Hypobaric Hypoxia Affects the Reproductive Physiology of Dairy Cattle

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ABSTRACT

As the altitude increases, the partial pressure of oxygen decreases, leading to hypoxic conditions and ultimately disturbing body homeostasis and affecting neuroendocrine function in cattle. These physiological changes cause low conception rate, early embryonic death, low fertility, etc., in cattle and other livestock species. So far, cattle's reproductive health associated with high-altitude hypoxic conditions has rarely been studied concerning reproductive physiology, endocrinology, and physio-biochemical perspective. Hence, this review discusses various physiological changes, hormonal disturbance, placenta development, haematological and biochemical changes, etc., which are associated with and affect cattle's reproductive physiology.

Introduction

Leh-Ladakh region, a northwestern Himalayan part referred to as high-altitude, has extreme climate and hypoxia that have deleterious effects on the survivability, productivity, and reproductive performance of various livestock species, including dairy cattle. The areas of Earth's surface (or in its atmosphere) that vary from 1500 to 3000 m above mean sea level (MSL) are classified as high altitude, more than 3000 m and below & equal to 5000 m, referred to as very high altitude (Fig. 1). However, an altitude of more than 5000 m is called extreme altitude (Fig. 1, Dunn, 1989).

This increase in altitude leads to increased hypoxia, further decreasing the oxygen supply to tissues due to low blood oxygen partial pressure (PO_2) (Beall et al., 1997).

This fall in oxygen partial pressure is linked to a fall in air pressure as the altitude increases, decreasing PO_2 at higher elevations. Other environmental stresses at high-altitude are low humidity, extreme temperature variation, high ultraviolet (UV) radiation, and poor nutrition, which negatively affect survivability, health, welfare, and dairy cattle production (Bharti et al., 2017).

All the dairy farmers of the high altitude region face difficulty in animal welfare and maintaining their rearing economy due to low milk yield. According to reports, our study observed the low survivability and production of high productive low-lander cattle due to physiological stress in this high-altitude environment. The critical factor is hypoxia which cannot be controlled through microenvironment management and limits the function of all vital
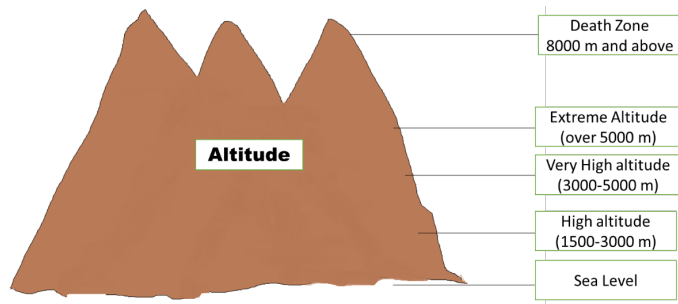
Fig 1. Categorisation of altitude

organs, e.g., lungs, heart, kidney, and brain (Bharti et al., 2017; Kumari et al., 2021). Numerous studies have demonstrated that hypoxia at high altitudes causes pulmonary hypertension and increases haematopoiesis in cattle. One of the most common diseases in cattle at high altitudes is pulmonary hypertension (brisket disease). It is caused by decreased blood oxygen saturation and affects the tissues' ability to transfer oxygen (Tucker and Rhodes, 2001). In this condition, cattle are seen with dull, debilitated, bulky dewlap/brisket, pulsating jugular veins, heart murmur sound on auscultation, gallop rhythm, and brisket oedema (Tucker and Rhodes, 2001).

Additionally, hypoxic conditions at high altitudes, which reduce the oxygen tension, result in haematopoiesis and cause an increase in erythrocytes to compensate for the low oxygen levels (Windsor and Rodway, 2007). Consequently, indigenous species living at high altitudes exhibit considerable changes in critical blood parameters compared to their lowland equivalents (Jain, 1993). In addition, climatic change, low ambient temperature, high altitude hypoxic stress, and poor body homeostasis all harm dairy cattle's reproductive, metabolic, and immunological health (Broucek et al., 1991; Bharti et al., 2017). There is a significant loss of metabolic energy when dealing with stress, reducing the energy available for growth and reproduction. Therefore, indigenous and exotic cattle don't always thrive at high altitudes. Due to cold stress, hypobaric hypoxia, inadequate food supply, including mineral deficiencies at high altitudes, a very long calving interval (2–4 years) was found in crossbred and native cattle due to anestrus, poor fertility, and embryonic mortality at an early stage (Dong et al. 2009; Bharti et al., 2017). So, only a small amount of information is available on the reproductive issues in cattle when exposed to high altitude hypoxic conditions. As a result, it is necessary to investigate various factors that can impact the reproductive health of cattle. In this review, we will discuss the elements that can impact the reproductive health of cattle (Fig. 2).
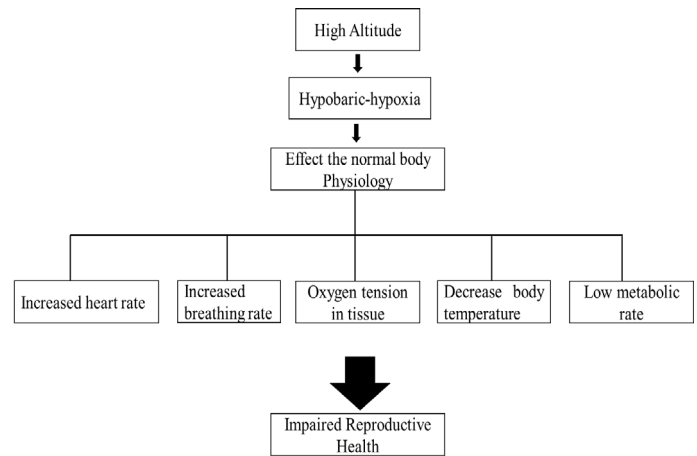

Fig 2. Biological impact of high-altitude environment on physiological responses and reproduction

Arterial blood saturation pressure

A low oxygen level or desaturation in the blood can occur at high altitudes due to low atmospheric pressure. Oxygen saturation levels refer to the quantity of oxygen bound or saturated by haemoglobin in a blood cell; oxygen saturation values ranging from 95% to 100% are regarded in healthy animals (Groves et al., 1993). Hypoxia is the blood's low partial pressure of oxygen (PO_2) that impairs the oxygen supply to tissues (Beall et al., 1997). The PO_2 gradient between alveolar gas and arterial blood typically results from a small amount of venous blood mixing and uneven ventilation-perfusion matching in the lungs (Groves et al., 1993; Ge et al., 1998). The O_2 unloading in the tissue capillary bed causes the PO_2 gradient among capillaries and tissues. When O_2 diffuses from blood's high PO_2 to interstitial fluid's low PO_2, the exchange of gases occurs at the arteries to the capillary bed (Groves et al., 1993; Ge et al., 1998). There is a quick fall in PO_2 due to gas exchange in tissues near the arterial input of the capillary bed (Black et al., 1980). The sudden transport of a lowland mammal to altitudes greater than 3000 m causes acute hypoxia due to the initial failure to increase ventilation and compensate for the low PO_2 levels (Houston, 1998; Hoppeler and Vogt, 2001). However, hypoxia has no effect on arterial PCO_2, but the increased rate of ventilation removes CO_2 and thus reduces arterial PCO_2 (Houston, 1998; Hoppeler and Vogt, 2001). Hence the CO_2 loss results in a lower $[H^+]$, the pH rises, and thus the blood alkalinity increases (Kayser et al., 1996). Central chemoreceptors are found in the brain, on the side of the medulla, where they are bathed by cerebrospinal fluid (CSF), and the decrease in PCO_2 causes the central receptors to slow down breathing (Fischer et al., 1999; Wenger, 2000). As more carbon dioxide is excreted

through the lungs due to the increased breathing rate, PCO_2 in plasma decreases, and eventually, PCO_2 in CSF also decreases, resulting in an increased pH, a signal to reduce the breathing rate (Kayser et al., 1996; Sheafor, 2003). The signal from the central chemoreceptors cancels out the signal from the peripheral chemoreceptors, resulting in a minimal net effect on lung ventilation rate (Vogt et al., 2001). The 'conflict' between peripheral and central chemoreceptors results in the continued production of neural signals that raise ventilation slightly, causing the CSF to become slightly alkaline. The choroid plexus responds by secreting CSF with less HCO_3^-, restoring the pH of the CSF to its 'normal' value (Fischer et al., 1999; Wenger, 2000). For 12–15 hours, this progressive compensation allows the signal from the peripheral chemoreceptors to express fully, causing ventilation to increase and PO_2 in the alveoli to rise (Fischer et al., 1999; Wenger, 2000). The blood remains alkaline for a few days, but the kidneys eventually correct the pH by excreting excess HCO_3 (Kayser et al., 1996; Vogt et al., 2001; Sheafor, 2003).

The increased oxygen-binding affinity of haemoglobin is another key principle for improving the circulatory conductance of O_2 in high-altitude mammals (Black et al., 1980). Following high altitudes, red blood cells stored primarily in the spleen are released (Weber et al., 1993). This raises the hematocrit level, immediately increasing the blood's capacity to carry oxygen. Within 12 hours, the rate at which red blood cells are formed begins to increase, mediated by the glycoprotein hormone erythropoietin, which stimulates cell division in hematopoietic stem cells in the bone marrow for RBC formation (Black et al., 1980; Beall et al., 1997). Another physiological response to high altitude is a rise in heart rate resulting in increased cardiac output. The amount of O_2 distributed to respiring tissues is determined by the tissue's blood flow rate and the value in the blood and tissues (Ge et al., 1998). Cardiac output can increase by up to five times its resting level at sea level (Ge et al., 1998). Many animals' metabolism and body temperature are reduced when their oxygen partial pressure is low. In mammals' central nervous system (CNS), the pre-optic region of the anterior hypothalamus is the centre of thermosensitive neurons that activate in response to hypothalamic temperature, influencing physiological changes. The cooling of body temperature by the hypothalamus in response to hypoxia conditions activated thermogenic pathways, causing shivering in animals. (Tattersall and Milsom, 2009) The thermoregulation area in the hypothalamus influences mammalian circulatory and breathing responses (Glenn and Milsom, 2009). Similarly, hypoxia causes several physiological processes to be accelerated, and much energy is used to keep the body in normal

homeostasis, which eventually impacts reproduction performance.

Oxygen dissociation curve

At high altitudes, oxygen saturation decreases in response to an increase in the production of red blood cells (RBC), which ultimately enhances haemoglobin (Hb) concentration and affinity of Hb towards oxygen (Fig. 3). Hb–O_2 affinity is protective of arterial O_2 saturation in hypoxia, although it can hinder O_2 unloading from the systemic circulation (Black et al., 1980). Since oxygen loading in the lungs and O_2 unloading in tissue capillaries must be optimised in high-altitude vertebrates, they face a physiological difficulty (Weber et al., 1993). The physicochemical operating conditions for Hb in the red blood cell and the inherent qualities of the Hb protein are reflected in the characteristics of blood oxygenation. In the lungs, where PO_2 levels are high, haemoglobin molecules load up with oxygen and release it to the respiring tissues (Black et al., 1980; Houston, 1998). Fig. 2 depicts an S-shaped or sigmoid oxygen dissociation curve (ODC) for the oxygen-transporting pigment haemoglobin. The P_{50} is the value of PO_2 at which a pigment releases 50% of its maximum oxygen capacity, and it measures the pigment's affinity for oxygen (Black et al., 1980; Houston, 1998). Therefore, the greater the number of P_{50}, the lesser the pigment's affinity for oxygen (Black et al., 1980; Houston, 1998). The ODC of haemoglobin is shifted to the right when its affinity for oxygen is reduced. In contrast, the ODC of haemoglobin is displaced to the left when it has a strong affinity for oxygen.
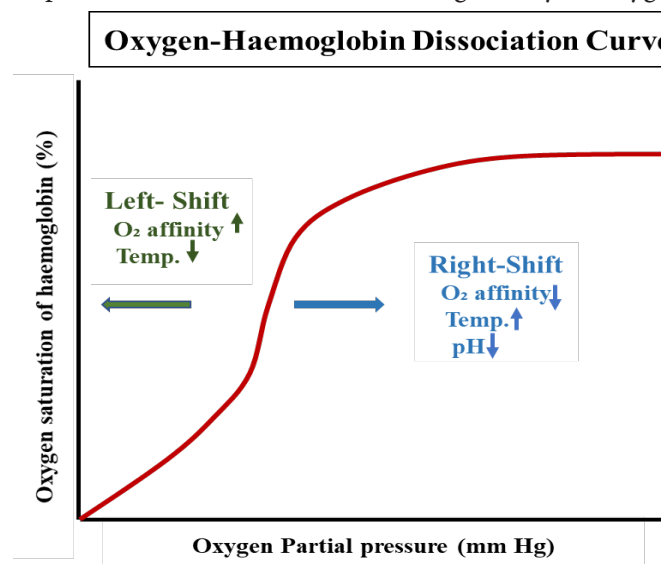

Fig 3. Changes in oxygen-haemoglobin dissociation curve towards right at high-altitude (https://step1.medbullets.com/respiratory/117014/oxygen-hemoglobin-dissociation-curve).

In response to hypoxia, the kidneys secrete erythropoietin, stimulating RBC production in the bone marrow (Semenza, 1994). Over the course of weeks to months, RBC mass rises in proportion to the severity of hypoxia. Accelerated new research into erythropoietin and iron metabolism has been made possible by two recently discovered new iron-regulating hormones (hepcidin and erythroferrone) as well as a newly discovered, highly specific erythropoietin receptor in the blood of high-altitude athletes (Ganz, 2013; Kautz et al., 2014; Villafuerte et al., 2014; Gassmann and Muckenthaler, 2015; Buratti et al., 2015; Kuhn, 2015). The rise in haemoglobin observed one to two days after ascent is attributable to haemoconcentration produced by reduced plasma volume rather than increased RBC mass.

The rate at which haemoglobin releases oxygen to tissues is governed by erythrocytes 2,3-diphosphoglycerate (2,3-DPG), with an increase in 2,3-DPG levels decreasing oxygen affinity and vice versa (MacDonald, 1977). These bovine P_{50} values are comparable to those found in other mammals. However, Fronticelli (1990) explains that the chloride ion (Cl^-) activity affects the cattle's low oxygen affinity of Hb. The Hb affinity to oxygen in cattle is particularly sensitive to the Cl^- level, acting as an alternate effector of the standard 2,3-DPG in humans and other animals. This is because human Hb and cow Hb have structural variances (Fronticelli, 1990; Clerbaux et al., 1993). The pH influence on cow ODC curves is lower than in humans, dogs, and horses. So, when an abrupt shift of the ODC is necessary to compensate for cellular hypoxia, then decreased pH is an unfavourable factor for adequate oxygen compensation to tissues level (Clerbaux et al., 1993). These hypoxic environmental conditions disturb cellular energy metabolism and normal physiological processes in cattle more considerable than the other species. However, their impact on overall body homeostasis and hormonal secretions needs to be studied and associated with the health and production of cattle. Furthermore, this study could also help identify other compensatory mechanisms to deal with hypoxia.

Poor cellular development and tissue necrosis

Many developmental processes and normal tissue homeostasis are regulated by oxygen. Oxidative metabolism, energy supply via ATP generation, and cell survival require oxygen (Rankin and Giaccia, 2016). Hypoxia is a primary reason for snoring, ischemic stroke, and heart disease; it can damage endothelial cells, hippocampal neurons, and myocardial cells, among many other cell types. These cell types play a critical role in the development and progression of these disorders (Wang et al., 1993; Feng et al., 2012; Faa et al., 2014). Studies have demonstrated that hypoxia damages and even kills cells primarily by oxidative stress, inflammation, acidosis (Distler et al., 2005; Guo et al., 2019), and apoptosis (Saraste and Pulkki, 2000). Hypoxia has been linked to apoptosis in numerous studies. Hypoxia can lead to apoptosis by inducing mitochondrial damage, calcium excess, an increase in oxygen free radicals, and so on (Guo et al., 2019).

Chronic hypoxia at high altitudes has been proven in numerous studies to affect muscle structure, resulting in a considerable reduction in fibre density (Green et al., 1989; Howald and Hoppeler, 2003). Reports revealed that altitude exposure affects enzyme activities up to 30% involved in aerobic oxidative metabolism and moderately decreases oxidative muscle capacity (Hoppeler and Vogt, 2001). In addition, skeletal muscle and RBCs include more proteins for the cellular transport of bicarbonate, protons, and lactates (Juel et al., 2003; Saunders et al., 2009). Chronic exposure to hypobaric hypoxia, which reduces cellular O_2 availability, was hypothesised to be the primary cause of decreased muscle cross-sectional area and oxidative activity (Hoppeler and Vogt, 2001). These changes correspond with decreased body weight and total muscle mass at high-altitude (San et al., 2013). In addition, hypoxia produces muscle exhaustion in the diaphragm and abdominal muscles, reducing breathing ability. Neary et al. (2013) investigated the arterial pressure in newborn calves and cows at high altitudes following transport from lowland to highland. He showed cows had a lower haematocrit but higher oxyhaemoglobin saturation than calves. This is significant since pulmonary hypertension in cattle is predicted by poor oxyhaemoglobin saturation (Will et al., 1962). Since foetal haemoglobin has a high affinity for oxygen and is detectable in calf blood 6–7 months after birth, one may predict calves have higher oxyhaemoglobin saturation than cows (Lee, 1971). The oxyhaemoglobin dissociation curve, on the other hand, is sigmoidal. When oxygen pressure is less than 60 mm Hg, oxyhaemoglobin saturation drops precipitously. The mean calf PO_2 pressure was as low as 52.6 mmHg (1 month) and was continuously lower than the mean value of 59.4 mmHg in cows (Neary et al., 2013).

Microvesicles (MVs) are subcellular components produced by many cell types. Normal cells can create a limited quantity of MVs, while activated or apoptotic cells make the vast majority. Under normal circumstances, cells create a negligible number of MVs; however, when cells are activated by hypoxia or oxidative stress, MV generation increases significantly (Zhao et al., 2015). MVs are crucial

during developing and progressing hypoxia-related diseases, inflammation, and apoptosis (Distler et al., 2005). The brain consumes nearly 20% of the body's oxygen consumption; hence, the brain is significantly affected at high altitudes (Li et al., 2013). Even though compensatory hyperventilation, tachycardia, and increased cerebral blood flow can partially maintain cerebral oxygen delivery at high altitudes, these mechanisms are insufficient (Li et al., 2013). Hypobaric hypoxia causes significant brain damage in humans and rats, altering cerebral blood flow, energy metabolism, and cognitive functions, including learning and memory (Semenov et al., 2008; Goodman et al., 2011; Babbar and Agarwal, 2012). In mitochondria, adequate oxygen is critical to producing ATP for cell viability, and hypoxic situations can disrupt the metabolic energy route, resulting in severe cell death and damage (Kann and Kovacs, 2007; Chen et al., 2013). Furthermore, Li et al. (2013) proved that nerve cells morphologically changed after rats were exposed to hypobaric hypoxia; however, as the exposure time increases, it causes severe damage to nerve cells and, in extreme cases, results in cerebral edema. Although no study on cell apoptosis in cattle at high-altitude hypobaric-hypoxia has been published so far, Nishimura et al. (2008) investigated whether hypoxia causes apoptosis in bovine luteal cells in in-vivo conditions. Since ovarian blood flow drops in ewes and cows during luteolysis, hypoxia plays a role in ruminant luteolysis (Wise et al., 1982; Acosta et al., 2002). Furthermore, hypoxia inhibits progesterone synthesis in bovine luteal cells by decreasing mitochondrial cytochrome P450 side-chain cleavage enzyme activity, implying that hypoxia accelerates functional luteolysis (Nishimura et al., 2006). The cow could not conceive due to lateral cell death and decreased progesterone concentration. However, most investigations on high altitude and hypoxia have focused on the loss of embryos or foetuses, the restriction of growth within the uterus, and the lowering of birth weight in animals (Hartinger et al., 2006). Under hypoxic conditions, the development of bovine follicles is constrained due to the suppression of the ER (Ma et al., 2019).

Cellular and systemic adaptive responses activate the Hypoxia-inducible factor (HIF) (Sendoel and Hengartner, 2014). HIF stimulates the expression of various genes involved in angiogenesis, cellular metabolism, proliferation, extracellular matrix production, and apoptosis regulation based on the cellular context (Wenger et al., 2005). So, HIF expression is crucial for folliculogenesis and luteolysis. Hence, several factors could influence female fertility by affecting the efficacy of the hypothalamus-hypophysis-ovarian axis, cyclic ovulatory activity, the quality of pre-ovulatory follicles/oocytes/embryos, and eventual embryo/fetus viability. All of these essential functions require a fully functional corpus luteum. Therefore, hypoxia and oxidative stress may contribute to poor corpus luteum activity in high-altitude cattle, resulting in low fertility.

Poor placental development

The placenta is the primary facilitator of nutrient transport from the mother to the foetus; its morphological and functional development is vulnerable to hypoxia; hence, the placenta is crucial in evaluating the impact of attitude on foetal outcomes (Robertson and Wilsterman, 2020). Hypoxia increases oxidative stress, which can cause damage to the placenta during parturition. High altitude-native mammals live in mountainous areas all year and go through their whole reproductive cycle in conditions of prolonged cold and hypoxia, which affects their reproductive health, and therefore, human and domesticated animals living at high altitudes are less fertile as compared to those living at sea level and lower altitude (Parraguez et al., 2006). So, low-lander, poorly adapted dairy cattle experience high degrees of infertility. Compared to adults, pre-natal, post-natal, and physiologically immature young mammals face more physiological challenges in cold, hypoxic conditions at high altitudes (Robertson and Wilsterman, 2020). The placenta is divided into two compartments: one for nutrient exchange and the other for connecting the mother and fetus vasculature and orchestrating the mother's physiology during pregnancy. However, gestational hypoxia affects both compartments, although the effect on foetal growth is unknown (Robertson and Wilsterman, 2020).

Soares et al. (2017) reported that gestational hypoxia leads to hypertrophy in the placenta's endocrine region, also known as the junctional zone in rodents. Some of the changes observed in guinea pigs and rats, gestational hypoxia, significantly impact the invasive trophoblast, a kind of trophoblast that arises from the intersection zone and is to account for invading and remodelling maternal vasculature (Soares et al., 2017). Interestingly, short exposure to hypoxia increases triggers these cells to migrate into maternal tissues, perhaps permitting more substantial vascular remodelling; chronic hypoxia inhibits these cells' remodelling behaviour (Zhou et al., 2013). Inadequate trophoblast remodelling results in inadequate blood flow or high blood pressure that could cause the placenta's structure to collapse and halt the nutrient and gas exchange between mother and fetus (Robertson and Wilsterman, 2020). Trophoblast inversion can lead to impaired fetus development or embryonic death in mammals; there is no report on cattle for such disorders, and further cattle studies are required to determine its effect.

A reduction in the diameter of foetal capillaries at high altitudes also characterises the vascular compartment of the placenta. This reduction in diameter may increase the surface area to volume ratio of the surface over which gas and nutrient exchange occur (Espinoza et al., 2001; Parraguez et al., 2010; Khalid et al., 2016). Similar reductions in foetal capillary width have been observed in humans that have adapted to live at high altitudes, which suggests that the rise in surface area to volume ratio is an adaptive response (Jackson et al., 1987). These impacts foetal and embryonic development when viewed through the perspective of pregnancy and embryonic development studies at high altitudes. So, hypoxia or oxygen tension significantly controls and facilitates foetal and embryonic development at high altitudes (Moore et al., 2011). Hence, understanding how hypoxia affects foetal and embryonic development is crucial because it highlights the relevance of pre-natal development concerning the risk of cardiovascular or other illnesses later in life (Barker, 1992; Moore et al., 2011). According to reports, the birth weight of newborns residing at high altitudes decreases compared to sea levels during the same gestation periods. However, not all newborns born to residents who stay at high altitudes are relatively small, and the majority of newborns fall within the typical weight range for their gestational age (Moore et al., 1998; Zamudio, 2003).

Contrary to suggestions that growth restriction at altitude is typical and allows for adaptation to reduced atmospheric pressure, many studies show that growth restriction at altitude is related to higher infant mortality and morbidity (Moore et al., 1998; Zamudio, 2003). The human foetus at high altitude is susceptible to hypobaric-hypoxia, which results in decreased maternal arterial PO_2 and uterine blood flow (Zamudio et al., 1995). The uteroplacental vascular growth factors produced by the placenta and human placental growth hormone can influence maternal metabolism to change the concentrations of nutrients needed for foetal growth in the blood (Parraguez et al., 2013; Parraguez et al., 2015). High-altitude women are more likely than their low-altitude counterparts to experience life-threatening pregnancy issues because of the placenta's potential influence on uterine blood flow and foetal growth. Although no data is available on the placenta development in cattle at high altitudes, the human and mouse data has been discussed to get a physiological mechanism of the effect of hypobaric hypoxia on placental development. Likewise, we can hypothesise that cattle may face similar difficulties in placental and fetal development under hypoxia.

Effect on reproductive hormone profile

Various physiological alterations, including altered hormone secretion, occur due to acute and chronic exposure to high altitudes. According to researchers, high altitude hypobaric-hypoxia could also affect the regulation and secretion of reproductive hormones, prolactin, and growth hormone (Humpeler et al., 1980; Knudtzon et al., 1989; Benso, 2007). In reaction to hypoxia, some endocrine or neuroendocrine mechanisms are triggered, while others are suppressed. Although adjacent zones in the same organ release cortisol and aldosterone hormones, hypoxia increases cortisol while decreasing aldosterone (Richalet et al., 2010).

In most studies, thyroid hormone levels have been reported to rise at higher altitudes, but TSH secretion is unaffected, and the processes underlying this dissociation remain unknown (Barnholt et al., 2006). TSH levels remain stable, but higher levels of total and free fractions of T3 and T4 are consistent with most prior investigations, implying that moderate hyperthyroidism may be required to tolerate the severe conditions of high altitudes (Basu et al., 1995; Ramirez et al., 1995). Increased amounts of 2,3-diphosphoglyceric acid in erythrocytes caused by thyroid hormones facilitate oxygen delivery to tissues by shifting the oxyhaemoglobin dissociation curve to the right, which is beneficial in hypoxia (Snyder and Reddy, 1970). The TSH-independent T4 spike has been explained in several ways. A change in the pace of hormone production, a disruption in the clearance process, or a haemoconcentration and vascular shift can all affect hormone levels. The increase in T4 at high altitudes cannot be exclusively attributed to haemoconcentration as determined by the total plasma protein concentration and dehydration (Surks, 1966). T3 uptake is unchanged or increased at high altitudes, implying a standard binding capacity; the finding corroborates that levels of free hormones increase along with those of total hormones (Basu et al., 1995). Increased basal metabolic rate has been linked to increased thyroid hormone levels at high altitudes (Surks et al., 1967). At altitude, cold can be an aggravating factor for thyroid function. Thyroid hormone imbalances in cattle have severe consequences and may affect the molecular mechanisms that control sexual development and behaviour, menstrual and estrous cycle control, ovulation, maternal capacity, pregnancy maintenance, post-natal and foetal growth, and lactation in cattle (Vasudevan et al., 2002; Leite et al., 2008; Silva et al., 2012). Both the direct action of THs in the reproductive organs and the activity of THs on the bioavailability of other

hormones and growth factors, which are also essential for the proper functioning of the female reproductive system, are responsible for these effects (Forhead and Fowden, 2014; Duarte-Guterman et al., 2014, Silva et al., 2018).

Neurotransmitters dopamine and noradrenaline have been shown to suppress prolactin release at high elevations, which may lead to pituitary depression (Ben-Jonathan and Hnasko, 2001). However, noradrenaline increases consistently under hypobaric-hypoxic conditions, but dopamine changes are inconsistent; as a result, prolactin secretions vary (Serebrovskaya et al., 2000; Panjwani et al., 2006). In response to hypoxia, erythropoietin (EPO) secretion increases in several central nervous system regions, promoting dopamine release and, as a result, inhibiting prolactin secretion (Markianos et al., 2006). Lacasse et al. (2019) reviewed the evidence that prolactin is required to initiate lactation in dairy cattle at parturition. Parturition in cattle is associated with high prolactin levels, whereas lowering prolactin levels prevents lactogenesis.

Increased levels of thyroid hormones, dopamine, and norepinephrine at high altitudes also regulate Growth Hormone (GH) secretion (Page et al., 1988). The action of catecholamines at varied regulatory levels and their rise in hypoxia may explain the varying GH responses at high altitudes. Prolonged exposure to altitude hypoxia induces significant hormonal alterations not driven by changes in the hypothalamic-hypophyseal axis (Richalet et al., 2010). Gonadotrophs contain GH binding proteins (GHBPs) and GH receptors (GHRs), and as GH concentration falls, so does LH/FSH secretion (Hull and Havery, 2002). GH insufficiency can have various effects, depending on the species of animal and the stage of reproduction it is in. GH can have stimulatory, inhibitory, or minimal effects on the secretion of LH and FSH (Hull and Havery, 2002). According to Sirotkin (2005), Rodent gonadotropin secretion is more responsive to GH regulation than the gonadotropin secretion of ruminants and primates.

There is a decrease in FSH and LH basal concentrations (Friedl et al., 1988). Catecholamines influence LH secretion; however, different catecholamines have opposite effects, like dopamine inhibits while noradrenaline stimulates gonadotropin levels (Richalet et al., 2010). According to Ma et al. (2019), hypoxic conditions disrupt estrogen levels, affecting folliculogenesis and resulting in infertility and ovarian cancer in sheep and mice. In-vitro hypoxia studies on bovine luteal cells by Nishimura et al. (2006) revealed that it inhibits progesterone synthesis, implying that hypoxia accelerates functional luteolysis, which further affects normal reproductive physiology.

So far, no such studies on cattle have been published that describe the consequences of being at a high altitude on cattle. Nonetheless, there are few studies on sheep, mice, and humans. As previously discussed, numerous studies have demonstrated that animals living at high altitudes suffer from health problems and have reduced reproduction. The detailed analysis of hypobaric-hypoxia's function in cattle reproduction has not been discussed. The hypobaric hypoxic condition affects the hormonal profile of cattle by causing luteal death, which alters the normal secretion of reproductive hormones, resulting in infertility or other reproductive diseases in cattle.

Haematology and blood biochemical changes under hypoxic condition

There is a significant loss of metabolic energy when dealing with high altitude stress, resulting in less energy available for production and reproduction, resulting in poor health and production of dairy cattle at high-altitude (Giri et al., 2017). Due to hyperventilation, both calves and cows developed respiratory alkalosis at high altitudes in the hypoxic environment, and this physiological condition is more common in lowlander animals when reared at high altitudes (Monge and Leonvelarde, 1991). Heamoglobin, erythrocytes count and mean corpuscular level are increased under hypoxia, which helps in acclimatisation at high altitudes (Brun-Hansen et al., 2006; Mohri et al., 2007; Bharti et al., 2017). However, these changes are insufficient to compensate for the decrease in atmospheric oxygen tension induced by high altitude and poor oxygen transport from the alveoli into the pulmonary circulation. Various researchers observe adverse changes in liver and kidney function in dairy cattle, which has a deleterious effect on neural-endocrine functions, resulting in an imbalance in various reproductive hormones. Therefore, the primary objective of restoring reproductive hormone levels and improving reproductive health in dairy cattle is to improve their nutrition and microenvironment. These farm managemental changes in high-altitude will reduce the adverse effect of hypoxia and cold stress on body homeostasis and improve neuro-endocrine function.

Conclusion

Hypobaric hypoxia at high-altitude brings physiological stress to dairy cattle through modulation of blood biochemical, endocrine, and other cellular functions. The reproductive health of native cattle and low-lander exotic

high-producing species are adversely affected due to hypoxia-induced changes in neuroendocrine secretions. It alters the average profile of hormones and metabolic functions in dairy cattle, leading to increased infertility and abortion. However, compared to exotic breeds at high altitudes, native cattle had a lower incidence of infertility. Therefore, there is a need to evaluate their reproductive health and physiology at high-altitude to develop ameliorative measures and breeding programs for higher fertility and cattle health.

Acknowledgements

References

Acosta TJ, Yoshizawa N, Ohtani M, Miyamoto A. Local changes in blood flow within the early and midcycle corpus luteum after prostaglandin F(2 alpha) injection in the cow. Biol Reprod. 2002;66(3):651-8. doi: 10.1095/biolreprod66.3.651.

Babbar R, Agarwal S. A new approach to hypobaric hypoxia induced cognitive impairment. Indian J Med Res. 2012;136(3):365-7.

Barker DJP, (1992). The fetal and infant origins of adult disease. British Medical Journal Books; London.

Barnholt KE, Hoffman AR, Rock PB, Muza SR, Fulco CS, Braun B, Holloway L, Mazzeo RS, Cymerman A, Friedlander AL. Endocrine responses to acute and chronic high-altitude exposure (4,300 meters): modulating effects of caloric restriction. Am J Physiol Endocrinol Metab. 2006;290(6):E1078-88. doi: 10.1152/ajpendo.00449.2005.

Basu M, Pal K, Malhotra AS, Prasad R, Sawhney RC. Free and total thyroid hormones in humans at extreme altitude. Int J Biometeorol. 1995;39(1):17-21. doi: 10.1007/BF01320888.

Beall CM, Strohl KP, Blangero J, Williams-Blangero S, Almasy LA, Decker MJ, Worthman CM, Goldstein MC, Vargas E, Villena M, Soria R, Alarcon AM, Gonzales C. Ventilation and hypoxic ventilatory response of Tibetan and Aymara high altitude natives. Am J Phys Anthropol. 1997;104(4):427-47. doi: 10.1002/(SICI)1096-8644(199712)104:4<427::AID-AJPA1>3.0.CO;2-P.

Ben-Jonathan N, Hnasko R. Dopamine as a prolactin (PRL) inhibitor. Endocr Rev. 2001;22(6):724-63. doi: 10.1210/edrv.22.6.0451.

Benso A, Broglio F, Aimaretti G, Lucatello B, Lanfranco F, Ghigo E, Grottoli S. Endocrine and metabolic responses to extreme altitude and physical exercise in climbers. Eur J Endocrinol. 2007;157(6):733-40. doi: 10.1530/EJE-07-0355.

Bharti VK, Giri A, Vivek P, Kalia S. Health and productivity of dairy cattle in high mountain cold desert environment of Leh-Ladakh: A review. Indian J Anim Sci, 2017:87(1): 3-10.

Black CP, Tenney SM. Oxygen transport during progressive hypoxia in high-altitude and sea-level waterfowl. Respir Physiol. 1980;39(2):217-39. doi: 10.1016/0034-5687(80)90046-8.

Broucek J, Letkovicová M, Kovalcuj K. Estimation of cold stress effect on dairy cows. Int J Biometeorol. 1991;35(1):29-32. doi: 10.1007/BF01040960.

Brun-Hansen HC, Kampen AH, Lund A. Hematologic values in calves during the first 6 months of life. Vet Clin Pathol. 2006;35(2):182-7. doi: 10.1111/j.1939-165x.2006.tb00111.x.

Buratti P, Gammella E, Rybinska I, Cairo G, Recalcati S. Recent advances in iron metabolism: relevance for health, exercise, and performance. Med Sci Sports Exerc. 2015;47(8):1596-604. doi: 10.1249/MSS.0000000000000593.

Chen L, Zhang X, Zhou W, Qiao Q, Liang H, Li G, Wang J, Cai F. The interactive effects of cytoskeleton disruption and mitochondria dysfunction lead to reproductive toxicity induced by microcystin-LR. PLoS One. 2013;8(1):e53949. doi: 10.1371/journal.pone.0053949.

Clerbaux T, Gustin P, Detry B, Cao ML, Frans A. Comparative study of the oxyhaemoglobin dissociation curve of four mammals: man, dog, horse and cattle. Comp Biochem Physiol Comp Physiol. 1993;106(4):687-94. doi: 10.1016/0300-9629(93)90382-e.

Distler JH, Pisetsky DS, Huber LC, Kalden JR, Gay S, Distler O. Microparticles as regulators of inflammation: novel players of cellular crosstalk in the rheumatic diseases. Arthritis Rheum. 2005;52(11):3337-48. doi: 10.1002/art.21350.

Dong S K, Wen L, Zhu L, Lassoie J P, Yan Z L, Shrestha K K, Pariya D, Sharma E. Indigenous yak and yak-cattle crossbreed management in high altitude areas of northern Nepal: A case study from Rasuwa district. African J Agri Res, 2009; 4: 957–67.

Duarte-Guterman P, Navarro-Martín L, Trudeau VL. Mechanisms of crosstalk between endocrine systems: regulation of sex steroid hormone synthesis and action by thyroid hormones. Gen Comp Endocrinol. 2014;203:69-85. doi: 10.1016/j.ygcen.2014.03.015.

Dunn MG. Exploring your world: The adventure of geography. Washington, DC: National Geographic Society, 1989.

Espinoza J, Sebire NJ, McAuliffe F, Krampl E, Nicolaides KH. Placental villus morphology in relation to maternal hypoxia

at high altitude. Placenta. 2001;22(6):606-8. doi: 10.1053/plac.2001.0696.

Faa A, Xanthos T, Fanos V, Fanni D, Gerosa C, Pampaloni P, Pais ME, Faa G, Iacovidou N. Hypoxia-induced endothelial damage and microthrombosis in myocardial vessels of newborn landrace/large white piglets. Biomed Res Int. 2014;2014:619284. doi: 10.1155/2014/619284.

Feng J, Wu Q, Zhang D, Chen BY. Hippocampal impairments are associated with intermittent hypoxia of obstructive sleep apnea. Chin Med J (Engl). 2012;125(4):696-701.

Fischer S, Clauss M, Wiesnet M, Renz D, Schaper W, Karliczek GF. Hypoxia induces permeability in brain microvessel endothelial cells via VEGF and NO. Am J Physiol. 1999;276(4):C812-20. doi: 10.1152/ajpcell.1999.276.4.C812.

Forhead AJ, Fowden AL. Thyroid hormones in fetal growth and prepartum maturation. J Endocrinol. 2014;221(3):R87-R103. doi: 10.1530/JOE-14-0025.

Friedl KE, Plymate SR, Bernhard WN, Mohr LC. Elevation of plasma estradiol in healthy men during a mountaineering expedition. Horm Metab Res. 1988;20(4):239-42. doi: 10.1055/s-2007-1010802.

Fronticelli C. A possible new mechanism of oxygen affinity modulation in mammalian hemoglobins. Biophys Chem. 1990;37(1-3):141-6. doi: 10.1016/0301-4622(90)88014-j.

Ganz T. Systemic iron homeostasis. Physiol Rev. 2013;93(4):1721-41. doi: 10.1152/physrev.00008.2013.

Gassmann M, Muckenthaler MU. Adaptation of iron requirement to hypoxic conditions at high altitude. J Appl Physiol (1985). 2015;119(12):1432-40. doi: 10.1152/japplphysiol.00248.2015.

Ge RL, Kubo K, Kobayashi T, Sekiguchi M, Honda T. Blunted hypoxic pulmonary vasoconstrictive response in the rodent Ochotona curzoniae (pika) at high altitude. Am J Physiol. 1998;274(5):H1792-9. doi: 10.1152/ajpheart.1998.274.5.H1792.

Giri A, Bharti VK, Kalia S, Ravindran TV, Ranjan P, Kundan TR, Kumar B. Seasonal changes in haematological and biochemical profile of dairy cows at high altitude cold desert, Indian J Anim Sci. 2017; 87: 723–27.

Goodman MD, Makley AT, Huber NL, Clarke CN, Friend LA, Schuster RM, Bailey SR, Barnes SL, Dorlac WC, Johannigman JA, Lentsch AB, Pritts TA. Hypobaric hypoxia exacerbates the neuroinflammatory response to traumatic brain injury. J Surg Res. 2011;165(1):30-7. doi: 10.1016/j.jss.2010.05.055.

Green HJ, Sutton JR, Cymerman A, Young PM, Houston CS. Operation Everest II: adaptations in human skeletal muscle. J Appl Physiol (1985). 1989;66(5):2454-61. doi: 10.1152/jappl.1989.66.5.2454.

Groves BM, Droma T, Sutton JR, McCullough RG, McCullough RE, Zhuang J, Rapmund G, Sun S, Janes C, Moore LG. Minimal hypoxic pulmonary hypertension in normal Tibetans at 3,658 m. J Appl Physiol (1985). 1993;74(1):312-8. doi: 10.1152/jappl.1993.74.1.312.

Guo Y, Tan J, Miao Y, Sun Z, Zhang Q. Effects of Microvesicles on Cell Apoptosis under Hypoxia. Oxid Med Cell Longev. 2019;2019:5972152. doi: 10.1155/2019/5972152.

Hartinger S, Tapia V, Carrillo C, Bejarano L, Gonzales GF. Birth weight at high altitudes in Peru. Int J Gynaecol Obstet. 2006;93(3):275-81. doi: 10.1016/j.ijgo.2006.02.023.

Hoppeler H, Vogt M. Muscle tissue adaptations to hypoxia. J Exp Biol. 2001;204(Pt 18):3133-9. doi: 10.1242/jeb.204.18.3133.

Houston C. Going higher: Oxygen, man and mountains. Mountaineer Books, Seattle, USA, 1998.

Howald H, Hoppeler H. Performing at extreme altitude: muscle cellular and subcellular adaptations. Eur J Appl Physiol. 2003;90(3-4):360-4. doi: 10.1007/s00421-003-0872-9.

Hull KL, Harvey S. GH as a co-gonadotropin: the relevance of correlative changes in GH secretion and reproductive state. J Endocrinol. 2002;172(1):1-19. doi: 10.1677/joe.0.1720001.

Humpeler E, Skrabal F, Bartsch G. Influence of exposure to moderate altitude on the plasma concentraton of cortisol, aldosterone, renin, testosterone, and gonadotropins. Eur J Appl Physiol Occup Physiol. 1980;45(2-3):167-76. doi: 10.1007/BF00421324.

Jackson MR, Mayhew TM, Haas JD. Morphometric studies on villi in human term placentae and the effects of altitude, ethnic grouping and sex of newborn. Placenta. 1987;8(5):487-95. doi: 10.1016/0143-4004(87)90077-4.

Jain NC. Comparative hematology of common domestic animals.In: Essentials of Veterinary Hematology, 1st ed. Lee & Febiger,Philadelphia, 1993.

Juel C, Lundby C, Sander M, Calbet JA, Hall Gv. Human skeletal muscle and erythrocyte proteins involved in acid-base homeostasis: adaptations to chronic hypoxia. J Physiol. 2003;548(Pt 2):639-48. doi: 10.1113/jphysiol.2002.035899.

Kann O, Kovács R. Mitochondria and neuronal activity. Am J Physiol Cell Physiol. 2007;292(2):C641-57. doi: 10.1152/ajpcell.00222.2006.

Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. Nat Genet. 2014;46(7):678-84. doi: 10.1038/ng.2996.

Kayser B, Hoppeler H, Desplanches D, Marconi C, Broers B, Cerretelli P. Muscle ultrastructure and biochemistry of lowland Tibetans. J Appl Physiol (1985). 1996;81(1):419-25. doi: 10.1152/jappl.1996.81.1.419.

Khalid MEM, Ahmed HS, Osman OM, Al Hashem FH. The relationship of birth weight, body shape and body composition at birth to altitude in Saudi Arabia. Int J Morphol. 2016; 34: 1109-1116. doi:10.4067/S0717-95022016000300048.

Knudtzon J, Bogsnes A, Norman N. Changes in prolactin and growth hormone levels during hypoxia and exercise. Horm Metab Res. 1989;21(8):453-4. doi: 10.1055/s-2007-1009260.

Kühn LC. Iron regulatory proteins and their role in controlling iron metabolism. Metallomics. 2015;7(2):232-43. doi: 10.1039/c4mt00164h.

Kumari P, Giri A, Bharti VK, Kumar K, Chaurasia OP. Evaluation of various biochemical stress markers and morphological traits in different goat breeds at high-altitude environment. Biological Rhythm Research, 2021; 52: 331-341.

Lacasse P, Zhao X, Vanacker N, Boutinaud M. Review: Inhibition of prolactin as a management tool in dairy husbandry. Animal. 2019;13(S1):s35-s41. doi: 10.1017/S1751731118003312.

Lee CK, Odell GV, Eliot FP, Anderson IL, Jones EW. Post-natal loss of bovine fetal haemoglobin. Am J Vet Res. 1971; 32(7):1039–1044.

Leite ED, de Freitas ES, de Almeida Souza C, de Melo Ocarino N, Cassali GD, Serakides R. Histomorphometry and expression of CDC-47 and caspase-3 in mammary glands of pregnant female rats with artificial hyperthyroidism. Pathol Res Pract. 2008;204(9):663-70. doi: 10.1016/j.prp.2008.04.002.

Li J, Qi Y, Liu H, Cui Y, Zhang L, Gong H, Li Y, Li L, Zhang Y. Acute high-altitude hypoxic brain injury: Identification of ten differential proteins. Neural Regen Res. 2013;8(31):2932-41. doi: 10.3969/j.issn.1673-5374.2013.31.006.

Ma L, Wang L, Gao H, Liu N, Zheng Y, Gao Y, Liu S, Jiang Z. Hypoxia Limits the Growth of Bovine Follicles in Vitro by Inhibiting Estrogen Receptor α. Animals (Basel). 2019;9(8):551. doi: 10.3390/ani9080551.

MacDonald R. Red cell 2,3-diphosphoglycerate and oxygen affinity. Anaesthesia 1977;32(6):544-53. doi: 10.1111/j.1365-2044.1977.tb10002.x.

Markianos M, Kosmidis ML, Sfagos C. Reductions in plasma prolactin during acute erythropoietin administration. Neuro Endocrinol Lett. 2006;27(3):355-8.

Mohri M, Sharifi K, Eidi S. Hematology and serum biochemistry of Holstein dairy calves: age related changes and comparison with blood composition in adults. Res Vet Sci. 2007;83(1):30-9. doi: 10.1016/j.rvsc.2006.10.017.

Monge C, León-Velarde F. Physiological adaptation to high altitude: oxygen transport in mammals and birds. Physiol Rev. 1991;71(4):1135-72. doi: 10.1152/physrev.1991.71.4.1135.

Moore LG, Charles SM, Julian CG. Humans at high altitude: hypoxia and fetal growth. Respir Physiol Neurobiol. 2011;178(1):181-90. doi: 10.1016/j.resp.2011.04.017.

Moore LG, Niermeyer S, Zamudio S. Human adaptation to high altitude: regional and life-cycle perspectives. Am J Phys Anthropol. 1998;Suppl 27:25-64. doi: 10.1002/(sici)1096-8644(1998)107:27+<25::aid-ajpa3>3.0.co;2-l.

Neary JM, Gould DH, Garry FB, Knight AP, Dargatz DA, Holt TN. An investigation into beef calf mortality on five high-altitude ranches that selected sires with low pulmonary arterial pressures for over 20 years. J Vet Diagn Invest. 2013;25(2):210-8. doi: 10.1177/1040638713478608.

Nishimura R, Komiyama J, Tasaki Y, Acosta TJ, Okuda K. Hypoxia promotes luteal cell death in bovine corpus luteum. Biol Reprod. 2008;78(3):529-36. doi: 10.1095/biolreprod.107.063370.

Nishimura R, Sakumoto R, Tatsukawa Y, Acosta TJ, Okuda K. Oxygen concentration is an important factor for modulating progesterone synthesis in bovine corpus luteum. Endocrinology. 2006;147(9):4273-80. doi: 10.1210/en.2005-1611.

Page MD, Dieguez C, Valcavi R, Edwards C, Hall R, Scanlon MF. Growth hormone (GH) responses to arginine and L-dopa alone and after GHRH pretreatment. Clin Endocrinol (Oxf). 1988;28(5):551-8. doi: 10.1111/j.1365-2265.1988.tb03690.x.

Panjwani U, Thakur L, Anand JP, Malhotra AS, Banerjee PK. Effect of simulated ascent to 3500 meter on neuro-endocrine functions. Indian J Physiol Pharmacol. 2006 50(3):250-6.

Parraguez VH, Atlagich M, Behn C, Bruzzone ME, Raggi LA. Fertility in ewes at high altitude: comparison between animals with long- and short-time residence at high altitude and the effect of antioxidant vitamins. Reprod Dom Anim, 2006; 41: 372.

Parraguez VH, Atlagich MA, Urquieta B, Galleguillos M, De Los Reyes M, Kooyman DL, Araneda S, Raggi LA. Expression of vascular endothelial growth factor and endothelial nitric oxide synthase is increased in the placenta of sheep at high altitude in the Andes. Can J Vet Res. 2010;74(3):193-9.

Parraguez VH, Mamani S, Cofré E, Castellaro G, Urquieta B, De Los Reyes M, Astiz S, Gonzalez-Bulnes A. Disturbances in Maternal Steroidogenesis and Appearance of Intrauterine Growth Retardation at High-Altitude Environments Are Established from Early Pregnancy. Effects of Treatment with Antioxidant Vitamins. PLoS One. 2015;10(11):e0140902. doi: 10.1371/journal.pone.0140902.

Parraguez VH, Urquieta B, Pérez L, Castellaro G, De los Reyes M, Torres-Rovira L, Aguado-Martínez A, Astiz S, González-

Bulnes A. Fertility in a high-altitude environment is compromised by luteal dysfunction: the relative roles of hypoxia and oxidative stress. Reprod Biol Endocrinol. 2013;11:24. doi: 10.1186/1477-7827-11-24.

Ramirez G, Herrera R, Pineda D, Bittle PA, Rabb HA, Bercu BB. The effects of high altitude on hypothalamic-pituitary secretory dynamics in men. Clin Endocrinol (Oxf). 1995;43(1):11-8. doi: 10.1111/j.1365-2265.1995.tb01887.x.

Rankin EB, Giaccia AJ. Hypoxic control of metastasis. Science. 2016;352(6282):175-80. doi: 10.1126/science.aaf4405.

Richalet JP, Letournel M, Souberbielle JC. Effects of high-altitude hypoxia on the hormonal response to hypothalamic factors. Am J Physiol Regul Integr Comp Physiol. 2010;299(6):R1685-92. doi: 10.1152/ajpregu.00484.2010.

Robertson CE, Wilsterman K. Developmental and reproductive physiology of small mammals at high altitude: challenges and evolutionary innovations. J Exp Biol. 2020;223(Pt 24):jeb215350. doi: 10.1242/jeb.215350.

San T, Polat S, Cingi C, Eskiizmir G, Oghan F, Cakir B. Effects of high altitude on sleep and respiratory system and theirs adaptations. Scientific World Journal. 2013;2013:241569. doi: 10.1155/2013/241569.

Saraste A, Pulkki K. Morphologic and biochemical hallmarks of apoptosis. Cardiovasc Res. 2000;45(3):528-37. doi: 10.1016/s0008-6363(99)00384-3.

Saunders PU, Pyne DB, Gore CJ. Endurance training at altitude. High Alt Med Biol. 2009;10(2):135-48. doi: 10.1089/ham.2008.1092.

Semenov DG, Samoilov MO, Lazarewicz JW. Preconditioning reduces hypoxia-evoked alterations in glutamatergic Ca2+ signaling in rat cortex. Acta Neurobiol Exp (Wars). 2008;68(2):169-79.

Semenza GL. Regulation of erythropoietin production. New insights into molecular mechanisms of oxygen homeostasis. Hematol Oncol Clin North Am. 1994;8(5):863-84.

Sendoel A, Hengartner MO. Apoptotic cell death under hypoxia. Physiology (Bethesda). 2014;29(3):168-76. doi: 10.1152/physiol.00016.2013.

Serebrovskaya TV, Karaban IN, Kolesnikova EE, Mishunina TM, Swanson RJ, Beloshitsky PV, Ilyin VN, Krasuk AN, Safronova OS, Kuzminskaya LA. Geriatric men at altitude: hypoxic ventilatory sensitivity and blood dopamine changes. Respiration. 2000;67(3):253-60. doi: 10.1159/000029507.

Sheafor BA. Metabolic enzyme activities across an altitudinal gradient: an examination of pikas (genus Ochotona). J Exp Biol. 2003;206(Pt 7):1241-9. doi: 10.1242/jeb.00226.

Silva JF, Ocarino NM, Serakides R. Thyroid hormones and female reproduction. Biol Reprod. 2018;99(5):907-921. doi: 10.1093/biolre/ioy115.

Silva JF, Vidigal PN, Galvão DD, Boeloni JN, Nunes PP, Ocarino NM, Nascimento EF, Serakides R. Fetal growth restriction in hypothyroidism is associated with changes in proliferative activity, apoptosis and vascularisation of the placenta. Reprod Fertil Dev. 2012;24(7):923-31. doi: 10.1071/RD11219.

Sirotkin AV. Control of reproductive processes by growth hormone: extra- and intracellular mechanisms. Vet J. 2005;170(3):307-17. doi: 10.1016/j.tvjl.2004.05.014.

Snyder LM, Reddy WJ. Mechanism of action of thyroid hormones on erythrocyte 2,3-diphosphoglyceric acid synthesis. J Clin Invest. 1970;49(11):1993-8. doi: 10.1172/JCI106419.

Soares MJ, Iqbal K, Kozai K. Hypoxia and Placental Development. Birth Defects Res. 2017;109(17):1309-1329. doi: 10.1002/bdr2.1135.

Surks MI, Beckwitt HJ, Chidsey CA. Changes in plasma thyroxine concentration and metabolism, catecholamine excretion and basal oxygen consumption in man during acute exposure to high altitude. J Clin Endocrinol Metab. 1967;27(6):789-99. doi: 10.1210/jcem-27-6-789.

Surks MI. Elevated PBI, free thyroxine, and plasma protein concentration in man at high altitude. J Appl Physiol. 1966;21(4):1185-90. doi: 10.1152/jappl.1966.21.4.1185.

Tattersall GJ, Milsom WK. Hypoxia reduces the hypothalamic thermogenic threshold and thermosensitivity. J Physiol. 2009;587(Pt 21):5259-74. doi: 10.1113/jphysiol.2009.175828.

Vasudevan N, Ogawa S, Pfaff D. Estrogen and thyroid hormone receptor interactions: physiological flexibility by molecular specificity. Physiol Rev. 2002;82(4):923-44. doi: 10.1152/physrev.00014.2002.

Villafuerte FC, Macarlupú JL, Anza-Ramírez C, Corrales-Melgar D, Vizcardo-Galindo G, Corante N, León-Velarde F. Decreased plasma soluble erythropoietin receptor in high-altitude excessive erythrocytosis and Chronic Mountain Sickness. J Appl Physiol (1985). 2014;117(11):1356-62. doi: 10.1152/japplphysiol.00619.2014.

Vogt M, Puntschart A, Geiser J, Zuleger C, Billeter R, Hoppeler H. Molecular adaptations in human skeletal muscle to endurance training under simulated hypoxic conditions. J Appl Physiol (1985). 2001;91(1):173-82. doi: 10.1152/jappl.2001.91.1.173.

Wang GL, Semenza GL. General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. Proc Natl Acad Sci U S A. 1993;90(9):4304-8. doi: 10.1073/pnas.90.9.4304.

Weber RE, Jessen TH, Malte H, Tame J. Mutant hemoglobins (alpha 119-Ala and beta 55-Ser): functions related to

high-altitude respiration in geese. J Appl Physiol (1985). 1993;75(6):2646-55. doi: 10.1152/jappl.1993.75.6.2646.

Wenger RH, Stiehl DP, Camenisch G. Integration of oxygen signaling at the consensus HRE. Sci STKE. 2005;2005(306):re12. doi: 10.1126/stke.3062005re12.

Wenger RH. Mammalian oxygen sensing, signalling and gene regulation. J Exp Biol. 2000;203(Pt 8):1253-63. doi: 10.1242/jeb.203.8.1253.

Will DH, Alexander AF, Reeves JT, Grover RF. High altitude-induced pulmonary hypertension in normal cattle. Circ Res. 1962;10:172-7. doi: 10.1161/01.res.10.2.172.

Windsor JS, Rodway GW. Heights and haematology: the story of haemoglobin at altitude. Postgrad Med J. 2007 Mar;83(977):148-51. doi: 10.1136/pgmj.2006.049734.

Wise TH, Caton D, Thatcher WW, Barron DH, Fields MJ. Ovarian function during the estrous cycle of the cow: ovarian blood flow and progesterone release rate. J Anim Sci. 1982;55(3):627-37. doi: 10.2527/jas1982.553627x.

Zamudio S, Palmer SK, Droma T, Stamm E, Coffin C, Moore LG. Effect of altitude on uterine artery blood flow during normal pregnancy. J Appl Physiol (1985). 1995;79(1):7-14. doi: 10.1152/jappl.1995.79.1.7.

Zamudio S. The placenta at high altitude. High Alt Med Biol. 2003;4(2):171-91. doi: 10.1089/152702903322022785.

Zhao XP, Wang M, Song Y, Song K, Yan TL, Wang L, Liu K, Shang ZJ. Membrane microvesicles as mediators for melanoma-fibroblasts communication: roles of the VCAM-1/VLA-4 axis and the ERK1/2 signal pathway. Cancer Lett. 2015;360(2):125-33. doi: 10.1016/j.canlet.2015.01.032.

Zhou J, Xiao D, Hu Y, Wang Z, Paradis A, Mata-Greenwood E, Zhang L. Gestational hypoxia induces preeclampsia-like symptoms via heightened endothelin-1 signaling in pregnant rats. Hypertension. 2013;62(3):599-607. doi: 10.1161/HYPERTENSIONAHA.113.01449.