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Research Progress on Luteinizing Hormone and Polycystic Ovary Syndrome

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Abstract: ***Polycystic ovary syndrome is a common endocrine disease in women of childbearing age, with an incidence of about 6% to 10%, which is the main cause of anovulatory infertility. With the development of assisted reproductive technology, up to 60% of patients with polycystic ovary syndrome need to be pregnant successfully through in vitro fertilization and embryo transfer. Ovarian controlled ovulation induction is an important process in assisted reproductive therapy. Luteinizing hormone plays an important role in the development and maturation of follicles in the ovary, and high levels of luteinizing hormone have a negative effect on pregnancy outcome. at present, it is still controversial that the appropriate level of luteinizing hormone will improve the pregnancy outcome, and the mechanism of how luteinizing hormone affects the pregnancy outcome is still unclear. This article will mainly review the above two aspects in order to provide reference for clinical research in the future.***

Keywords: Assisted reproductive technology, Luteinizing hormone, Polycystic ovary syndrome, Follicle stimulating hormone**.**

1. Introduction

Polycystic ovary syndrome (PCOS) is mainly characterized by hyperandrogenemia, persistent anovulation and polycystic changes of the ovary. It is a common cause of ovulation disorders, oligomenorrhea, hirsutism and other common causes. The incidence of PCOS in women of childbearing age can reach 6% to 10%. Related studies have pointed out that about 75% of PCOS patients lead to infertility due to anovulation, seriously affecting the quality of life of patients. Luteinizing hormone (LH) is a key factor in inducing hormone secretion and follicular development and maturation. The increase of LH level may adversely affect the pregnancy outcome, and effectively inhibit the increase of serum LH level in the early follicular phase, which is the key link in the treatment of controlled superovulation in in vitro fertilization-embryo transfer (IVF-ET). Either too high or too low serum LH level in controlled ovarian hyperstimulation cycle can lead to adverse pregnancy outcome of IVF-ET. How to control the level of serum LH to enable infertile patients to obtain appropriate and high-quality eggs and achieve satisfactory treatment outcome has gradually become the focus of doctors in the field of reproduction.

2. An Overview of Luteinizing Hormone

LH is a glycoprotein hormone secreted by Gonadotropin (Gn) cells in the anterior pituitary. LH can induce ovary to produce steroid hormone and play a role in ovulation and egg implantation into uterus, which is helpful to regulate the length of menstruation in women's menstrual cycle [1]. The release of LH requires a complex neuronal and glial circuit that directs various peripheral and central hormones to kisspeptin neurons. Circadian rhythm regulation interacts with Gonadotropin-releasing hormone-releasing hormone (GnRH) neurons to activate the anterior pituitary and release a large amount of LH [2]. A member of the family of glycoprotein hormones consisting of alpha and beta protein subunits. LH and FSH have different physiological functions and corresponding specific antigenicity, mainly because their α subunit amino acid composition and sequence are the same, but β subunit peptide chain is different. β subunit and α subunit peptide chain must be combined into complete molecules in order to have biological activity, and then play different clinical roles. The production or insufficient action of LH and FSH will affect gametogenesis and gonadal steroid production, thus reducing female fertility [3]. FSH and LH play an important role in follicular growth, development and maturation. In the early stage of follicular development, LH binds to LH receptors on thecal cells, converts cholesterol into androgen and transports cholesterol to granulosa cells. Under the stimulation of FSH, it can promote the aromatization of granulosa cells and transform androgen into estrogen.

3. Clinical Characteristics of Luteinizing Hormone in Patients with Polycystic Ovary Syndrome

PCOS is a common endocrine disease, which mainly affects women of childbearing age. Clinical manifestations include menstrual disorders, hyperandrogenemia, infertility, ovarian polycystic changes and abnormal metabolic function. The main causes of infertility include abnormal metabolism of hormone function, such as hyperandrogenemia, hyperinsulinemia, excessive secretion of LH and increased level of LH/FSH [4]. The hypothalamus-pituitary-ovary (HPO) axis regulates ovarian function, including follicular recruitment, oocyte selection, regular cycles and steroid hormone biosynthesis. GnRH stimulates pituitary gonadotropin synthesis and secretion of gonadotropins LH and FSH. Importantly, high and low GnRH pulse frequencies are beneficial to LH or FSH secretion, respectively, and these effects are mainly mediated at the gonadotropin gene transcription level. Changes in the frequency and amplitude of GnRH pulses allow fine-tuning of FSH and LH release, and control the relative amount of circulating gonadotropin,

resulting in different and dynamic changes in FSH and LH concentrations (the so-called LH/FSH ratio increases in PCOS) [5].It is worth noting that although GnRH release cannot be measured directly in humans, animal studies have confirmed that each GnRH pulse can trigger LH secretion bursts. The continuously increasing frequency of LH pulse and the increase of LH/FSH ratio indicate that the secretion of GnRH pulse is overactive, indicating that GnRH pulse dysfunction in patients with PCOS. Abnormal gonadotropin secretion is an important cause of ovarian hyperandrogenism and ovulation dysfunction in patients with PCOS. LH is the main irritant of the ovary, and hyperandrogenism in PCOS usually occurs after the increase of LH secretion in puberty. In PCOS women, long-acting GnRH agonists can inhibit gonadotropin secretion and significantly reduce circulating androgen concentration. In addition, the relative lack of FSH restricts follicular development, leading to ovulation dysfunction in PCOS. Persistent high GnRH pulse frequency is the main reason for excessive LH and relative lack of FSH in patients with PCOS [6]. Because the serum LH concentration of PCOS patients increased significantly, in contrast, the FSH concentration of PCOS women decreased significantly. Therefore, an increase in LH/FSH ratio is usually reported [7].

Change, rather than an increase in GnRH secretion itself. Excessive secretion of LH seems to be the result of impaired regulatory function. In PCOS, pituitary and hypothalamus showed decreased sensitivity to the inhibitory effect of exogenous progesterone on LH secretion, and luteal lack of periodic progesterone synthesis. The results show that [8]. Women between the ages of 26 and 35 are more likely to develop PCOS, which highlights the importance of this age group in risk assessment and preventive measures. In addition, the study confirmed that obesity has a significant impact on the prevalence of PCOS, and overweight women are more susceptible to PCOS.

4. Effect of Luteinizing Hormone on Reproductive Function in Patients with Cystic Ovary Syndrome

4.1 Effect of Luteinizing Hormone on Patients with Polycystic Ovary Syndrome

The incidence of PCOS is high in women of childbearing age, and its pathogenesis is not completely clear. It is the main cause of anovulatory infertility, accounting for about 70% [9]. The main pathophysiology of PCOS is the increase of serum insulin level and the decrease of islet function. Usually, hyperinsulinemia will lead to excessive secretion of sex hormones in the ovary, stimulate the pituitary secretion of a large amount of LH, inhibit liver SHBG synthesis, and significantly increase free androgen, resulting in increased FAI, resulting in follicular atresia, resulting in ovulation disorders. Zarei et al. [10] isolated a 54 amino acid, namely Kiss-1 peptide or kisspeptin, from human placenta for the first time. The study found that kisspeptin increased in PCOS patients with high LH levels and normal weight [11]. This peptide plays a key role in the secretion and reproduction of GnRH, and its receptor mutation can lead to abnormal hormone secretion during puberty and infertility. Kisspeptin has been proved to be involved in the regulation of hypothalamus-pituitary-gonadal function, and it is also an important factor that induces GnRH secretion and affects LH secretion. The ability of Kisspeptin to induce LH secretion in vivo, and the results suggest that there is a significant positive correlation between LH and kisspeptin levels. The increase of free androgen levels in PCOS patients may be due to insulin resistance (IR) in these patients increased androgen synthesis in PCOS patients and inhibited the production of SHBG in the liver. IR is related to the decrease of kisspeptin concentration. Basic experiments and clinical studies have shown that LH plays an important role in follicular development and oocyte maturation, so maintaining an appropriate level of LH is essential for normal ovulation [12].

4.2 Effect of Luteinizing Hormone / Follicle Stimulating Hormone on Patients with Polycystic Ovary Syndrome

Epidemiological statistics show that about 30%-50% of PCOS patients have elevated basal serum LH levels. LH and FSH play different roles in different stages of follicular development. The hypersecretion of GnRH is regulated by GnRH and ovarian steroids, which leads to the increase of LH release and the normal or decrease of FSH release, which leads to the increase of LH/FSH ratio, which leads to follicular maturation disorder and even infertility. The incidence of elevated LH/FSH ratio is affected by race and environment, and the data are inconsistent around the world. The incidence of high LH/FSH in PCOS patients in Europe and the United States is lower, while the incidence of increased LH/FSH ratio in PCOS patients in Japan is the highest, which is about 81.9%. Xia et al [13] According to the relationship between the increase of LH/FSH and reproductive results, it was found that LH/FSH increased and ovulation table decreased in patients with PCOS. The increase of LH/FSH ratio may have adverse effects on the number of follicles and oocytes, follicular quality, oocyte maturation and granulosa cell function. The lower level of FSH in patients with PCOS significantly inhibited periodic follicular recruitment and no dominant follicle formation. The increase of LH level may promote follicular atresia or corpus luteum advance.

5. Effect of Luteinizing Hormone on Pregnancy Outcome

Embryo quality, endometrial receptivity, and stable hormone levels after transplantation are key factors for a good pregnancy outcome. At present, the mechanism of how luteinizing hormone affects pregnancy outcome is not clear.

5.1 Effect of Luteinizing Hormone on Endometrium

The level of LH can affect the secretion of estrogen and progesterone before and after ovulation, and play an important role. The decrease of LH level can lead to delayed response to FSH, abnormal sensitivity, decrease of estrogen and progesterone synthesis due to follicular growth and development, endometrial receptivity and adverse pregnancy outcome. The incidence of thin endometrium is higher in elderly women. with the increase of age, the local blood flow of endometrium is slow, the estrogen and progesterone receptor decreases, and the endometrium becomes thinner gradually. Estrogen and progesterone is a hormone that regulates the growth and development of endometrium. It

must bind to its receptors in order to play a biological role in promoting endometrial vascular remodeling, endometrial proliferation and repair. The expression of estrogen receptor in thin endometrial stromal cells decreased significantly in proliferative phase and secretory phase, and the expression of estrogen receptor in glandular epithelial cells was significantly lower than that in normal endometrium.

The secretory transformation of endometrium is induced by progesterone. due to the accelerated secretory transformation of endometrium and the subsequent changes of gene and protein expression in endometrium, it is speculated that the premature increase of progesterone will have a negative effect on the implantation window. Although GnRH analogues are used to inhibit premature LH proliferation, up to 38% of COH-IVF cycles show that this premature progesterone increase in progesterone is critical to the development of implanted receptive endometrium, and high circulating progesterone levels accelerate endometrial differentiation and have a negative effect on pregnancy rates. Elevated progesterone levels reduce the chance of implantation by changing uterine-embryo synchronization. The lack of LH in the late follicular phase of the stimulation cycle may make the production of follicular progesterone exceed the limit of LH activity and lead to the premature increase of progesterone. In fact, a randomized trial comparing serum and follicular fluid progesterone levels in patients treated with rFSH or hMG found that the use of rFSH instead of hMG in gonadotropin regimens led to higher progesterone levels, further supporting the theory that follicle formation leads to premature luteinization of granulosa cells in the absence of sufficient LH activity [14].GnRH-a may lead to excessive inhibition of LH, which has a negative effect on the outcome of IVF-ET. The optimal LH activity is essential for the quality and function of oocytes, as well as for oocyte proliferation and cytoplasmic maturation [15]. The LH peak leads to the transformation of granulosa cells and intimal cells into granular corpus luteum and membrane luteal cells, respectively. These steroid-producing cells cooperate with non-steroid-producing (endothelial, immune and fibroblast) cells, so these cells are essential for the synthesis and secretion of steroids [16]. The genes involved in steroid production stimulate theca cells to produce androgens. LH can increase the re-synthesis of ovarian hormones to regulate ovarian growth and differentiation after ovulation, which is very important in endometrial preparation for implantation and maintenance of pregnancy. Low LH level can inhibit the growth or even stagnation of endometrium, and damage endometrial receptivity and implantation rate.

5.2 Effect of Luteinizing Hormone on Embryo Quality

GnRH is responsible for stimulating the production and release of LH and FSH. LH secretion reflects the pulse release of GnRH and stimulates cholesterol to synthesize androstenedione and testosterone induced by theca cells. Hyperandrogenemia is a key feature of PCOS, which affects ovarian function. Androgens are thought to stimulate the growth of preantral and small antral follicles through androgen receptors. In women with PCOS, androgen receptors may increase their activity in the hypothalamus, ovary, skeletal muscle or adipocytes. The follicles in the ovary are composed of oocytes, granulosa cells and theca cells. The follicle starts from the primordial follicle, which contains oocytes surrounded by monolayer granulosa cells and basal layer. Hyperandrogenemia may have a negative effect on the development and quality of oocytes by increasing the level of reactive oxygen species [17].

In the process of reproduction, primordial follicles and primary follicles continue to grow into secondary follicles and larger follicles, resulting in a gradual decrease in the primordial follicle pool. In addition, the primordial follicular cistern may also be reduced due to the apoptosis of resting follicles. The initial recruitment of primary follicles from primordial follicles and the development of primary follicles into secondary follicles are generally considered to be regulated by gonadotropin-independent ovarian factors, but more and more data suggest that gonadotropin may also affect preantral follicle development. In PCOS, the increase of LH level and the decrease of FSH level lead to the increase of LH/FSH ratio. About 55-75% of PCOS women have higher LH/FSH ratios, which may be due to higher LH levels rather than reduced FSH production. This leads to the increase of androgen secretion in ovarian theca cells, the stagnation of follicles, the accumulation of small antrum follicles and the increase of AMH (Anti-Mullerian Hormone, AMH) levels. AMH itself increases the ratio of LH/FSH and inhibits the conversion of androgen to estrogen, both of which lead to an increase in androgen levels [18]. Hyperandrogenemia in patients with PCOS can accelerate the formation of preantral and small antral follicles. Granulosa cells are considered to be the only source of AMH in the ovary. The mouse model showed that AMH was released during the development of primordial follicles into small antral follicles, but the release of AMH decreased as the follicles developed to the preovulatory stage. Because PCOS ovaries usually have more preantral follicles and small follicles, they usually produce more AMH than normal ovaries. In addition, each follicle in PCOS produces more AMH than normal follicles [19]. FSH can promote the development of small antral follicles to ovulation. AMH can not only inhibit the aromatase activity induced by FSH, but also counteract the growth-promoting effect of FSH on granulosa cells, thus preventing the production of estradiol. In patients with polycystic ovary syndrome, high levels of AMH can inhibit the role of FSH, thus interfering with the growth and development of antral follicles. As a result, the growth function of preantral follicles stimulated by FSH was weakened. This suggests that elevated AMH levels may play a role in the cause of anovulation in patients with PCOS [20].

5.3 Effect of Luteinizing Hormone Level on Pregnancy Outcome

Liu et al. [21] showed that the increase of basal LH level and LH/FSH ratio in patients with PCOS did not affect the outcome of IVF/ICSI cycle treated by GnRH-ant regimen. The level of endogenous LH cannot fully show the follicular development of patients, and the role of LH in PCOS has not been fully studied. Because low levels of androgen can promote follicular growth and development, high levels of LH in the follicular phase lead to increased androgen secretion, which inhibits follicular maturation and leads to ovulation disorders. High levels of LH can inhibit oocyte meiosis inhibitory factor, make oocytes mature earlier, lead to oocyte

aging, reduce fertilization rate, affect embryo formation, and reduce embryo implantation rate. In GnRH-ant regimen, the transient early rise of endogenous LH does not affect the pregnancy outcome, but it is necessary to control the elevated LH in time to avoid early follicular ovulation or luteinization; early addition of antagonists at low levels of estrogen can reduce the early LH peak.

Previous studies have shown that during ovulation induction with GnRH-ant regimen, low levels of LH had no effect on normal fertilization rate, high quality embryo rate and cumulative live birth rate, and could predict more follicles obtained. Although the level of LH has no effect on the final pregnancy outcome, it is still necessary to monitor the level of LH in the process of GnRH-ant superovulation to avoid the disturbance of follicular maturation and development caused by premature LH peak, so as to achieve a satisfactory number of eggs. In physiological state, the change of LH level is more important for follicular growth and development, and it only needs to occupy less than 1% receptor to synthesize enough steroids to maintain the normal process of follicular growth and development. Wang et al. [22] showed that the fluctuation of serum LH level in GnRH-ant may affect the pregnancy outcome of PCOS patients treated with IVF-ET, and the ratio of basic LH to trigger day LH may be a more sensitive index to evaluate the potential of LH level on embryonic development in PCOS patients. Oocyte growth and development, embryo quality and endometrial receptivity are usually affected by premature luteinization of follicles. Simultaneous increase of serum LH and P levels can lead to premature luteinization of follicles. Although increased LH at early onset in GnRH-ant does not affect pregnancy outcome in patients with PCOS, attention should be paid to the risk of early ovulation and premature luteinization of follicles. Maintaining an appropriate level of LH during ovulation can not only improve the pregnancy rate of fresh transfer cycle, but also provide a theoretical basis for subsequent frozen embryo transfer. It can interact with FSH in the middle and late stages of follicles, play a positive role in the growth and development of follicles, and participate in the selection of dominant follicles. Wang et al. [23] studies have shown that the implantation rate, clinical pregnancy rate and live birth rate of fresh week embryo transfer can be increased by adding r-hLH in the early follicular length scheme in elderly infertile patients but cannot increase the cumulative live birth rate.

Zhai et al. [24] studied that during the fresh transplantation cycle, the live birth rate in the GnRH-ant group was significantly lower than that in the warehouse GnRH-a group. Paying close attention to the endometrial thickness on the day of HCG may lead to a similar pregnancy rate in fresh transplant cycles between GnRH-ant and warehouse GnRH-a protocols. Efforts should be made to improve endometrial receptivity in order to increase the pregnancy rate of fresh embryo transfer. For PCOS patients, in order to ensure the pregnancy rate and reduce the incidence of moderate and severe OHSS, it is best to carry out frozen embryo thawing transfer after ovulation induced by GnRH-ant protocol.

6. Summary and Prospects

It has been basically agreed that the increase of LH will have a negative effect on the pregnancy outcome. At present, it has been reported that slightly higher serum LH levels on the day after the addition of antagonists can increase the excellent embryo rate and live birth rate of IVF-ET, and the results of other studies show that the slight increase of LH does not affect the pregnancy outcome. However, the specific mechanism of how the increase of LH level affects the pregnancy outcome is still controversial. And whether there is an appropriate LH threshold level can improve the pregnancy outcome of PCOS patients, still need a large number of clinical data and more in-depth research to further verify. PCOS patients are often accompanied by increased endogenous LH secretion. LH plays an important role in follicular development and oocyte maturation. Appropriate LH water level plays an important role in good pregnancy outcome. Future research on LH on assisted reproductive technology is still a key and difficult point, because some studies suggest that the live birth rate of frozen embryo transfer cycle is higher than that of fresh embryo transfer cycle. Follow-up researchers can study frozen embryo cycle transfer and different ovulation induction schemes, in order to take corresponding measures to improve the clinical pregnancy rate or live birth rate of assisted reproductive technology.

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