



Letrozole-Induced Ovarian Hyperstimulation Syndrome Resulting in Quadruplet Pregnancy in a Young Nulligravida: A Case Report

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Abstract:

Letrozole, an aromatase inhibitor, is widely used for ovulation induction due to its favorable safety profile, lower estrogen levels, and reduced risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy compared to clomiphene citrate and gonadotropins. Despite this, excessive ovarian response and high-order multiple gestation may rarely occur.

We report a case of a 23-year-old nulligravida with primary infertility who underwent ovulation induction with letrozole. During her second cycle, she developed mild to moderate OHSS and subsequently conceived a quadruplet intrauterine pregnancy. One gestational sac underwent spontaneous demise, followed by selective fetal reduction from triplets to twins at 12 weeks of gestation. The antenatal period was uneventful until spontaneous preterm labour at 30 weeks, resulting in the vaginal delivery of live preterm twins.

This case highlights that although letrozole is considered a low-risk ovulation-induction agent, clinicians should remain vigilant for rare complications such as OHSS and high-order multiple pregnancies. Careful monitoring and thorough patient counselling are essential to ensure optimal maternal and fetal outcomes.

Keywords: Letrozole; Ovulation induction; Ovarian hyperstimulation syndrome; Quadruplet pregnancy; High-order multiple gestation; Selective fetal reduction

Introduction

Letrozole, an aromatase inhibitor, is widely used for ovulation induction because it typically results in monofollicular development, lower estradiol levels, and reduced risk of ovarian hyperstimulation syndrome (OHSS) compared with clomiphene citrate or gonadotropins [1,2]. The reported incidence of multiple gestation during letrozole cycles is low (3–7%), and high-order multiple pregnancy is extremely uncommon [1,3]. However, sporadic cases of multifollicular recruitment, OHSS, and triplet or quadruplet gestations have been described [4,5].

We present a rare case of letrozole-induced OHSS complicated by a quadruplet pregnancy in a young infertile woman, highlighting that even low-risk oral agents can occasionally provoke excessive ovarian response.

Case Presentation

A 23-year-old nulligravida attended the Obstetrics & Gynaecology outpatient department at AIIMS Bilaspur with a 2-year history of primary infertility. She had regular 30–32-day cycles, no dysmenorrhea, and no symptoms suggestive of endocrine disorders. Her BMI was 21 kg/m². Baseline hormonal profile (TSH, prolactin, AMH) and pelvic ultrasound were within normal limits. Semen analysis of her partner was normal.

Treatment Course

She underwent ovulation induction (OI) with letrozole 5 mg/day from cycle day 3–7 for two consecutive cycles. During the second cycle, she reported progressive abdominal distension and discomfort near ovulation. Transvaginal ultrasound revealed:

- Bilaterally enlarged ovaries
- Multiple large follicles
- Minimal free fluid in the pelvis

The findings suggested moderate OHSS. She was managed conservatively with fluids, rest, and close follow-up.

Pregnancy Outcome

A urine pregnancy test at 5 weeks was positive. Early ultrasound revealed a quadruplet intrauterine gestation with four distinct gestational sacs, all with fetal poles and cardiac activity.

At 8 weeks, one sac showed absent cardiac activity, suggestive of vanishing fetus phenomenon.

After multidisciplinary counselling, the couple opted for selective fetal reduction. At 12 weeks, transvaginal fetal reduction was performed, reducing a triplet gestation to a dichorionic diamniotic twin pregnancy.

Antenatal Course & Delivery

The remainder of her antenatal period was uneventful, with appropriate fetal growth and no recurrence of OHSS.

At 30 weeks, she presented in spontaneous preterm labour and delivered live preterm twins vaginally. Both neonates required NICU admission for prematurity and respiratory support.

Mother recovered well postpartum.

Discussion

Letrozole is regarded as a safer alternative to clomiphene because of its shorter half-life, favourable endometrial effects, and tendency toward monofollicular ovulation [1]. The risk of OHSS with letrozole is significantly lower owing to lower estradiol concentrations; however, excessive FSH rise due to aromatase inhibition can occasionally lead to multifollicular recruitment, particularly in young patients or those with increased ovarian reserve [3,4].

Although uncommon, letrozole-induced multifollicular development and OHSS have been reported, especially with higher doses (5 mg) or in women with mild PCOS spectrum [4,5]. The development of a quadruplet pregnancy following oral OI alone is exceptionally rare. Most reported high-order pregnancies associated with letrozole involve 3–4 dominant follicles, mirroring the pattern observed in this patient.

The occurrence of OHSS in our patient is biologically plausible: multiple corpora lutea and increased vascular endothelial growth factor (VEGF) secretion can lead to capillary leakage and third-space fluid accumulation despite lower estradiol levels in letrozole cycles [6].

Selective fetal reduction was indicated to reduce risks of extreme prematurity, hypertensive disorders, and perinatal morbidity associated with high-order multiple gestation [7]. Despite reduction to twins, the patient delivered preterm at 30 weeks—a well-recognized risk in multifetal pregnancies, even post-reduction.

This case emphasizes that letrozole is not exempt from causing OHSS or high-order multiple gestation, and clinicians should:

- Use individualized dosing
- Monitor follicular development closely
- Consider cycle cancellation when excessive follicles develop
- Provide comprehensive counselling regarding potential outcomes

Conclusion

Letrozole is a safe and effective ovulation-induction agent; however, rare cases of OHSS and high-order multiple pregnancy can occur, particularly in young women with high ovarian reserve. Vigilant monitoring and timely counselling are essential to ensure safe reproductive outcomes. This case contributes to the growing body of evidence that even low-risk oral stimulation protocols require careful surveillance.

Patient Consent

Written informed consent was obtained from the patient for publication of this case.



Figure:1a



Figure:1b



Figure:1c



Figure:2a



Figure:2b



Figure:3

Figure:1(a, b &c)-Tetrachorionic Tetraamniotic Quadruplet gestation(Four live intra-uterine G-Sacs corresponding to 7 weeks gestation) with thick walled cystic lesions in bilateral ovaries

Figure:2(a&b)-Tetrachorionic Tetraamniotic Quadruplet gestation with spontaneous reduction to the triplets. Bilateral enlarged ovaries showing features of hyperstimulation. Fetus A is down & to maternal left. Fetus B is up and in the fundus. Fetus C is down & to the maternal right.

Figure:3-Dichorionic Diamniotic Twin pregnancy with fetuses corresponding to Fetus A [27] weeks [5] days with (Variable) presentation, Fetus B [27] weeks [3] days with [Variable] presentation

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