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Case Report

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Successful Intrauterine Insemination Following Estradiol Pretreatment in a Patient with Primary Ovarian Insufficiency: A Case Report

Trang Nguyen Khanh Huynh [1], Minh Phuc Khanh Huynh [2*], Loc Thai Ly [2]

1- Department of Obstetrics and Gynecology, Pham Ngoc Thach University of Medicine, Ho Chi Minh City, Vietnam
2- Department of Infertility, Hung Vuong Hospital, Ho Chi Minh City, Vietnam

Abstract

Background: Premature ovarian insufficiency (POI) is a clinical condition characterized by impaired ovarian function to secrete gonadal hormones, leading to hypoestrogenism and amenorrhea before the age of 40. Oocyte depletion in POI significantly reduces the chance of spontaneous conception, making infertility a key concern. Various in vitro fertilization (IVF) stimulation protocols, including estrogen pretreatment, have been investigated to facilitate conception with autologous oocytes in patients with POI. The principle of estrogen pretreatment involves administering exogenous estrogen to suppress elevated pituitary gonadotropins (FSH and LH), thereby restoring normal follicular development.

Case Presentation: This article presents a case of a 32-year-old patient with POI, characterized by severely diminished ovarian reserve, as evidenced by an AMH level of 0.03 *ng/ml* and an antral follicle count (AFC) of 1. Our patient had been attempting to conceive for 14 months and reported shortened menstrual cycles. Hysterosalpingography revealed bilaterally patent fallopian tubes, and the patient's partner demonstrated normozoospermia. The patient was initially scheduled for IVF with controlled ovarian stimulation and estrogen pretreatment. However, a spontaneously matured follicle was detected during the course of estrogen therapy. Consequently, the patient was advised to undergo intrauterine insemination (IUI) following ovulation triggering with human chorionic gonadotropin (hCG). The procedure resulted in a clinical pregnancy and culminated in a term live birth.

Conclusion: In POI patients using for estrogen pretreatment autologous oocytes, may enhance ovarian responsiveness. If a mature follicle emerges during estrogen pretreatment, ovulation induction with IUI offers a viable path to natural conception.

** Corresponding Author:*
Minh Phuc Khanh Huynh,
Department of Infertility,
Hung Vuong Hospital, Ho Chi Minh City, Vietnam
E-mail: huynhminh1504@gmail.com

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Introduction

Primary ovarian insufficiency (POI) is characterized by a decline in ovarian function before the age of 40, resulting in subnormal sex steroid production and elevated gonadotropin levels (1). It manifests clinically with menstrual disturbances, infertility, and long-term systemic consequences primarily related to estradiol deficiency, such as increased risks of cardiovascular disease, osteoporosis, and cognitive impairment (2).

The prevalence of POI varies depending on population and study design. In a longitudinal cohort study by Coulam et al., POI was identified in 1% of 1,858 women born between 1928 and 1932 (3). Luborsky et al. later reported a prevalence of 1.1% in a cross-sectional study from 2003, with higher rates observed among African-American and Hispanic women compared to Caucasian and Asian-American populations (4). More recently, a

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Swedish national registry study reported a prevalence of 1.8% (5), while a global meta-analysis estimated the pooled prevalence to be approximately 3.7%, underscoring the global relevance of POI (6).

The pathophysiology of POI involves impaired negative feedback from diminished estradiol production, leading to elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). As a result, folliculogenesis and ovulation are disrupted, contributing to infertility. Diagnosis is based on clinical and biochemical criteria, including menstrual irregularities and elevated FSH levels. While shortened cycles may precede amenorrhea, the most widely accepted diagnostic criteria are those proposed by the European Society of Human Reproduction and Embryology (ESHRE): (1) oligo/amenorrhea for at least four months, and (2) elevated FSH levels >25 *mIU/ml* on two separate occasions at least four weeks apart (7). Diminished ovarian reserve is typically evidenced by low anti-Müllerian hormone (AMH <1.2 *ng/ml*) and reduced antral follicle count (AFC <5) (8).

POI has a heterogeneous etiology, encompassing genetic and chromosomal abnormalities, autoimmune conditions, iatrogenic factors (*e.g.*, chemotherapy, radiotherapy, pelvic surgery), and, less commonly, infections (2). The primary focus of management of POI includes symptom control, hormone replacement, and long-term health risk mitigation (2). Nevertheless, fertility preservation and conception remain key concerns, particularly in young women. In vitro fertilization (IVF) using donor oocytes remains the most effective fertility option in women with POI; however, attempts at conception using autologous oocytes continue in select cases. Ovarian stimulation protocols for these patients are often challenged by low ovarian reserve, but various strategies, including estradiol pretreatment, have been proposed to improve follicular recruitment (9, 10). Estradiol pretreatment can suppress endogenous FSH and LH levels, potentially promoting follicular synchrony and up-regulation of FSH receptors on granulosa cells (11, 12). Check et al. demonstrated that combining pituitary suppression with human menopausal gonadotropin (hMG) stimulation could restore ovulation (13). Moreover, rare spontaneous pregnancies during cyclic estradiol–progestin therapy have been reported, presumably due to improved gonadotropin regulation and enhanced follicular sensitivity (14, 15). Consistent with these observations, previous reports have documented successful pregnancies in patients with primary ovarian insufficiency following estradiol pretreatment and ovulation induction, including conception achieved through intrauterine insemination (IUI). Notably, Piedade et al. described a successful IUI pregnancy after estradiol supplementation in a patient with POI, supporting the feasibility of this approach (16).

This case report describes a patient with POI who demonstrated spontaneous follicular maturation during oral estradiol valerate pretreatment administered within an IVF protocol, an observation that has been rarely documented. In this individual case, the presence of a single mature follicle together with endometrial development prompted a deliberate conversion from IVF to IUI to optimize both efficacy and cost. This strategy resulted in a clinical pregnancy and full-term live birth, highlighting the novel possibility that IUI may be feasible in highly selected POI patients under specific clinical circumstances.

Case Presentation

A 32-year-old woman and her 35-year-old husband presented to the Infertility Department of Hung Vuong Hospital on 25 April 2024 with a 14-month history of primary infertility. The couple had no history of prior pregnancies or contraceptive use. The patient worked in an office environment with no exposure to gonadotoxic agents and reported no history of surgery, radiation, or chemotherapy. Her menstrual cycles were regular but shortened, occurring every 20 days with a duration of 5–7 days. The last menstrual period (LMP) was on 21 April 2024. She first attended the infertility clinic on cycle day 5 (25 April), and returned for a second visit on 10 May 2024 (cycle day 4), following a new LMP on 7 May 2024.

Investigation: On general examination, the patient was in good overall health. She measured 171 *cm* in height and weighed 71 *kg*, with a body mass index (BMI) of 24. Vital signs were within normal limits: pulse rate 88 *bpm*, blood pressure 110/60 *mmHg*, temperature 37°*C*, and respiratory rate 20 breaths per minute. Physical examination revealed no abnormalities.

Laboratory evaluation showed a markedly diminished AMH level of 0.03 *ng/ml*, indicating severely reduced ovarian reserve. Thyroid function was within normal limits, with a thyroid-stimulating hormone (TSH) level of 1.63 *mIU/L* and free T4 of 19.7 *pmol/L*. Serum prolactin was

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also normal at 4.55 *ng/ml*. Assessment for 21-hydroxylase antibodies could not be performed due to unavailability at our center. Infectious disease screening was negative for hepatitis B surface antigen (HBsAg), anti-HCV, HIV (rapid test), and syphilis; tuberculosis screening was negative. Vaginal PCR testing for Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) was also negative. Transvaginal ultrasound showed a normal uterus with bilaterally small ovaries, each containing one antral follicle. Hysterosalpingography (HSG) confirmed bilateral tubal patency.

On 10 May 2024 (cycle day 4), transvaginal ultrasound showed one antral follicle in the left ovary (AFC=1). Hormonal profiling demonstrated an elevated serum FSH level of 20.3 *IU/L*, LH of 6.31 *IU/L*, low estradiol at 39.7 *pg/ml*, and a testosterone level of 0.17 *ng/ml*.

The husband's semen analysis, performed after seven days of abstinence, showed a volume of 3.2 *ml* with normal viscosity and pH (7.5). Sperm concentration was 64 *million/ml*, with total motility of 52%, including 15% rapid progressive and 37% slow progressive motility. Morphologically normal forms accounted for 1%, and no leukocytes were detected.

Karyotype analysis confirmed a normal chromosomal complement: 46,XX in the the patient and 46,XY in her partner. FMR1 premutation analysis could not be performed as it was not available at our center.

Treatment: Based on elevated FSH levels and a low AMH level, the patient was diagnosed with infertility due to POI with severely diminished ovarian reserve and was counselled regarding conception via IVF. An antagonist stimulation protocol with oral estradiol valerate pretreatment was selected in accordance with our center's guidelines.

Treatment commenced on 10 May 2024 (cycle day 4), with oral estradiol valerate (Valiera) initiated at a dose of 2 *mg/day*. A follow-up was scheduled after one week to assess the hormonal response.

On 17 May 2024, serum FSH was 22.3 *IU/L* and estradiol 160 *pg/ml*. Ultrasound revealed a developing follicle (17 *mm*) in the left ovary and one antral follicle in the right ovary. Due to elevated FSH, the estradiol valerate dose was increased to 4 *mg/day* and continued for one week.

At follow-up on 24 May 2024, FSH had decreased to 4.06 *IU/L*, LH was 7.79 *IU/L*, and estradiol had increased to 419 *pg/ml*. Ultrasound demonstrated a mature follicle measuring 20 *mm* and an endometrial thickness of 10 *mm* with a trilaminar pattern. Estradiol valerate was continued at 4 *mg/day*, with the next assessment scheduled for 28 May.

On 28 May 2024, hormonal parameters were favorable: FSH 2.48 *IU/L*, LH 3.77 *IU/L*, and estradiol 627 *pg/ml*. The dominant follicle had reached 23 *mm*, and the endometrial thickness remained at 10 *mm* with a persistent trilaminar pattern (Figure 1). In view of the development of a single follicle and cost considerations, the patient was counselled regarding conversion from IVF to IUI, which she consented. Ovulation was subsequently triggered with 5,000 *IU* of intramuscular human chorionic gonadotropin (hCG, IVF-C; Huong Viet Pharmaceutical J.S.C., Ho Chi Minh City, Vietnam), and IUI was scheduled for 30 May.

On 30 May, the husband's sperm was processed using the density gradient centrifugation (DCG) technique. Post-wash semen analysis showed a volume of 0.5 *ml*, progressive motility of 98%, and a concentration of 24 *million/ml*. IUI was performed without difficulty. Following the procedure, the patient was prescribed vaginal micronized progesterone (Utrogestan; Besins Healthcare, Belgium) at a dose of 400 *mg* per day for luteal phase support and advised to return for follow-up after two weeks. The clinical progression during treatment is summarized in table 1.

Follow-up: On 6 June 2024, the patient obtained a positive result on a home urine pregnancy test, which was confirmed at Hung Vuong Hospital with a serum β-hCG level of 3,855 *IU/L*. Transvaginal ultrasound revealed a gestational sac measuring 5×3 *mm* and a hemorrhagic corpus luteum cyst in the left ovary measuring 23×20 *mm*. Follow-up ultrasound on 22 June 2024 confirmed an intrauterine pregnancy with ongoing fetal car-

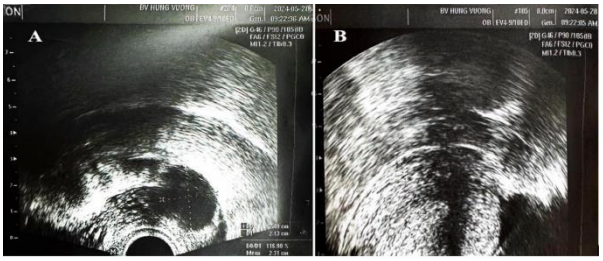

Figure 1. Transvaginal ultrasound images on 28 May 2024 demonstrating a dominant follicle measuring 23 *mm* (A) and an endometrial thickness of 10 *mm* with a persistent trilaminar pattern (B)

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Table 1. Summary of clinical progression

	10/5/2024	17/5/2024	24/5/2024	28/5/2024
FSH (*IU/L*)	20.3	22.3	4.06	2.48
LH (*IU/L*)	6.31	-	7.79	3.77
Estradiol (*pg/ml*)	39.7	160	419	627
Follicle mean diameter (*mm*)	8	17	20	23
Endometrial thickness (*mm*)	6	7	10	10
Estradiol valerate dose (*mg/day*)	0	2	4	4

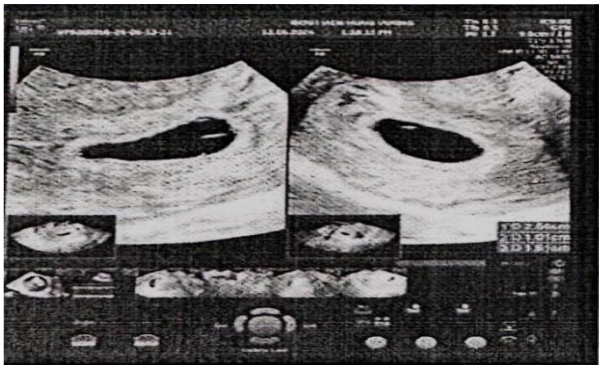

Figure 2. Follow-up transvaginal ultrasound on 22 June 2024 confirming an intrauterine pregnancy with ongoing fetal cardiac activity and a CRL of 8 *mm*

diac activity and a crown–rump length (CRL) of 8 *mm* (Figure 2). At 12 weeks' gestation, the pregnancy remained viable, with normal findings on ultrasound and non-invasive prenatal testing (NIPT). The pregnancy progressed without complications and culminated in a full-term live birth. Written informed consent for publication of this case report was obtained from the patient, and the study was conducted in accordance with institutional ethical standards.

Discussion

In a cohort study of 358 women with POI, spontaneous ovarian function, defined by the resumption of menses and/or normalization of FSH levels, was observed in 24% of cases, while the spontaneous pregnancy rate remained low at 4.4% (17). These findings underscore the limited likelihood of natural conception in POI and the modest efficacy of conventional fertility treatments. Consequently, oocyte donation (OD) is widely regarded as the most effective strategy for achieving pregnancy in this population. However, for patients who strongly desire to conceive using autologous oocytes, emerging evidence suggests that estradiol pretreatment may offer a promising alternative. Observational studies report pregnancy rates of 4.8% with estradiol replacement therapy alone, and ovulation induction protocols have shown pregnancy rates of up to 6.3%, although trials using gonadotropin-releasing hormone agonists (GnRH-a) failed to show significant improvement over placebo (18-20).

Several studies have highlighted the role of estradiol in restoring ovarian responsiveness. A 1990 study reported a 20% pregnancy rate (19/91) in patients with more than 12 months of amenorrhea who underwent estradiol pretreatment followed by hMG stimulation, whereas no pregnancies were achieved when hMG was administered without prior estradiol replacement (13). Similarly, a 2007 study involving POI patients with over six months of amenorrhea demonstrated that hMG stimulation under estradiol replacement resulted in follicular growth in 36% and clinical pregnancy in 16% of cases, with no follicular development in the group that received hMG alone (10). These findings suggest that estradiol pretreatment may be critical in restoring follicular sensitivity to gonadotropins. Recent data also support specific protocol refinements. Ishizuka et al. reported a live birth rate of 37.3% in POI patients with less than four years of amenorrhea undergoing ovarian stimulation with hormone replacement therapy, indicating that such an approach may be effective prior to proceeding with OD (21). Moreover, Tartagni et al. demonstrated that ethinyl estradiol pretreatment enhances ovulation induction success, recommending that FSH levels be sup-pressed to below 15 *mIU/ml* before initiating stimulation (10). Mechanistically, estradiol sup-presses circulating FSH and may promote the re-expression of FSH receptors in remnant follicles, enhancing granulosa cell responsiveness to exogenous gonadotropins. Experimental studies further suggest

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that estradiol not only facilitates receptor regeneration but may also improve FSH binding affinity (11, 12, 20).

Some women with karyotypically normal primary ovarian insufficiency retain intermittently functional ovarian follicles; however, excessive LH exposure may inappropriately induce premature luteinization and impair normal follicular function, a mechanism through which estradiol pretreatment may be beneficial by suppressing LH secretion (22). Based on this growing body of evidence, our center has implemented an estradiol pretreatment protocol for ovarian stimulation in POI patients seeking conception with autologous oocytes. In the present case, the patient expressed a strong preference to use her own oocytes. Estradiol valerate was administered to suppress elevated FSH and LH levels, resulting in resumed follicular development and maturation of a dominant follicle. The clinical course in this case closely resembled a step-down FSH protocol, where high endogenous FSH levels were gradually brought into a range conducive to follicular growth. Given that only a single follicle developed, and considering the high cost of IVF to retrieve a single oocyte, the patient was offered a conversion to IUI. This was deemed appropriate given her bilateral tubal patency and her partner's normal semen parameters. The patient consented, and the IUI resulted in a successful, full-term pregnancy at significantly reduced cost.

To our knowledge, this is one of the few reported cases demonstrating successful pregnancy via IUI following oral estradiol valerate pretreatment in a POI patient. This case highlights that follicular development may resume during oral estradiol valerate pretreatment, and that when favorable conditions are present, including a mature follicle, normal tubal anatomy, and normal semen parameters, IUI may represent a viable and cost-effective alternative to IVF. While promis-ing, this approach may not be generalizable to all POI patients, as response to treatment remains highly variable. Further prospective studies are needed to better define predictive factors for suc-cessful follicular recruitment and to evaluate the role of IUI following oral estradiol valerate pre-treatment in this unique patient population.

Conclusion

This case suggests that, in a highly selected infertile patient with primary ovarian insufficiency treated with autologous oocytes, estradiol pretreatment may be associated with improved ovarian responsiveness. In this individual case, the development of a mature follicle during the pretreatment phase allowed ovulation induction followed by IUI, which appeared to be a feasible and cost-effective approach to achieve conception. However, this observation is based on a single case and should not be generalized; further studies are required to clarify its potential applicability.

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Conflict of Interest

The authors declare no conflict of interest.

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