

The effect of leuprolide acetate in aiding induction of ovulation in hypergonadotropic hypogonadism: a case report

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Leuprolide acetate (LA) is a long-acting, gonadotropin-releasing hormone analog (GnRHa). At first, the leuprolide may stimulate the pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) because of its agonist action, but it will eventually inhibit the pulsatile release of GnRHa, thus causing the suppression of LH and FSH.^{1,2}

A technique has been described³ where ovulation can be achieved in some patients with hypergonadotropic hypogonadism. High-dose estrogen (HDE) therapy is used to suppress the gonadotropins in an attempt to theoretically restore receptors in the follicle that may have been down-regulated by the high gonadotropin levels; ovulation then would be restored by directly stimulating the ovaries with human menopausal gonadotropins (hMG).³ Some patients, however, may not be able to tolerate the HDE, so another option would be to use the leuprolide acetate, which would suppress LH and FSH.

The possibility also exists that, if one fails to induce ovulation with hMG/HDE, suppression of gonadotropins with leuprolide followed by hMG may result in successful ovulation.

A case of hypergonadotropic hypogonadism is described where multiple cycles of ovulation induction with the hMG/HDE technique was achieved, followed by resistance to this approach. Successful ovulation then was achieved with leu-

prolide/hMG therapy. However, in three cycles, successful ovulation was achieved with leuprolide exclusively without any hMG.

MATERIALS AND METHODS

The patient was a 43-year-old woman interested in becoming pregnant. Her menarche was at age 14 and her menstrual cycles occurred monthly up to age 36, when oligomenorrhea developed and, finally, amenorrhea at age 38. The patient's husband had azoospermia and they requested artificial insemination by donor (AID). The patient was discovered to have a serum estradiol (E_2) level of 20 ng/ml. Her serum LH and FSH levels were at 58 and 45 mIU/ml, respectively, while the serum thyroxin (T4), triiodothyronine (T3 uptake), thyroid-stimulating hormone (TSH), testosterone, cortisol, dehydroepiandrosterone sulfate (DHEA), and glucose were all normal. Repeat gonadotropin levels were similarly elevated (serum LH, 72; FSH, 61). Since all other endocrine studies were normal, we did not measure antibodies against endocrine glands (e.g., thyroid antibodies).

The patient was given a course of hMG therapy, but despite 40 ampules of hMG (75 IU/ml), her E_2 failed to rise above 20 ng/ml. A second attempt to stimulate ovulation failed, despite 44 ampules of hMG.

The patient was treated with the hMG/HDE technique using ethinyl E_2 at 0.05 mg/day.³ The patient successfully ovulated 12 of 18 times using this technique. She conceived on her seventh cycle, as confirmed by an hCG β -subunit level of 1079

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mIU/ml 20 days from conception. Unfortunately, a spontaneous abortion occurred (pelvic sonography revealed a single intrauterine gestational sac measuring $18 \times 15 \times 10$ mm with an internal echo of 4 mm, consistent with a fetal pole but no viability).

The patient became relatively refractory to this therapy, failing to ovulate in 5 of 11 attempts, including her last three trials. The serum E_2 level never reached 100 pg/ml in the last three attempts, and never reached 30 pg/ml in her last attempt.

The patient was switched to LA instead of ethinyl E_2 for gonadotropin suppression prior to hMG stimulation. The patient was made aware of the fact that this drug was not approved for the use in ovulation induction, but only for prostatic cancer therapy. The employment of the LA for this use was approved by the chief of the division of reproductive endocrinology at Jefferson University and by the human research committee. The intention was to give the drug subcutaneously at 1 mg/day for 3 weeks and then also to begin the hMG therapy. However, by day 10 of LA therapy, the patient noticed abundant cervical mucus and sonography indicated a 22-mm diameter follicle associated with a serum E_2 level of 285 pg/ml. Two days later, her follicle decreased 11 mm, associated with a rise in the serum progesterone (P) level to 2.3 ng/ml, indicative of the release of the ovum. The LA was stopped after ovulation and was restarted on day 1 of her ensuing menses.

The patient ovulated the next cycle just with the LA and then one time again in the next four treatment cycles. The LA/hMG technique was successful in ovulation induction in the three cycles where LA alone was unsuccessful. Unfortunately, a pregnancy has not occurred with either LA alone or LA/hMG therapy, possibly related to her age (45 years) since initiating LA therapy. During the total combined ovulations between HDE/hMG, LA/hMG, or LA alone (32), only one mature follicle was stimulated each cycle.

DISCUSSION

Though spontaneous ovulations have been documented rarely in women with hypergonadotropic amenorrhea, the likelihood of this happening fortuitously in three of eight treatment cycles with LA seems highly unlikely. The exact mechanism of its action in ovulation induction in this circumstance is unknown. Though initially this GnRHa may stimulate the gonadotropins,⁴ and perhaps ovulation occurred through this mechanism, it must be recalled that the patient initially failed to stimulate with hMG alone. Though one might hypothesize

the apparent ovulation to LA alone the first time to be on the basis of rebound ovulation from previous hMG/HDE therapy, this seems less likely than a direct effect of LA in view of failing to ovulate three consecutive times prior to the LA therapy with hMG/HDE and also the failure to stimulate a serum E_2 level above 30 ng/ml during the last attempt.

The possibility exists that some degree of suppression of gonadotropins occurred,⁵ allowing some degree of restoration of previously down-regulated gonadotropin receptors and enabling the response to endogenous gonadotropins. Unfortunately, gonadotropins were not measured at the time of starting LA therapy, which might have strengthened this hypothesis.

SUMMARY

A 43-year-old woman with a history of 5 years of amenorrhea sought help in achieving a pregnancy. Her gonadotropins were found to be elevated and thus she was diagnosed as having ovarian failure. She was made to ovulate on many occasions by suppressing her gonadotropins first with estrogen, then stimulating her ovaries with hMG. However, she became refractory to this therapy and she was switched from estrogen to LA to suppress gonadotropins. The woman ovulated three times just with leuprolide therapy before any hMG was added. A possible hypothesis is that, on the way down to subnormal levels of LH and FSH, a critical level of gonadotropins was attained where they were still high enough to stimulate the follicles, but low enough to allow restoration of gonadotropin receptors, which previously had been down-regulated by the elevated gonadotropin levels.

REFERENCES

1. Sandow J: Clinical applications of LHRH and its analogues. *Clin Endocrinol (Oxf)* 18:671, 1983
2. Yen SSC: Clinical applications of gonadotropin-releasing hormone and gonadotropin-releasing hormone analogs. *Fertil Steril* 39:257, 1983
3. Check JH, Chase JS: Ovulation induction in hypergonadotropic amenorrhea with estrogen and human menopausal gonadotropin therapy. *Fertil Steril* 42:919, 1984
4. Faure W, Labrie F, Belanger A, Lemay A, Raynaud JP, Von der Ohe M, Fazekas ATA: Sensitivity of luteinizing hormone and gonadal steroid responses to single intranasal administration of an LHRH agonist (Hoe-766) in young normal adult men. *J Endocrinol Invest* 5:355, 1982
5. Bergquist C, Niliius SJ, Bergh T, Skarin G, Wide I: Inhibitory effects on gonadotrophin secretion and gonadal function in men during chronic treatment with a potent stimulatory luteinizing hormone-releasing hormone analogue. *Acta Endocrinol (Copenh)* 91:601, 1979