude (Gonzales *et al.* 2009), likely due to better placental perfusion of lower viscosity blood.

Pregnancy complications preeclampsia

Preeclampsia occurs in ~2–8% of pregnancies at low altitude and is part of a spectrum of hypertensive disorders of pregnancy (HDP) that includes gestational hypertension, preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and eclampsia. It has been attributed to impaired trophoblast invasion and resultant incomplete maternal spiral artery remodeling when detected early (<34 weeks), and to maternal factors when manifesting later (Staff 2019). While clearly the placenta plays a major role, as HDP resolve within days of birth and removal of the placenta, other factors are also likely important for several reasons. Incomplete spiral artery as well as neighboring myometrial artery remodeling is not specific to preeclampsia, as it also occurs in IUGR (Lyall *et al.* 2013). The systemic nature of HDP is associated with increased markers of oxidative stress and loss of VEGF activity due to elevated sFlt-1 and/or reduced PlGF production, increased soluble endoglin, reduced nitric oxide and other vasodilator gasotransmitters (CO, H₂S), elevated endothelin-1, increased activin A and inhibin A, and alterations in various miRNA (Ahmed *et al.* 2017, Phipps *et al.* 2019). Changes on the maternal side of the uteroplacental circulation also play crucial roles (Than *et al.* 2018, Ridder *et al.* 2019). For example, transcriptomic analyses in a landmark study employing chorionic villous sampling during the first trimester showed that the pathways affected in women who later developed preeclampsia were not those typically associated with hypoxia or oxidative stress, but rather with defective pre-decidualization or decidualization (Founds *et al.* 2009, Conrad *et al.* 2017), pointing to crucial roles for the ‘soil’ and not just the ‘seed’.

Preeclampsia and the other HDP are more common at high than low altitudes in Colorado and Bolivia (Palmer *et al.* 1999, Keyes *et al.* 2003, Bailey *et al.* 2020) but unknown is whether this is also true in Tibet or Ethiopia. In a recent comprehensive study of all births to Colorado residents from 2007 to 2016 ($n = 652,028$), we showed that each disorder separately or all combined was 33% more common at altitudes above than below 2500 m (Bailey *et al.* 2020). The increased incidence of HDP at high altitudes is an important contributor to the altitude-associated reduction in birth weight, accounting for half the birth-weight fall in Bolivia (Keyes *et al.* 2003).

While, as noted above, multigenerational high-altitude residents are relatively protected from fetal growth restriction, it is not clear whether such protection extends to preeclampsia and other HDP but suggesting that it may, lower rates of preeclampsia/gestational hypertension have been reported for Tibetan than Han residents of Lhasa (3658 m) in the Tibet Autonomous Region of China (Miller *et al.* 2008). Current data are insufficient to address whether Andeans are also protected. Suggesting that they might be is that pregnant

Andean compared with European women have lower sFlt-1 levels and sFlt-1/PLGF ratios (Davila *et al.* 2010), both of which are protective against preeclampsia (Chaiworapongsa *et al.* 2014). Andeans may also benefit from higher levels of anti-oxidants (Julian *et al.* 2012), progesterone, estrone, 17-beta estradiol and estriol (Charles *et al.* 2014). Cortisol levels are lower as well, with lower cortisol and higher estriol being associated with greater uterine artery diameter and blood flows in Andeans. But nonetheless preeclampsia and other HDP are frequent complications of pregnancy in La Paz, Bolivia and, in early-onset cases, are accompanied by elevated uterine artery resistance indices and reduced volumetric blood flow (Browne *et al.* 2011).

Preeclampsia is a major cause of maternal mortality at high altitude, being among the leading causes in Bolivia which has the second highest rate of maternal mortality in South America (Toledo-Jaldin *et al.* 2019). Preeclampsia is also associated with increased infant mortality and risk of cardiovascular and other diseases for both mother and offspring mortality later in life (Bellamy *et al.* 2007). Greater attention is needed for improving its diagnosis and treatment in all locales, but especially in the predominantly low- to middle-income countries where 99% of preeclampsia deaths occur (Duley 1992). The study of preeclampsia continues to be challenging given that (1) while at least some of its signs or symptoms can be invoked in animal models, it is a uniquely human disease; (2) longitudinal studies of its time course are difficult at a 2–8% incidence rate and (3) evaluation of predictive biomarkers or potential therapies is limited by the large number that are needed to treat when the incidence is low (i.e. 500 at a 2% incidence vs 56 at an 18% incidence (Askie *et al.* 2007)). Thus, studies at high altitude offer an important setting for potentially furthering our knowledge of responsible mechanisms and developing new therapies (Bailey *et al.* 2020).

Infant survival

The greatest predictors of infant mortality are birth weight and gestational age. Hence clearly the reduction in birth weights seen at high altitude poses a risk for infant survival. While gestational age is little affected in healthy pregnancy, it is often reduced in preeclampsia as the result of spontaneous preterm delivery or clinical decision to deliver if maternal and/or infant health is threatened.

Given the lower average birth weights at high altitudes, it would be expected that neonatal and, by extension, infant mortality would be increased. This is supported by older studies in Colorado in which mortality rates at high altitudes were higher than those observed at lower elevations (McCullough & Reeves 1977) but mortality rates at high altitudes in the state no longer differ by altitude (Unger *et al.* 1988). Bolivia’s infant mortality

rate is high (35.3/1000 livebirths) and twice the South American average. While the reporting of infant deaths is incomplete and multiple socioeconomic, health-care and other factors complicate their interpretation, the limited data available indicate that infant mortality rates increase with elevation in Bolivia (Giussani 2002). Mortality estimates for the Tibet Autonomous Region, the high-altitude regions of the adjacent Qinghai Province in China, or the high compared to low altitude regions Peru or Ethiopia are not, to our knowledge, available.

There is some, albeit limited, evidence that postnatal mortality may be lower in Tibetan than Han residents of high altitude under conditions of comparable health care. We collected birth weights and prenatal as well as postnatal mortality data in 495 consecutive deliveries over an 18-month period at eight hospitals or clinics serving predominantly rural or small communities at altitudes from 2700 to 4700 m in Tibet (Moore *et al.* 2001a). The women delivering during this period had a total of 863 prior pregnancies and 734 babies born previously. From these data we calculated postnatal mortality but, in the absence of data as to when deaths had occurred, were not able to provide age-specific estimates. Postnatal mortality increased with elevation in Tibetans. While sample sizes were too small to assess altitudinal effects in Han, postnatal mortality across all altitudes was nearly one-third lower in Tibetans than Han (120 vs 320 deaths per 1000 livebirths).

Compared to the 96–98% value seen at sea level, SaO_2 is lower in neonates and infants born at high altitude; at 1600 m in Denver, values are 92–94% during the first 3 months of age, and 81 to 91% during the first 4 months of life in Leadville, CO (3100 m) (Niermeyer *et al.* 1993). In Lhasa (3658 m), SaO_2 values in babies born to healthy mothers declined from birth to 4 months of age, with values being markedly and consistently higher in Tibetan than Han infants. Specifically, SaO_2 ranged from 94 to 88% at birth and 88–86% at 4 months of age in the Tibetans vs 92–80% at birth to 85–76% at 4 months of age in the Han babies for the awake or quiet sleep states, respectively (Niermeyer *et al.* 1995). Limited SaO_2 data in 15 healthy Andean babies born in La Paz, Bolivia (3600 m) also showed an age-related decline. Across all study times, values were higher in Tibetan than Andean babies in all but the feeding state; Andean values were higher than those seen in the Han babies while feeding and also tended to be higher after 1 month of age in the awake, active or quiet sleep states (Niermeyer *et al.* 2015).

Pulmonary arterial pressure (Ppa) normally undergoes a rapid fall in the first days after birth at low altitude, but this decline can be prolonged or absent in babies born at high altitudes without supplemental O_2 administration. Elevated Ppa and an increased prevalence of patent ductus arteriosus have been described at high altitudes in Andean and Himalayan regions (Sime *et al.* 1963). Accurate prevalence data with which to compare

indigenous and newcomer groups are not available, although there is some suggestion that such disorders may be more common in Han than Tibetan infants (Sui *et al.* 1988), possibly due to their better-sustained SaO_2 during early infancy.

With the increasing recognition of the importance of impaired intrauterine or early post natal development for susceptibility to cardiovascular and other diseases later in life (Barker 1999), it is of interest that middle- to older-aged men with the condition known as chronic mountain sickness (CMS) more often weighed less at birth than their equal-aged counterparts (Moore *et al.* 2007). CMS is a syndrome characterized by hemoglobin levels more than 3 standard deviations above the mean, hypoxemia especially during sleep and often pulmonary hypertension but without other underlying cardiopulmonary disease. It occurs in 8–10% of lifelong or multigenerational high-altitude resident males in South America but only rarely in Tibetans and has not been described in Ethiopia. CMS appears to have a hereditary component (Zhou *et al.* 2013), with several candidate genes being identified (Gazal *et al.* 2019). In 18–25 year old men with a preclinical form of CMS, in which hemoglobin levels are elevated but only 2 standard deviations above the mean and otherwise healthy, Dr Colleen Julian together with her Bolivian colleagues showed that those with preclinical CMS were four times more often hypoxic during perinatal life, three times more often born to preeclamptic mothers (Julian *et al.* 2015), had higher levels of the oxidative stress marker 8-iso-PGF $_{2\alpha}$ and lower SaO_2 during sleep than similarly aged controls (Julian *et al.* 2013).

Future perspectives

Studies at high altitude have proven instructive for increasing our understanding of the effects of hypoxia on reproduction and of the processes of human adaptation. Given the increasing recognition of the importance of early-life events for lifelong health, they hold promise for improving our understanding of health determinants later-in-life as well. Since most of the world's 140 million high-altitude residents live in LMIC, increased research on both the mechanisms responsible for pregnancy, fetal and other reproductive disorders in developing countries as well as for improving the treatments or preventive therapies for such conditions are warranted.

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