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Review

Humans at high altitude: Hypoxia and fetal growth☆

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ABSTRACT

High-altitude studies offer insight into the evolutionary processes and physiological mechanisms affecting the early phases of the human lifespan. Chronic hypoxia slows fetal growth and reduces the pregnancy-associated rise in uterine artery (UA) blood flow. Multigenerational vs. shorter-term high-altitude residents are protected from the altitude-associated reductions in UA flow and fetal growth. Presently unknown is whether this fetal-growth protection is due to the greater delivery or metabolism of oxygen, glucose or other substrates or to other considerations such as mechanical factors protecting fragile fetal villi, the creation of a reserve protecting against ischemia/reperfusion injury, or improved placental O_2 transfer as the result of narrowing the A-V O_2 difference and raising uterine Pv_{O_2}. Placental growth and development appear to be normal or modified at high altitude in ways likely to benefit diffusion. Much remains to be learned concerning the effects of chronic hypoxia on embryonic development. Further research is required for identifying the fetoplacental and maternal mechanisms responsible for transforming the maternal vasculature and regulating UA blood flow and fetal growth. Genomic as well as epigenetic studies are opening new avenues of investigation that can yield insights into the basic pathways and evolutionary processes involved.

1. Introduction

Studies at high altitude provide an important perspective for understanding energetics and oxygen transport in human beings. While much can be learned from whole animal, cell-based and other model systems as noted elsewhere in this issue, human studies are of special importance given the profound species differences in physiological and evolutionary processes. Exemplifying the former is the uniquely human susceptibility to the pregnancy disorder of preeclampsia and the latter is the variation between taxonomic groups in survival probabilities following conception. As shown in Fig. 1, mammals compared to other vertebrates such as fish, reptiles, or birds have an improved chance of survival. This relates, in part, to variation in r- vs. k-selection strategies among these animals (Stearns, 1992), but these too are evolutionary processes. Survival probabilities are further enhanced in placental (eutherian) compared to egg-laying or marsupial (metatherian or prototherian) mammals given their longer intrauterine period. Social factors further benefit postnatal survival, with human beings and other primates surviving well past the end of the reproductive period. All these influences have the effect of concentrating the period of differential mortality prior to the end of the reproductive period to the perinatal period (i.e., the interval from conception through infancy), subjecting embryonic and fetal life to considerable selective pressure and making this period of special relevance for understanding evolutionary process.

We approach the evolutionary processes affecting embryonic and fetal development through the lens of pregnancy studies at high altitude given the importance of O_2 tension as both a regulator and enabler of embryonic and fetal development, and the pervasive reduction in O_2 tension in the inspired air at high altitude. Studies at high altitude have clinical and public health importance as well. There are 140 M persons living at above 2500 m (the conventional definition of high altitude as that where arterial O_2 saturation (SaO_2) measurably begins to fall), comprising the largest group of persons at risk of fetal growth restriction (Krampl, 2002). Additional large numbers of persons visit high altitude or experience intermittent hypoxia due to anemia, cardiovascular or pulmonary diseases. Recognition of the importance of prenatal development for the risk of cardiovascular or other disorders later in life (Barker, 1992) further underscores the importance of understanding the mechanisms by which hypoxia influences fetal and embryonic development.

We begin by reviewing the history of research on fetal growth and embryonic development at high altitude. The physiological

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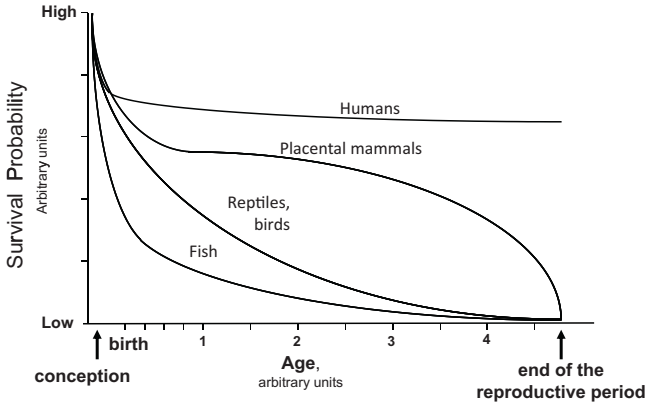

Fig. 1. A theoretical model for describing variation in the probability of survival from the time of conception through the end of the reproductive period in various taxonomic groups. The protection afforded by the shell of an egg as well as other factors increase survival probability in reptiles and birds relative to fish. Placental mammals have a further advantage commensurate with their longer period of intrauterine protection and improved survivorship during adult years. Since considerable differential mortality occurs soon after conception in all groups, the effects of natural selection are especially concentrated in the perinatal period, with this being particularly true in humans and other placental mammals.

processes governing fetal oxygen supply and their variation among human populations are then considered, first emphasizing those maternal attributes that determine the amount of oxygen and other nutrients that are transported to the uteroplacental circulation and then considering placental factors. The results of recent genome scans are also considered as these can provide new insights into the physiological pathways involved.

2. History of research concerning fetal growth and embryonic development at high altitude

Research on fetal growth at high altitude began before studies of embryonic development. Recognition of human variation in fetal growth at high altitude has further enlarged our appreciation of the physiological responses involved.

2.1. Fetal growth

While difficulties posed by high altitude for human or nonhuman animal reproduction have been recognized for some time, systematic scientific studies aimed at investigating the mechanisms responsible began in the 1950s. At that time "premature" was used to describe any "baby [who] weighs 2500 g or less regardless of the period of gestation" (Moore, 2001b). Since it was recognized that small-sized babies were more likely to die but it was considered impractical to record the length of gestation, birth weight was used as a single standard for identifying at-risk babies. Surprisingly this remained World Health Organization policy until 1975 when shortened gestation and fetal growth restriction were recognized as separable causes of low birth weight. Studies in Colorado were an important impetus for this change since it was there that fetal growth restriction was first demonstrated to lower birth weight independently of gestational age on a population scale.

In the 1950s Colorado had the highest "prematurity" rate in the country (Lichty et al., 1957). Dr. John Lichty was recruited from New York state to determine its cause (Moore, 2001b). Notably, one of his team's first actions was to revise the 1949 Colorado birth certificate form to include pregnancy duration. Their state-wide review showed that the counties with the highest "prematurity" rates were located at high altitudes, the highest of which was Lake County whose population was centered in Leadville at 3100 m (10,200 ft). There the average birth weight was 2655 g and 45% of newborns weighed less than 2500 g (5.5 lbs). Comparison of the Lake County records with those from Denver (1600 m, 5280 ft) and Baltimore (sea level) revealed that the entire birth-weight distribution shifted leftward with increasing elevation, but no change occurred in gestational age (Lichty et al., 1957). Ethnicity, prepregnant body weight, pregnancy weight gain, week of onset of prenatal care, number of prenatal visits, maternal nutrition (by 24-h dietary recall), delivery type, or levels of trace metals in the water supply could not explain the results observed. Reinforcing reduced O_2 availability as the likely cause, Leadville newborns had higher cord hemoglobin levels and lower SaO_2 values prior to the first breath than babies born in Denver. However, until recently the Colorado pediatric and obstetrical communities continued to think that factors such as ethnicity and inadequate medical care rather than altitude per se were primarily responsible (Moore, 2001b; Schwartz, personal communication).

Studies in the 1950s were also taking place in the Peruvian Andes by a distinguished group of scientists headed by Donald Barron from Yale University. Their work was aimed at discovering how fetal development was possible at an altitude of 4900 m where less than half as much oxygen was present in the inspired air compared to sea level. It was known from Joseph Barcroft's pioneering observations that normal fetal development takes place in a low-oxygen environment, with placental intervillous O_2 tensions being approximately 20 mm Hg at 7–10 weeks of gestation or one-third the values present on the maternal side of the placenta (Rodesch et al., 1992; Stave, 1970). Unless compensations occurred, halving maternal inspired O_2 tensions would reduce fetal oxygenation below levels compatible with life, let alone those needed for fetal growth and development. Their studies in native sheep (which interestingly did not demonstrate lower birth weights) revealed that compensations occurred at each step in the oxygen transport chain, with the greatest change being a markedly higher uterine artery (UA) blood flow. These investigators speculated that if similar increases occurred in humans at high altitude, intervillous O_2 tensions would only be slightly reduced compared to sea level (Metcalfe et al., 1967), an observation that was remarkably prescient given the reports to be published some 50 yrs later.

More recent studies show that birth weight falls, on average, 102 g per 1000 m elevation gain and that approximately three times as many babies are born who are small for their gestational age and sex (SGA[1]) at high compared to low altitude (Jensen and Moore, 1997; Julian et al., 2007; Krampl, 2002). While the birth-weight reduction can be modeled as linear in large samples, finer-scale analyses reveal that it begins gradually and becomes marked at altitudes >2500 m (8000 ft) (Mortola et al., 2000). The birth weight reduction can be observed after 29–31 wk gestation in babies born prematurely (Unger et al., 1988) or 25–29 wk by fetal biometry (Krampl et al., 2000). While poor nutrition, low socioeconomic status, primiparity, and limited health care contribute to birth-weight variation in any population, such factors cannot account for the altitude-associated fall (Giussani et al., 2001; Jensen and Moore, 1997; Keyes et al., 2003). Approximately half the fall can be attributed to a tripling of the incidence of preeclampsia[2] (PE) (Jensen and Moore, 1997; Keyes et al., 2003; Palmer et al., 1999). However since only about half the babies born to PE women are growth restricted and SGA and PE are, increasingly, being recognized as having distinct etiologies (Rajakumar et al., 2007), chronic

[1] Birth weights <10th percentile of sea-level values for a given gestational age and sex (Williams et al., 1982).

[2] Two or more resting blood pressures >140/90 mm Hg accompanied by ≥1+ proteinuria (or ≥300 mg in 24 h) after the 20th week of pregnancy in a previously normotensive women.