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Review Article

High Altitude and Human Reproductive Function

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ABSTRACT

Altitude has been reported to have significant effects on the metabolic, cardiovascular and ophthalmological and reproductive function due to prolonged exposure. However, the human body can adjust to acute and chronic reductions in its oxygen supply by increasing respiratory rate, chemical changes in the blood, and by increasing the production of red blood cells. In males, reproduction could be affected by hypoxia at different levels. This could be at hormonal level, during spermatogenesis with epididymal, seminal vesicular and testicular weight could also be significantly reduced. Chronic state of hypoxia can alter erectile physiology, thus triggering the onset of erection dysfunction (ED). The reproduction in species that have adapted to conditions at high altitude is possible, making adaptation to high altitude vital for survival and for successful reproduction. This review highlight changes in reproductive function consequent to high altitude exposure.

Keywords: High altitude, erectile dysfunction, sperm, ovary

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INTRODUCTION

Human is physiologically affected by hostile environment such as humid coastal area, scorching heat of the desert and frigid high altitude. High altitude is one of the most severe environments posing challenge to human survival and performance. To live in or travel to a high altitude one need to adapt to and overcome intense low ambient temperature, low humidity, high power solar radiation and low atmospheric pressure (Barnholt *et al*, 2006).

High altitude (beyond 9000 feet) above sea level has low atmospheric pressure which decreases the oxygen partial pressure in the ambient air implying that the number of molecules of oxygen present per breath decreases, even with unaltered relative percentage of oxygen. Oxygen being a primary requirement for life processes, its inadequate bio-availability to tissues or organs leads to inadequate biological processes such as energy production, biosynthesis and breakdown of cellular component, reproduction and mental coherence (Benso *et al*., 2007).

Human populations, including the Tibet in Asia, the Andes of the Americas, and the Ethiopia in Africa, living in high altitude, have acquired the ability to survive at extremely high altitudes associated with heritable behavioural and genetic changes.

Although other human populations would suffer serious health consequences, the indigenous inhabitants of these regions thrive well in the highest part of the world with respect to regulatory system of oxygen respiration and blood circulation, these people have undergone extensive physiological and genetic changes when compared to the general lowland population (Benzo *et al*. 2007).

Different population and societies have a long antiquity at high altitudes, yet much of the early knowledge of whether male and females had normal reproductive fitness comes from chronicles written by Europeans colonizing the Andes (Gonzales, 2011). Given the difference of fertility rates between new comers to high altitude and indigenous peoples, local biologists, biological anthropologists, and geneticists began to investigate the manner in which high altitude environment impact reproduction. **S**tudies tend to produce contradicting results. The first fertility studies to investigate

the effect of altitude on fertility among sheep, cattle, cats and rabbits demonstrated a short-term exposure of high altitude resulted in temporary infertility (Monge, 1942; Monge and Mori Chavez, 1942). Studies in the late 20th century have shown that fertility is lower in high altitude than in low altitude (Collins, 1983). Studies that shown the fecundity rate among Peruvian highlanders have found to be from one to two births less than of lowland Peruvians of the same ethnic background. In fact, highland native who move to low altitudes show markedly higher rates of fertility than their counterparts who remain in the highlands (Abelson, 1976). On the contrary, some studies have also suggested that population fertility appears to be unaffected among natives to high altitude environments (Hoff, 1984).

The development of modern transportation facilities has increased the number of individuals visiting high– altitude locations (>2500mm) and exposure to low oxygen content condition that triggers a series of physiologic responses intend to maintain adequate tissue oxygenation (Rimoldi *et al.*, 2010). There are enormous inter individual variabilities that may be further amplified by environmental factors such as cold temperature, low humidity, exercise and stress. The adaptive mechanisms, although generally tolerated by most healthy subject, may induce major effects on biological system with prolonged exposure (Hansen *et al*., 2000).

Previous research has shown that altitude has several effects on humans including acute mountain sickness, high –altitude pulmonary oedema and high altitude cerebral oedema (Karakucuk and Mirza, 2000). Altitude has also been known to have significant changes on the metabolic, cardiovascular and ophthalmological parameters due to prolonged exposure (Paven *et al.*, 2004).

Previous studies also reported that there are various physiological responses to prolonged exposure to high altitude in aircrews. The rate of hypertension in 1,000 pilots was estimated to be 4.2% and there were obvious differences among the different age teams, though no obvious difference was found among those who fled different kind of planes (Li-Huiroung *et al.*, 2008).

Solorera *et al.* (2013) reported that maximum blood pressure and heart rate values were higher in hypertensive pilots as compared with the control group. Tang and Wil (2011) concluded that there was high prevalence of controllable cardiovascular risk factors in Chinese pilots. It was reported that significance difference existed on the rates of hypertension, total cholesterol, triglyceride, low high density lipoprotein – cholesterol smoking and abnormal BMI among pilots from different regions (all $p<0.01$). Results from the annual aeromedical examination on the analysis of electrocardiogram (ECG) of pilots exposed to prolonged high altitude also showed decadal changes in aircraft pilots (Orhui *et al.*, 2011). Karacucuk and Mirza, (2000) observed various effects of prolonged high altitude on human beings as altitude related illness are a frequent cause of morbidity and occasional mortality in travellers and aircrews throughout the world. Abdias *et al.*, (2012) documented that exposure to prolonged high altitude can be associated with both beneficial and detrimental effects on health. This includes reduced frequencies of obesity, diabetes and coronary heart disease and the increased frequency of systemic and pulmonary hypertension and the potential consequences of high-altitude renal syndrome.

Vangelova and Zlatev, (1994) in a study of gravitational induced hormonal changes and blood concentrations of serotonin and histamine also reported significant elevation in biochemical parameters in pilots using simulated aerial combat maneuvers (SACM). Malcolm *et al., (*1976) in a study of some aircrew exposed to prolonged altitude revealed some changes in the biochemical and physiological parameters indicating that climatic conditions can prestress an aircrew before a flight, and lead to impaired adaptation to the additional strains of exacting work in rapidly changing surroundings of temperature, humidity and time.

HIGH ALTITUDE AND HUMAN REPRODUCTION

At high altitude, atmospheric pressure and oxygen partial pressure are lower than at sea level which results in hypoxia due to low availability of oxygen which inhibits diffusion of oxygen from the air into the lungs. Various physiological conditions including human reproduction could be severely affected at high altitude. Altitude-initiated stress, hypoxia may affect the process of reproduction at several stages: gonadal hormones such as LH (luteinizing hormone), FSH (follicle stimulating hormone), estrogen, progesterone and testosterone, gametogenesis, the ovarian cycle and menstruation, birth weights, still birth rates, infant mortality, postpartum behaviour, menopause. Hypoxia inducible factors are key transcription factors that mediate gene regulatory changes to hypoxic stress in both adult and embryonic development (Kimberley *et al*., 2010).

At high altitude the testicular tissue is greatly affected and affects physiological processes as a result. The dysfunction of leydig cell caused by hypoxia emanated from high attitude decreases testosterone production (Saxena, 1995). Testosterone is a sex hormone produced by the testes that lead to the development of male sexual characteristics, stimulates the activity of the male secondary sex characteristics, and prevents changes in them following castration. Chemically, testosterone is 17-beta-hydroxy-4-androstene-3-one. Both steroidogenesis and spermatogenesis are stimulated by the release of gonadotropins LH and FSH. Gonadotropins are glycoprotein polypeptide hormones secreted by gonadotrope cells of the anterior pituitary of vertebrates (Parhar *et al.*, 2002). The follicle-stimulating hormone (FSH) and luteinizing hormone (LH), are released under the control of gonadotropin-releasing hormone (GnRH) from the arcuate nucleus and preoptic area of the hypothalamus. The target of gonadotropins in males is the testis.

Gonadotropins released by the hypophysis enter the blood stream to reach the testicle, where Luteinizing hormone (LH) stimulates Leydig cell steroidogenesis in the interstitium, whereas FSH, by stimulation of Sertoli cells, helps to maintain spermatogenesis in the seminiferous tubule. The control mechanisms for FSH secretion seem to be influenced not only by testosterone and its metabolic derivative, estradiol, but also by activins and inhibins produced by Sertoli cells (Clermont *et al*., 1972). Little is known about the relationship between hypoxia and steroidogenesis, and the scarce studies performed in humans have been carried out with reduced sample sizes. It has been observed that in a small group of men exposed to an

altitude of 4,300 m above sea level, their plasma testosterone level rose by 30% after the third day of exposure (Barnholt *et al.,* 2006). In another study in which 10 mountaineers stayed in the Himalayas for a period of 60 days at 5000 m above sea level, hormonal measures indicated reduced testosterone levels at the end of the period (Benso *et al.,* 2007). In experimental mice exposed to normobaric hypoxia, testosterone levels (plasma and intratesticular) were highest at 24 hours for plasma testosterone and 48 hours for intratesticular testosterone. The early increment of both intratesticular and plasma testosterone might be mediated by Vascular Endothelial Growth Factor (VEGF), as postulated by Hwang *et al* (2007) and consistent with a raise in VEGF in mice after 24 hours of hypoxia (Madrid, 2011, Madrid *et al.,* 2011). Plasma and testicular testosterone return to normal levels after 48 and 72 hours, respectively (Madrid, 2011, Madrid *et al.,* 2011). These results are in agreement with published data on early testosterone increments in mountaineers exposed to high altitude or in newborns exposed to neonatal hypoxia (Barnholt *et al.,* 2006, Boksa *et al.,* 2008, Gonzales *et al.,* 2011). Testosterone has a well-known relaxing effect on smooth muscle which can induce a vasodilator effect in minutes (Costarella *et al.,* 1996, Honda *et al.,*1999, Webb *et al.,* 1999), an effect that could be part of the hypoxia response mechanisms in the testicles (Madrid, 2011). Testosterone seems to have a relevant role in high altitude adaptation owing to its identity as an erythropoietic hormone which acts directly on bone marrow at the level of polychromatophilic erythroblasts (Gonzales *et al*., 2011). Thus, testosterone administration has been shown to stimulate the production of red blood cells in males, especially elderly males, and it is associated with the increment of hemoglobin that occurs during puberty in young men (Bassil *et al.,* 2009, Coviello *et al.,* 2008). Thus, an early rise in testosterone in hypoxia and its role as a vasodilation agent is consistent with its possible role in early vascular changes in the hypoxic testis, as well as its being a likely coactivator of the erythropoietic response in hypoxia, acting both as a local paracrine hormone and as an endocrine signal toward bone marrow cells.

Male reproductive function

Spermatogenesis could also be another physiological process which could be affected by hypoxia, studies have shown that hypoxia could cause oligospermia and promote increased apoptosis (Gasco *et al.,* 2003). Epididymal, seminal vesicular and testicular weight reduced greatly. This process (spermatogenesis) represents a delicate balance between cell proliferation, differentiation, and apoptosis. In most mammals, the testicles are kept in the scrotum 2 to 7°C below body core temperature, and the spermatogenic process proceeds with blood and oxygen supply that is fairly independent of changes in other vascular beds in the body. Despite this apparently well-controlled local environment, pathologies such as varicocele or testicular torsion and environmental exposure to low oxygen (hypoxia) can result in changes in blood flow, nutrients, and oxygen supply along with an increased local temperature that may induce adverse effects on Leydig cell function and spermatogenesis (Juan *et al.,* 2012).

Sertoli cells, which nurture and support developing spermatocytes, secrete a fluid into seminiferous tubules that helps transport sperm to the genital ducts. The ductuli efferentes possess cuboidal cells with microvilli and lysosomal granules that modify the ductal fluid by reabsorbing some fluid. Once the semen enters the ductus epididymis, the principal cells, which contain pinocytotic vessels indicating fluid reabsorption, secrete glycerophosphocholine which most likely inhibits premature capacitation. The accessory genital ducts, the seminal vesicle, prostate glands, and the bulbourethral glands, produce most of the seminal fluid.

The seminal plasma provides a nutritive and protective medium for the spermatozoa during their journey through the female reproductive tract. The normal environment of the vagina is a hostile one for sperm cells, as it is very acidic (from the native microflora producing lactic acid), viscous, and patrolled by immune cells. The components in the seminal plasma attempt to compensate for this hostile environment. Basic amines such as putrescine, spermine, spermidine and cadaverine are responsible for the smell and flavor of semen. These alkaline bases counteract and buffer the acidic environment of the vaginal canal, and protect DNA inside the sperm from acidic denaturation. According to Fahim *et al* (2009), it is thought that the gonads of people living at high altitudes gradually lose their potency. Several low-pressure experiments in animals exposed to high altitude have reported decreased testis weight and destruction of germinal epithelium which may account for the impairment of spermatogenesis, and destruction of germinal epithelium; however, the duration of these changes is not precisely known nor is it known whether adaptation takes place (Fahim *et al.,* 2009). The reduction in testicular weight which is experienced at high altitude may be as a result of testicular degeneration, tends to affect the normal physiology of male reproduction and coitus where the organs have shown reduced potency (Fahim *et al.,* 2009).

Human male reproductive function depends on a complex interaction between a physiological erection and sperm production. Verratti *et al* (2012) that a chronic state of hypoxia can alter erectile physiology, thus triggering the onset of erectile dysfunction (ED). Oxygen availability and delivery could play an important role in the regulation of local penile erection-related mechanisms and low oxygen supply levels may be considered an aetiological factor in ED (Verratti *et al.,* 2007; Verratti *et al.,* 2011). In a study by Gustavo *et al*., (2007), it was observed that reproduction in species that have adapted to conditions at high altitude was possible which makes adaption to high altitude important for survival and for successful reproduction.

Erection/ejaculation/ erectile dysfunction: An erection or penile erection/tumescence is a physiological phenomenon in which the penis becomes firmer, engorged and enlarged. Penile erection is the result of a complex interaction of psychological, neural, vascular and endocrine factors, and is often associated with sexual arousal or sexual attraction, although erections can also be spontaneous. ED is the inability to achieve or sustain an erection suitable for sexual intercourse. Causes include medications, chronic illnesses, poor blood flow to the penis, drinking too much alcohol, or

being too tired. Higher altitudes (HA) bring about various changes in physiology of the body due to decreased atmospheric pressure and less oxygen tension. As the human body goes beyond 7,000 feet above sea level, the saturation of oxy hemoglobin begins to fall (Young, *et al.,* 2002). Recent trials have shown that nitric oxide (NO) synthesis and functional integrity of penis smooth muscles depend on an adequate oxygen supply (Moreland *et al., 1998,* Sa´enz de Tejada *et al.,* 2004).

In a study by Verratti *et al*. (2007) the relationship between Sleep Related Erections (SRE), erectile dysfunctions and hypoxia was carried out. It was seen that SREs are involuntary physiological phenomenon that occur in healthy men 4– 5 times a night during rapid eye movement (REM) sleep phase, each of 30–45 min for a total of 80– 180 min (Karacan *et al.,* 1989). The physiological role of SREs is not completely known, probably they play a role in metabolic processes at the base of erectile function and in corpus cavernosum perfusion and oxygenation (Kim *et al.,* 1998). Nitric oxide is thought to be a very important agent in erection as it is a vasodialator. Nitric oxide is a gas that diffuses into target tissues where it activates guanylate cyclase and catalyzes the formation of cyclic guanosine-30, 50-monophosphate (cGMP) from guanosine-50 -triphosphate. cGMP initiates a cascade of intracellular events and reduces intracellular calcium which leads to relaxation of penis smooth muscles (Arnold *et al.,* 1977). Nitric oxide synthesis is mediated by NO synthetase, which requires both L-arginine and oxygen as substrates. Oxygen is involved in penis erection mechanism through regulation of NO synthesis in the corpus cavernosum tissue and through the regulation of other vasoactive substances (Palmer *et al*., 1989, Kwon *et al*., 1990). Vasoconstrictor substances prevail when there are low O_2 tensions, while there is a prevalence of NO and prostaglandin E1 (PGE) when there are high O_2 tensions (Moreland *et al*., 1998, Hirshkowitz *et al*., 2005). Low O_2 tensions can interfere with NO synthesis and secretion or alter its availability upon release. Moreover, it is possible that the target cell (the smooth muscle), under hypoxic conditions, is less responsive to NO. Thus low O_2 tensions can inhibit the relaxation of trabecular smooth muscle. A direct demonstration of regulation role of oxygen is provided by the measurement of NO synthase activity in rabbit corpus cavernosum cytosol preparations. Hypoxia causes a significant reduction of NO synthase activity. This suggests that oxygen can be a rate-limiting factor for NO production in the penile corpus cavernosum (Kim *et al*., 1991; Kim *et al*., 1993). Acute hypoxia increases the afferent sympathetic activation (Hansen *et al*., 2000, Xie *et al*., 2001) which increases vasoconstriction activity (Rowell *et al*., 1989). If erection is affected, ejaculation may also be affected since erection preceeds ejaculation.

Sperm function: Germ cell apoptosis and DNA damage are common features in hypoxia which may lead to infertilty. Rat seminiferous tubules are thought to be under an oxygen tension lower than the interstitial oxygen tension in normal conditions (Giaccia *et al.,* 2004). Despite various controversies about the correct values of oxygen tension in the seminiferous tubules, it has been proven that the testicular interstitial oxygen tension is approximately 20% of the testicular artery blood oxygen pressure (i.e., 12 to 15 mmHg) (Free *et al.,* 1976). It is expected that the oxygen tension decreases under low atmospheric oxygen pressure (which is the condition at high altitude) or under reduced blood flow to the testis (testiscular torsion). The distribution of oxygen in the testis is determined by the testicular microvasculature, thereby making the access of spermatogenic cells to oxygen to be determined by the diffusion of oxygen in the interstitium and semniferous tubules (Juan *et al.,* 2012).

According to Juan *et al*. (2012) chronic hypoxia induces a state of reversible oligozospermia (low sperm concentration in semen) in healthy men, sperm motility and count was also reduced which can be related to increased germ cell apoptosis in hypoxic state. Degeneration of germinal epithelium, folding of the basement membrane, degeneration and detachment of germ cells changes in lipid droplets in Sertoli cells, and an increase in lipoperoxidation has been associated with hypoxia (Farias *et al.,* 2005, Liao *et al.,* 2010). The degeneration of testicular and increased apoptosis of the germ cells experienced at high altitude is mediated by an increase in intratesticular or seminal reactive oxygen species (ROS). In several studies, intracellular ROS can increase in hypoxic conditions which induces oxidative stress (Farias, *et al.,* 2010, Vargas *et al.,* 2011) and this was as a result of vascular changes that are associated with increase in testicular temperature on an average of 1.5°C (Farias *et al.,* 2005).

In the testis, the generation of ROS seems to be of paramount importance in germ cell apoptosis and DNA damage (Makker *et al.,* 2009). At physiological levels, ROS are essential for normal reproductive functioning, acting as metabolic intermediates and regulating vascular tone, gene expression, and sperm capacitation (Sikka *et al.,* 2001; Makker *et al.*, 2009). Heat stress induces oxidative stress, triggering cell survival or apoptosis depending on the cell type and the extent of the insult. This heat stress appears related to ROS-generating enzymes that produce ROS as by-products of their enzymatic activity. Xanthine oxidase (XO) catalyzes the conversion of hypoxanthine and xanthine to uric acid, producing hydrogen peroxide as a by-product, and XO inhibitors suppress testicular germ cell apoptosis induced by experimental cryptorchidism (testis subjected to the core body temperature) (Kumagai *et al.,* 2002). There is a lack of information, however, about whether or not other ROS-generating enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), NADPH oxidase (NOX), and the mitochondrial NADH-CoQ oxido-reductase are activated after testicular heat stress. In other oxidative processes, nitric oxide (NO) is synthesized intracellularly through the action of a family of nitric oxide synthetase (NOS) enzymes. These NOS enzymes catalyze the NADPH- and -dependent oxidation of L-arginine to L-citrulline, producing NO (Hill *et al.,* 2010). This molecule is a free radical and is chemically more stable and less reactive than other ROS such as the superoxide anion or hydrogen peroxide (Pacher *et al.,* 2007). Furthermore, NO in the presence of ROS can form the highly reactive oxidant peroxynitrite (Calcerrada *et al.,* 2011). In monkey testes, endothelial nitric oxide synthetase (eNOS) and inducible NOS (iNOS) were found to be expressed in Sertoli and germ cells. No obvious alterations in eNOS levels were detected after heat stress, but the levels of iNOS increased

three days after heat treatment compared with the controls showing a robust increase in iNOS expression in germ cells (Guo *et al.,* 2009). Thus, heat stress seems to induce NO production and it might contribute to oxidative damage in germ cells. The molecular targets that are modified by NO production and the consequences of this reactive nitrogen species (RNS) in testis physiology and pathophysiology are still unknown and further research in this area is suggested.

HIGH ALTITUDE AND FEMALE REPRODUCTION

As much as high altitude affects male reproduction, same goes for females. Various physiological functions are also affected in females just as it was seen in males. Successful reproduction requires efficient functioning of the female reproductive organs and the proper control of reproductive hormones to avoid infertility. From various studies, it was evident that the condition at high altitude (hypoxic state where there is low partial and atmospheric pressure of oxygen) tends to induce stress (Crognier *et al.,* 2002). Victor *et al*. (2013) demonstrated that the deleterious effects of hypoxia-induced oxidative stress at a high altitude may be prevented by daily administration of antioxidant vitamins, which increase the plasma progesterone concentrations throughout pregnancy (Parraguez *et al.,* 2010) and improve placental structure and fetal growth (Parraguez *et al.,* 2010). Yi-Fan jiang *et al*. (2011) also reported that hypoxia is important physiological process that ensures corpus luteum (CL) formation and development, thereby playing a significant role in steroidogenesis. Menstrual cycle is affected and the hormones (progesterone and estrogen) regulating different phases are also affected. A number of different factors may affect female fertility by affecting the functionality of the hypothalamus-hypophysis-ovarian axis, cyclic ovulatory activity, the quality of preovulatory follicles/oocytes/embryos and/or subsequent embryo/fetal viability. All of these critical roles require the presence of a fully functional corpus luteum (Parraguez *et al*., 2011). It has also been reported that the progesterone secretion was downregulated and the process of apoptosis was promopted in the luteal cells isolated from bovine CL at the middle stage (Nishimura *et al*.,2006, 2008).

Menstrual cycle: Monthly ovum is released into the uterus waiting to be fertilized by sperm. The absence of sperm leads to menstruation. Menstrual cycle is the regular natural change that occurs in the female reproductive system (specifically the uterus and ovaries) that makes pregnancy possible (Silverthorn *et al.,* 2013, Sherwood *et al.,* 2013). The cycle is required for the production of ovocytes, and for the preparation of the uterus for pregnancy (Silverthorn *et al.*, 2013). The first period usually begins between twelve and fifteen years of age, a point in time known as menarche. They may occasionally start as early as eight, and this onset may still be normal. The average age of the first period is generally later in the developing world and earlier in developed world. The typical length of time between the first day of one period and the first day of the next is 21 to 45 days in young women and 21 to 35 days in adults (an average of 28 days) (Laufer *et al.,* 2006). Menstruation stops occurring after menopause which usually occurs between 45 and 55 years of age. Bleeding usually lasts around 2 to 7 days.

The menstrual cycle is governed by hormonal changes. Each cycle can be divided into three phases based on events in the ovary (ovarian cycle) or in the uterus (uterine cycle) (Silverthorn *et al.,* 2013). The ovarian cycle consists of the follicular phase, ovulation, and luteal phase whereas the uterine cycle is divided into menstruation, proliferative phase, and secretory phase.

Stimulated by gradually increasing amounts of estrogen in the follicular phase, the latter part of this phase overlaps with the proliferative phase of the uterine cycle, discharges of blood (menses) flow stop, and the lining of the uterus thickens. Follicles in the ovary begin developing under the influence of a complex interplay of hormones through the influence of a rise in follicle stimulating hormone (FSH). During the first days of the cycle, a few ovarian follicles are stimulated and after several days one or occasionally two become dominant (non-dominant follicles shrink and die). Approximately mid-cycle, 24–36 hours after the luteinizing hormone (LH) surges, the dominant follicle releases an ovocyte, in an event called ovulation. After ovulation, the ovocyte only lives for 24 hours or less without fertilization while the remains of the dominant follicle in the ovary become a corpus luteum; this body has a primary function of producing large amounts of progesterone. Under the influence of progesterone, the uterine lining changes to prepare for potential implantation of an embryo to establish a pregnancy. If implantation does not occur within approximately two weeks, the corpus luteum will involute, causing a sharp drop in levels of both progesterone and estrogen. The hormone drop causes the uterus to shed its lining in a process termed menstruation.

Follicular phase ranges vary among women, a luteal phases lasting for less than 2 weeks is considered a "luteal defect" due to low levels of the hormone progesterone and an insufficient production of uterine lining, which inhibits a female's reproductive abilities. Fecundability may be correlated to cycle length, which determines the number of opportunities for conception in a given time span (Wood and Weinstein, 1988). Because ovarian follicle growth is characterized by cell growth and rapid cell divisions, hypothetically, hypoxia may slow this process and thereby disrupt phase lengths (Wood and Weinstein, 1988).

Female Fertility

Infertility is a condition which has been associated with women at high altitude (Escudero *et al*., 1996). Assessing how hypoxic stress impacts fertility alone is problematic because fertility is also affected by many cultural, social, and behavioral factors. Populations residing at high altitudes may have less developed health, social, and communication infrastructures than those residing at sea level.

In a review by Crognier *et al*. (2002) it was concluded that, the elements of Aymara fertility presented composed of a reproductive pattern shaped by a late onset of fertility and a late beginning of childbearing, associated with a rather short reproductive span and large birth intervals. These characteristics could fit well with a scenario of physiological stress, in which poor conditions of health and nutrition, exacerbated by hypoxia, induce impairment of either fecundity or fertility processes. In particular, this could be the reason for the late age at menarche recorded among peasant

girls. The huge discrepancy between the current observations and those of various other authors on adolescents living in the city of La Paz emphasizes the deep contrast in living conditions between rural and urban settlements, and the variety of environmental effects that are known to affect sexual maturation. James, (1966) argued that the physiological effects of altitude were responsible for a seemingly lower fertility among indigenous populations. In a research carried out by Parraguez *et al.* (2013), it was observed that the corpora lutea of sheep that were native and naïve to a high altitude were, overall, smaller in size than the corpora lutea of ewes at a low altitude. The occurrence of growth deficiencies in the corpora lutea has been classically linked to ovarian causes (inadequate development and maturation of preovulatory follicles (Keisler *et al*., 1989) and/or systemic causes (inadequate LH secretion, which is necessary for the final maturation of the preovulatory follicles and, subsequently, adequate development of the corpora lutea (Campbell *et al*., 1999, Adams *et al.*, 1999).

The existence of augmented plasma progesterone concentrations during the late luteal phase may compromise female fertility by affecting the final development and maturation of the preovulatory follicle of the subsequent cycle. Furthermore, alterations in follicular development diminish a follicle's ability to ovulate an oocyte that can be fertilized and develop into a viable embryo (Gonzalez-Bulnes *et al*., 2005). Progesterone exerts an inhibitory action on gonadotropin-releasing hormone release from the hypothalamus (Nett *et al*., 1987), resulting in inadequate stimulation of gonadotrophs for LH synthesis. The hormone LH is pivotal for final maturation of preovulatory follicles (Campbell *et al.*, 1999), progesterone levels that are too high may interfere with this process. In sheep, as in other species, it is well known that large follicles have lower functionality in the mid-luteal phase (Contreras-Solis *et al.*, 2007) when progesterone concentrations are at the maximum level. Ovulation in defective follicles results in lower fertility (Viñoles *et al.*, 1999), which can contribute to the lower fertility observed at a high altitude.

Reproductive Hormones

In normal physiology in females, certain hormones are responsible for successful reproduction. At high altitude certain changes occur which lead to changes in the level of these hormones thereby affecting reproduction and menstrual cycle as illustrated above.

In females, the levels of progesterone are relatively low and flat during the follicular (pre-ovulatory) phase, then rising to reach a peak approximately half-way through the luteal (post-ovulatory) phase before returning to basal levels, signaled by the onset of menstrual bleeding. Because the absence or reduction of a rise and peak in progesterone is considered indicative of subfecundity, progesterone levels are an excellent proxy for measuring fecundity. Vitzthum and coworkers (Vitzthum *et al*., 2001) have documented hormonal level in females at high altitude and deduced that two higher altitude samples (Bolivia and winter Nepal) are nearly identical and substantially higher than the low-altitude Zaire sample. Interestingly, while lower than that of Polish women during the post-harvest season (a period roughly comparable with the seasons during which the winter Nepal and Bolivia data were collected), these samples from higher altitudes display progesterone levels greater than that of the low-altitude (700 m) sample of Polish women during the peak of harvesting. The lowest value is seen in the Nepal sample during the monsoon season, a period of far greater energetic stress than characterizes the seasons when data for the other samples were collected (Vitzthum *et al.*, 2001).

Table 1:
Implication of high-altitude exposure on reproductive function

Type of study	Affected region	Outcome	References
Human	Fecundity	Decreased fecundity rate	Collins, 1983
Human	Testicles	Decreased testosterone production	Sexena, 1995 Benso *et al*., 2007
Animal	Leydig cell	Decreased testosterone production	Hwang *et al*., 2007
Human	Sperm function	Oligospermia, Increased apoptosis	Juan *et al*., 2012
Animal	Testicles	Reduced weight, destruction of germinal epithelium and increased lipoperoxidation	Fahim *et al.*, 2009; Liao *et al.*, 2010.
Human	Penis	Erectile dysfunction	Verratti *et al.*, 2012; Tejada *et al.*, 2004
Animal	Pregnancy	Reduce progesterone and reduced fetal growth	Parraguez *et al.*, 2010
Human	Menstrual cycle	Slows down menstruation cycle and reduces the cycle length	Wood and Weinstein, 1988
Animal	Corpora lutea	Reduced size	Parraguez *et al.*, 2013
Human	Female Hormone	Increased progesterone	Vitzthum *et al.*, 2001

In a study the differential hormone profiles, specifically time between the gonadotropin peak/release of luteinizing hormone (LH) and ovulation, between high and low altitude populations may indicate an ovulatory disorder. Escudero *et al*. (1996) compared samples from Lima (sea level) (150 m) and Cerro de Pasco (high altitude region) (4340), Peru. Females in Cerro de Pasco had smaller pre-ovulatory follicle diameters and lower estrogen production during the late follicle phase. Estradiol levels only increased 80% between Cerro de Pasco females compared to 137.3% among females in Lima. Additionally, the luteinizing hormone peaked earlier among women in Cerro de Pasco compared to women in Lima. Yet, both groups of females exhibited the same duration of the luteal phase and the same endometrium measurements between high and low altitudes (Escudero *et al*., 1996). Escudero and colleagues (1996) conclude that the differences in hormone profiles during menstrual cycle between high altitude and sea level samples are a result of low barometric pressure.

Conclusion

The cumulation of the effects of high altitude (which is a state of hypoxia i.e reduced partial and atmospheric oxygen pressure) affects human reproduction as shown and summarized in Table 1. Reduced partial oxygen pressure affects spermatogenesis by germinal epithelium degeneration and increased apoptosis which affects male fertility. The association of hypoxia to leydig cells dysfunction which affects testosterone production may affect male sex drive and erection. Although, it has been seen that hypoxia tends to initially increase testosterone levels as a compensation for low oxygen and blood flow since it acts as a stimulator of erythropoesis. The relationship between hypoxia and erectile dysfunction shows that hypoxia causes a significant reduction of NO synthase activity which makes NO is a signal for erection being a vasodialator and aids filling of erectile tissue. This suggests that oxygen can be a rate-limiting factor for NO production in the penile corpus cavernosum. Acute hypoxia also, increases the afferent sympathetic activation which increases vasoconstriction activity. These breaches of physiological processes are thought to affect male fertility. Similarly, exposure to high altitude causes various changes in physiological functions and oxidative stress consequently affecting fertility, hypothalamus-hypophysis-ovarian axis, cyclic ovulatory activity, the quality of preovulatory follicles and/or subsequent embryo viability

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