Advance Research Journal of medical and clinical science
Received 11 Jan 2023 | Revised 13 Jan 2023 | Accepted 17 Jan 2022 | Published Online 24 Jan 2023

DOI: https://doi.org/10.52845/rrarjmcs/2023/9-1-2

ARJMCS 09 (1), 1093–1097 (2023)

ISSN (O) 2455-3549

ICV 2020 = 86.28

REVIEW- ARTICLE

Hypoxia and ovarian function: A mini-review

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Abstract

Background: Hypoxia has a negative effect on the reproductive system; specifically, women in high-altitude have a higher probability of assisted reproduction due to low ovarian reserve function areas than do those in low-altitude regions of the same age group. However, data regarding the effect of hypoxia on ovarian function in women is insufficient. At present, there only a few observational studies on the changes in sex hormones in relation to hypoxia exist, and there has been little research conducted on the mechanism. Therefore, this mini-review synthesized the current knowledge of the mechanistic relationship between hypoxia and ovarian function. Existing studies have shown that hypoxia can affect ovarian function, but further in-depth research and more attention to this area of study are required.

Keywords: Hypoxia, ovarian function, high altitudes, hypothalamic-pituitary-ovarian axis, HIF-1α

1 | INTRODUCTION

The substantially low-oxygen environment at high altitudes impacts all aspects of human health. Specifically, women in high-altitude areas compared with those in low-altitude regions of the same age group have a higher probability of assisted reproduction due to low ovarian reserve function (1). This may be explained by the fact that a high level of HIF-1α in females may lead to abnormal sex hormone levels and weakened ovarian reserve (2). However, at present, there is lack of evidence determining whether a low-oxygen environment at high altitudes can affect reproductive capacity; existing studies are mainly limited to the observation of female fertility in geographic plateau areas and the change of sex hormone levels in animal and human blood under hypoxic conditions. Studies of the effects of hypoxia on the human reproductive system have focused on males (3), (4), (5), (6), while those showing related mechanisms, cellular processes, and genetic changes are relatively lacking. Therefore, reproduction in women of high-altitude areas may be affected (7). In this review, we assessed the existing research on the effects of hypoxia on female ovarian function.

Generally, a well-functioning hypothalamic-pituitary-ovarian axis is essential for maintaining normal ovarian hormone function, and any of links in this axis can therefore be affected by changes in ovarian hormone secretion, and vice versa; when

the hypothalamus or pituitary is affected so is ovarian function The effect of high-altitude hypoxia on the human body is holistic, and therefore sex hormone levels and ovarian reserve function of women in this area may be affected (7).

2 | GONADOTROPIN-RELEASING HORMONE (GNRH)

GnRH, which is secreted by the hypothalamus, stimulates or inhibits the secretion of pituitary Gonadotropin. The hypothalamic-pituitary-adrenal axis regulates the stress response (8), and the reproductive function of female animals is primarily regulated by the HPO axis. Additionally, the neuroendocrine system coordinates the body's response to hypoxia, which can cause a series of gene expression and metabolic changes in tissues and cells. In fact, early studies showed exposure to hypoxia to cause a decrease in GnRH (9). Mechan -istically, hypoxia-reoxygenation activates nuclear factor-κB (NF-κB) via the protein kinase B (Akt)/ forkhead box protein O1 (FOXO1) pathway, thereby inhibiting Gnrh1 (10).

3 | FOLLICLE-STIMULATING HORMONE (FSH) AND LUTEINIZING HORMONE (LH)

Clinically, we evaluated ovarian function mainly by FSH, LH, estrogen and progesterone. FSH and LH are glycoprotein hormones secreted by gonadotropin cells in the anterior pituitary gland, which promote gonadal development and maintain reproductive function (11). Although FSH and LH respond to GnRH similarly at high altitudes and sea level, the HPO axis is disturbed by hypoxia, and the baseline level of FSH decreases when exposed to high altitudes (12). The results of one animal study showed that exposure to hypoxia can increase serum FSH levels and follicular atresia, which is consistent with the clinical manifestations of patients with ovarian dysfunction (13). Moreover, exposure to hypoxia for short or long periods affects the development and function of the corpus luteum (14). Various studies have shown that the expression of female FSH, LH, and E2 at high altitudes is greater than that in the conventional set (2).

4 | ESTROGEN AND PROGESTERONE

Estrogen and progesterone are another important aspect of assessing ovarian function. Basal FSH, LH, and estrogen levels can reflect ovarian function (15). In plateau regions of high altitude, women may exhibit excessive sex hormones such as estrogen (2). In one study, estradiol levels were shown to exhibit more dynamic changes based on altitude, with greater increases during the early follicular phase and greater decreases during the late follicular phase in women at high altitudes than those at sea level. Additionally, during ovulation, estradiol levels were shown to be higher at high altitudes (16). In female rats, exposure to acute and chronic hypobaric hypoxia has been shown to cause low circulatory progesterone levels (17). Moreover, estrogen levels are known to increase and progesterone levels are known to decrease following intermittent hypoxia exposure (18).

Although ovarian follicles are thought to have the ability to adapt to hypoxic conditions since they are surrounded by a dense basal lamina with no vascular supply (19), studies have shown that high-altitude hypoxia can indeed cause changes in ovarian sex hormones. This may further affect the reproductive function of the ovaries, even though little research has been conducted regarding hypoxia and ovarian sex hormone changes. However, one study provided evidence that patients undergoing laparoscopic ovarian cystectomy and adjuvant hyperbaric oxygen therapy could significantly improve postoperative ovarian reserve function with remarkable effects (20). This may indicate that there is an effect of hypoxia on ovarian function, with several possible explanatory mechanisms.

Supplementary information: *The online version of this article (https://doi.org/10.52845/rrarjmcs/2023/9-1-2) Contains supplementary material, which is available to authorized users.*

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HIF-1α

HIF-1αis a well-known factor that is highly expressed during hypoxia. During the ovarian cycle, dynamic changes in blood flow to the ovaries affect the regulation of ovarian cycles (21). These changes in blood flow are associated with vascular endothelial growth factor (VEGF), which is regulated by HIF-1α. The expression of VEGF mRNA in the ovary has been associated with follicle selection and corpus luteum function in primates (22). Moreover, VEGF-induced angiogen -esis is required for follicle development and corpus formation, and ovulation is intrinsically linked to HIF-1αthrough sex hormones (23). Additionally, HIF-1α regulation mechanisms have been implicated in the pathogenesis of numerous aging-related chronic diseases, and a relationship between HIF-1αand ovarian failures is suspected. (24)

5 | AUTOPHAGIC

Autophagy is known to maintain cellular homeostasis and energy balance, and this imbalance is related to the occurrence and development of many conditions such as tumors and immune dysfunction (25), (26). It can play an important regulatory role when there are external stimuli such as hypoxia. Specifically, recent studies have shown that autophagy in ovarian cells is associated with follicular development and atresia (27). Autophagy is also closely associated with premature ovarian insufficiency (28), (29) and can be induced by HIF-1 acting downstream of BNIP3 (30). Further, reducing the autophagy of granulosa cells down-regulates HIF-1α and BNIP3 expression and decreases primordial follicle depletion and follicle atresia, thus improving ovarian reserve and fertility in mice (31).

Mitochondrial function

Cellular hypoxia significantly suppresses mitochondrial gene expression (32), and mitochondrial dysfunction due to aging and hypoxia may be the primary cause of infertility in animals of advanced age (33). Moreover, mitochondrial activity is a key determinant of reproductive capacity (34), and its dysfunction can result in the dysfunction of oocytes and their surrounding cumulus granulosa cells along with apoptosis, leading to follicular atresia or even failure, resulting in decreased ovarian reserve function (35)

Endoplasmic reticulum (ER) stress

Hypoxia can activate ER stress. ER stress is a important factor closely related to inflammation and oxidative stress. As a protective response, its functional disorder can induce cell death (36). ER stress is also involved in the induction of apoptosis in granulosa cells and follicular atresia (37). Further, transplantation of human placenta-derived mesenchymal stem cells has been shown to ameliorate ovarian failure in mice by inhibiting ER stress-induced granulosa cell apoptosis, contributing to the restoration of ovarian function (38).

6 | CONCLUSION

Several existing studies and animal models have shown a causal association between hypoxia and ovarian function. However, further in-depth research and more attention to this area of study are warranted to fully elucidate the mechanism and to improve the treatment of female infertility in high-altitude areas.

Acknowledgments

We would like to thank Editage (www.editage.cn) for English language editing.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This research was supported by the Kunlun talent and high-level innovative project in Qinghai.

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