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A Clinical Pregnancy Case of a PCOS Patient Treated with a Long Protocol Combined with Artificial Insemination (AIH)

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ABSTRACT
To report a case of a polycystic ovary syndrome (PCOS) patient who successfully conceived after treatment with a long protocol combined with artificial insemination (AIH). A retrospective summary and analysis were conducted on a PCOS patient who had undergone three previous unsuccessful AIH attempts, declined in vitro fertilization-embryo transfer (IVF-ET) assistance, and successfully conceived after the fourth AIH treatment. The patient was treated with a GnRH agonist (GnRHa) long protocol and human menopausal gonadotropin (HMG) for controlled ovarian hyperstimulation. On day 4 of her menstrual cycle, she received 3.75mg of Beiyi (a GnRH agonist) for pituitary downregulation. On day 53 of downregulation, HMG was administered intramuscularly to initiate the stimulation cycle. When the follicle diameter reached 17.5mm, one dose of Aize was injected subcutaneously at 8 PM, and AIH was performed approximately 39 hours later. The patient successfully conceived 14 days later and delivered a healthy female infant via cesarean section at 40 weeks of gestation. For PCOS patients, conventional ovulation induction protocols are commonly used. If conventional ovulation induction and multiple attempts of guided intercourse or AIH in the outpatient setting fail, and the patient declines IVF-ET, adopting a long protocol combined with AIH represents a novel approach. Based on the natural follicular development pattern, accurate identification of the degree of pituitary-ovarian axis downregulation, appropriate use of downregulation dosage and timing, and flexible selection of GnRH initiation time can help these patients achieve the optimal assisted reproduction method.

KEYWORDS
Polycystic ovary syndrome; Long protocol; Artificial insemination

The issue of assisted reproduction in patients with polycystic ovary syndrome (PCOS) has been a persistent topic in the field of assisted reproductive technology. Treatment options include lifestyle interventions, menstrual cycle and metabolic adjustments, management of hyperandrogenism and insulin resistance, and selecting appropriate assisted reproduction protocols for PCOS patients with persistent anovulation or oligoovulation. In vitro fertilization-embryo transfer (IVF-ET) is considered a third-line treatment option for PCOS patients with infertility. Additionally, since PCOS patients are at high risk for ovarian hyperstimulation syndrome (OHSS), traditional long protocols are not typically preferred. The objective is to continuously explore and improve treatment methods based on experiences of repeated ovulation induction, multiple guided intercourse or artificial insemination (AIH) failures, while respecting patients' wishes to avoid complex IVF-ET techniques and achieving successful pregnancy in as simple a manner as possible. In this case, the male partner was unable to ejaculate during intercourse, and the female partner had PCOS with oligoovulation. After three unsuccessful attempts of conventional ovulation induction combined with AIH, it was inferred that this treatment was ineffective. Switching to a long protocol combined with AIH was a novel attempt, particularly for young patients who temporarily do not consider IVF-ET treatment.

1 Case Summary

The patient was a 29-year-old female, 153cm tall, and weighed 50kg, with a gravida 0, para 0 status. She had her first menstrual period at the age of 12 and had a history of irregular menstruation, with cycles ranging from 5-7 days every 30-50 days. She registered her marriage in 2017 and had not conceived despite not using contraception for 5 years. Her husband was unable to ejaculate during intercourse. From March to May 2022, the patient underwent three cycles of ovulation induction and AIH in our department without success. She had a previous diagnosis of hyperprolactinemia and was treated with bromocriptine. The patient's laboratory tests showed: follicle-stimulating hormone (FSH): 3.1mIU/mL, luteinizing hormone (LH): 3.11mIU/mL, estradiol (E2): 29pg/ml, progesterone (P): 0.1ng/ml, testosterone (T): 0.58ng/ml, prolactin (PRL): 113ng/ml (after standard treatment, PRL was 12.4ng/ml upon reevaluation). Glucose tolerance and insulin release tests indicated insulin resistance. Transvaginal ultrasound revealed polycystic ovaries bilaterally. Hysterosalpingography showed patent bilateral fallopian tubes. Pituitary MRI, chromosomal analysis, and thyroid function tests were all normal. The male partner's semen analysis showed a concentration of 64×10^6/ml, motility (PR) of 76%, and a teratozoospermia rate of 97%. Chromosomal and other tests were normal. The patient visited our department in January 2022, and after completing the aforementioned tests, she was treated with Diane-35 for two menstrual cycles to regulate her menstruation, along with metformin 0.5g/day to manage insulin resistance and bromocriptine 2.5mg/day to

control hyperprolactinemia. From March to May 2022, she was treated with clomiphene citrate (CC), human menopausal gonadotropin (HMG), and letrozole (LE) + HMG ovulation induction protocols, followed by AIH during the ovulatory period, but all attempts resulted in ovulation without conception. In June 2022, a hysteroscopy performed in our department showed a normal uterine cavity. During a follow-up visit in September 2022, the patient was informed about the option of IVF-ET for assisted reproduction, but she declined and requested another attempt at AIH. On September 1, 2022, which was day 4 of her menstrual cycle, a transvaginal ultrasound showed a physiological cyst of 33mm×23mm in the right ovary and a physiological cyst of 12mm×6mm in the left ovary, with an endometrial thickness of 2.4mm. She was administered a subcutaneous injection of Beiyi 3.75mg (leuprolide acetate 3.75mg/dose) for pituitary downregulation, along with one box of oral Youshiyue, while the doses of metformin and bromocriptine remained unchanged. During a follow-up visit four weeks later, a transvaginal ultrasound showed an increase in the size of the physiological cyst in the right ovary to 52mm×32mm, while the cyst in the left ovary had disappeared, and the endometrial thickness was 2.4mm. Blood tests showed LH: 0.78mIU/mL, E2: 17pg/ml, and P: 0.25ng/ml. No specific treatment was given. During a follow-up visit 10 days later, a transvaginal ultrasound showed a reduction in the size of the physiological cyst in the right ovary to 26mm×17mm, and the endometrial thickness was 3.2mm. No specific treatment was given. During a follow-up visit one week later, a transvaginal ultrasound showed the physiological cyst in the right ovary to be 25mm×17mm, with seven small follicles visible in each ovary, and the endometrium was type A with a thickness of 4.7mm. No specific treatment was given. One week later, which was day 53 of downregulation, a transvaginal ultrasound showed the physiological cyst in the right ovary to be 17mm×8mm, with the largest follicle in the right ovary being 13mm and 9.5mm, and the largest follicle in the left ovary being 12mm. The endometrium was type A with a thickness of 6.6mm. The HMG ovulation induction protocol was initiated, and she received an intramuscular injection of HMG 75IU once on the same day. On day 55, a transvaginal ultrasound showed a dominant follicle of 16mm in the right ovary, and the endometrium was type A with a thickness of 6.8mm. Blood tests showed LH: 2.27mIU/mL, E2: 105pg/ml, and P: 0.13ng/ml. She received another intramuscular injection of HMG 75IU and oral Bujiale 4mg/day to increase endometrial thickness. On day 57, a transvaginal ultrasound showed the dominant follicle in the right ovary to be 17mm, and the endometrium was type A with a thickness of 7.3mm. She received another intramuscular injection of HMG 75IU and continued oral Bujiale. On day 58, a transvaginal ultrasound showed the dominant follicle in the right ovary to be 17.5mm, and the endometrium was type A with a thickness of 7.3mm. At 8 PM that evening, she received a subcutaneous injection of Aize 250ug once.

2 Discussion

The down-regulation ovarian stimulation protocol, also known as controlled ovarian stimulation (COS), originated in 1984. This combination of gonadotropin-releasing hormone agonist (GnRH-a) and gonadotropin (Gn) has increased the recruitment of antral follicles, synchronized follicular development, and blocked the estrogen-GnRH-a-LH feedback loop. It allows for flexible timing of oocyte retrieval and prevents premature endogenous LH surges, remaining a primary approach in in vitro fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) treatment [1]. The regulatory effects of GnRH-a on the pituitary-ovarian gonadal axis are divided into two phases: ① The flare-up phase, also known as the excitation effect, is characterized by a transient and rapid increase in serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the early stages of medication, which facilitates follicular recruitment. ② The down-regulation phase: Seven to eight days after administration of the long-acting formulation, it is primarily characterized by pituitary receptor desensitization and depletion. FSH and LH levels decrease below baseline within 14 days, resulting in a pharmacological hypopituitarism state, with estrogen levels even reaching menopausal levels, thereby achieving down-regulation. In this case, a long-acting formulation of GnRH-a (3.75 mg) was used, resulting in a complete castrate state of the pituitary. After complete metabolism, pituitary function recovers [2]. Additionally, Choi JH et al. [3-4] reported on the localization and expression of GnRH-a and its receptors in human ovarian epithelium, luteinized granulosa cells, follicles, and the endometrium, explaining that GnRH-a can also directly act on the reproductive system to improve the local intrauterine and ovarian microenvironments and enhance their responsiveness. It can stimulate local ovarian receptors independently of a hypogonadotropic environment, activate factors such as vascular endothelial growth factor (VEGF) in follicles, and protect ovarian granulosa cells. It can also affect insulin-like growth factor-I (IGF-I) and steroidogenic acute regulatory protein (StAR) secretion, improving the microenvironment and enhancing ovarian sensitivity to Gn, thereby promoting follicular development [5]. GnRH-a also has a protective effect on the gonadal axis, such as by upregulating the expression of anti-apoptotic molecules like sphingosine-1-phosphate in the gonad [6]. Moreover, prolonged menstrual suppression in patients pretreated with GnRH-a can increase endometrial pinopodes and promote the expression of αvβ3 integrin, a marker of endometrial receptivity, thereby enhancing endometrial receptivity and sensitivity [7]. Other studies have shown [8-9] that GnRH-a acts on the endometrium to inhibit local inflammatory responses through phosphorylation and cytokine regulation, improving the reproductive microenvironment and

facilitating embryo implantation. Mabuchi et al.[10] demonstrated that GnRH-a can interfere with the TGF-β receptor signaling pathway by stimulating the expression of Smad proteins (Smad-3, Smad-4, Smad-7) in endometrial epithelial and stromal cells, inhibiting the secretion of TGF-β in the endometrium, keeping the "window of implantation" open, and thus facilitating embryo implantation.

The patient in this case is a woman with polycystic ovary syndrome (PCOS), a common endocrine disorder in reproductive-age women. The primary clinical features include occasional or persistent anovulation, obesity, polycystic ovarian morphology, insulin resistance, and hyperandrogenemia, representing a pathological state caused by endocrine and metabolic abnormalities [11]. PCOS spans the entire lifespan of women from adolescence to menopause and is closely related to women's health. However, the etiology of PCOS remains unclear, its pathogenesis is complex, clinical heterogeneity is significant, diagnostic criteria are controversial, and treatment options and management strategies vary [12]. PCOS is the primary cause of infertility due to ovulation disorders in reproductive-age women. For patients with PCOS, conventional ovulation induction and multiple outpatient guided intercourse or artificial insemination by husband (AIH) are common treatment options. However, in recent years, IVF-ET has also become a primary means of helping PCOS infertile patients achieve pregnancy by promoting the development of multiple follicles to improve pregnancy rates [13]. Letrozole (LE) is the preferred first-line drug for infertility in PCOS patients undergoing conventional ovulation induction, serving as an induction agent for pure anovulatory PCOS patients. Current clinical evidence [14] suggests that LE does not increase teratogenicity compared to other ovulation-inducing drugs and has a lower risk of multiple pregnancies compared to clomiphene citrate (CC). The use of Gn is a second-line therapy for PCOS. The PCOS Evidence-Based Guideline recommends that GnRH antagonist protocols should not be prioritized over GnRH agonist protocols for PCOS patients undergoing IVF or ICSI to improve clinical pregnancy or live birth rates [15]. GnRH antagonist protocols are used in PCOS patients undergoing IVF/ICSI because this protocol allows for the use of agonist triggering and freezing of all suitable embryos produced, significantly reducing the risk of severe ovarian hyperstimulation syndrome without affecting cumulative live birth rates. IVF is effective for anovulatory PCOS patients, and selecting single embryo transfer can reduce the risk of multiple pregnancies. Due to the potential risks of pregnancy complications in PCOS, single embryo transfer should be preferred.

For PCOS patients who do not become pregnant after conventional ovulation induction and multiple outpatient guided intercourse or AIH and do not accept IVF-ET, even though the long-acting GnRH-a-derived COS protocol is often used in IVF, we can still attempt to use the long protocol combined with AIH for treatment, as in this case. In this case, we considered the patient's individual differences and endocrine environment characteristics, selected an appropriate ovulation induction protocol, successfully improved her endometrial receptivity while obtaining dominant follicles using the long protocol, and selected the most appropriate timing for AIH, thereby enhancing her pregnancy rate. Therefore, correctly identifying the degree of pituitary-ovarian axis down-regulation, rationally using GnRH-a doses and timing, and flexibly selecting Gn initiation and AIH timing are crucial for achieving satisfactory and effective outcomes in individualized treatment for different infertile patients.

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