

Mild increases in serum FSH in late follicular phase increases the risk of the luteinized unruptured follicle: case report

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Summary

Purpose: To find a case that will support the concept that mild elevation of serum follicle stimulating hormone (FSH) levels in late follicular phase may interfere with the release of the oocyte from the follicle. **Materials and Methods:** Oocyte release was determined in a woman in a complete natural cycle vs cycles where a boost of very low dose FSH was given, human chorionic gonadotropin (hCG) 10,000 units or leuprolide acetate 1 mg every 12 hours x two doses was given in FSH stimulated cycles. **Results:** Oocyte release occurred in all natural cycles vs none of the mildly stimulated cycles. **Conclusions:** Mild changes in the FSH level in the late luteal phase may affect the production of certain FSH dependent factors needed to release the oocyte.

Key words: Luteinized unruptured follicle syndrome; Gonadotropin; Human chorionic gonadotropin; Leuprolide acetate; Natural cycle.

Introduction

In any given menstrual cycle, a woman can develop a dominant follicle, generate a luteinizing hormone (LH) surge from a corpus luteum, and have spontaneous menses two weeks after the induction of progesterone (P) secretion and yet technically not ovulate because the oocyte was not extruded from the follicle [1]. This is known as the luteinized unruptured follicle (LUF) [2].

A global review of the world literature concluded that although LUF does exist as a clinical phenomenon in natural cycles, but from a clinical standpoint it probably does not constitute a syndrome [3]. However, in women treated with gonadotropin and human chorionic gonadotropin (hCG), data demonstrated 91% of 128 woman who presented evidence of oocyte release in cycle one demonstrated a definite release in cycle two; only 6% of 16 women who failed to release an oocyte in cycle one showed evidence of release in cycle two [4].

Thus the possibility exists that the use of FSH drugs creating a change in the normal LH-FSH-estradiol (E2) relationships during the follicular phase may cause a greater chance of the various chemical and cytokines produced to negatively influence oocyte release from the follicle [5].

A case is presented demonstrating this hypothesized phenomenon in one individual, i.e., oocyte release with natural cycles, but LUF even with very mild FSH stimulation.

Case Report

The patient is a 40-year-old woman presenting with primary infertility. She had a history of diminished oocyte reserve with her highest serum FSH at 31 mIU/ml.

Evaluating natural cycles in her first cycle of evaluation, she attained a mature follicle with her peak serum E2 of 282 pg/ml on a cycle day 8 with a 22.9 mm follicle and the follicle completely collapsed two days later to < 10 mm, thus showing evidence of oocyte release. She had similar findings in cycle 2, which was completely natural.

In cycle three her day 4 serum FSH was 27.9 mIU/ml with a serum E2 of 48 pg/ml. She wanted to be more aggressive, so on cycle day 10 she was boosted with 150 IU exogenous FSH (Gonal-F®) and 1 mg of Ganirelix. Her serum E2 initially dropped to 163 pg/ml on day 11 from 242 on day 10. Serum P remained low at 0.6 ng/ml, but eventually she reached a 333 pg/ml serum E2 with an 18, 14, and 12 mm follicle. The LH rose from 4.3 mIU/ml to 24.6 mIU/ml, therefore 10,000 units of hCG was given. The 12 mm follicle increased to 21.7 mm and the 18 mm follicle increased to 37.5 mm in average diameter and the 14 mm remained about the same three days later - indicative of LUF.

For cycle four she tried a natural cycle again and attained a 19.1 mm follicle with a serum E2 of 311 pg/ml. She was given leuprolide acetate in lieu of hCG 1 mg every 12 hours and demonstrated oocyte release.

For cycle five she failed to attain a mature follicle, so it was decided to boost with FSH again. In cycle six she attained an 18.2 mm follicle on day 16 with a serum E2 of 436 pg/ml, P of 0.4 ng/ml, LH of 6 mIU/ml, and an FSH of 15.8 mIU/ml. Following leuprolide acetate 1 mg every 12 hours x two doses, the 18.2 mm follicle increased to a 20.2 mm and serum P rose to 3.3 ng/ml, indicative of non-release again.

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Discussion

One question that arises about LUF is whether one can be sure that merely failing to demonstrate sonographic follicle collapse is definitely indicative of oocyte release. Support that sonography can indeed detect oocyte release from the follicle is the fact that in one study, the pregnancy rate in the first and second gonadotropin stimulated cycle, the pregnancy rate was 13.5% and 15.7% when oocyte release was demonstrated, but was zero in both cycles when LUF was diagnosed [4].

One study found that LUF occurred in about 5% of natural cycles [5]. Yet given 35 more cycles in these same women, LUF only occurred in one (about 3%) [5]. Others claim that LUF may occur in about 7% of natural cycles [6]. The incidence of LUF may increase significantly if one evaluates LUF in natural cycles of women with unexplained infertility [7].

The woman described in the case report consistently released her oocytes in natural cycles but failed all FSH stimulated cycles although at most she received a tiny boost from the late follicular phase and despite receiving 10,000 units of hCG. A previous publication found that leuprolide acetate, a gonadotropin releasing hormone agonist (GnRH-a), by causing release of endogenous LH and FSH, had a high success rate in advancing oocyte release in women failing to release with FSH stimulation and hCG [8]. Indeed the woman did release following leuprolide acetate injection in a natural cycle (though it may not have been needed), but failed when given just a mild boost of FSH despite leuprolide acetate.

This case demonstrated that LUF is not from failure to generate an LH surge but possibly failure to generate a biologically active LH surge. The case strongly suggests that increasing FSH even mildly in the late follicular phase causes some change in the factors that are needed for oocyte release [5].

This case report suggests that if oocyte release occurs in natural cycles, one cannot assume that oocyte release will occur in subsequent cycles, even if only a boost of low-dose FSH is given to merely help ensure adequate follicular maturation. Some assume there is no downside to improve follicular maturation with a small dosage of FSH. This case shows that the LUF syndrome is one potential negative effect of mild FSH stimulation.

References

- [1] Coulam C.B., Hill L.M., Breckle R.: "Ultrasonic evidence for luteinization of unruptured preovulatory follicles". *Fertil. Steril.*, 1982, 37, 524.
- [2] Check J.H., Chase J.S., Adelson H.G., Dietterich C.: "New approaches to the diagnosis and therapy of the luteinized unruptured follicle syndrome". *Int. J. Fertil.*, 1986, 30, 29.
- [3] Katz E.: "The luteinized unruptured follicle and other ovulatory dysfunctions". *Fertil. Steril.*, 1988, 50, 839.
- [4] Check J.H., Adelson H.G., Dietterich C., Stern J.: "Pelvic sonography can predict ovum release in gonadotropin treated patients as determined by pregnancy rate". *Hum. Reprod.*, 1990, 5, 234.
- [5] Check J.H.: "Understanding the physiology of folliculogenesis – serves as the foundation for perfecting diagnosis and treatment of ovulatory defects". *Clin. Exp. Obstet. Gynecol.*, in press.
- [6] Hamilton C.J.C.M., Wetzels L.C.G., Evers J.L.H., Hoogland H.J., Muijtjens A., de Haan J.: "Follicle growth curves and hormonal patterns in patients with the luteinized unruptured follicle syndrome". *Fertil. Steril.*, 1985, 43, 541.
- [7] Liukkonen S., Koshimies A.I., Tenhunen A., Ylostalo P.: "Diagnosis and luteinized unruptured follicle (LUF) syndrome by ultrasound". *Fertil. Steril.*, 1984, 41, 26.
- [8] Check J.H., Nazari A., Barnea E.R., Weiss W., Vetter B.H.: "The efficacy of short term gonadotrophin releasing hormone agonists versus human chorionic gonadotrophin to enable oocyte release in gonadotrophin stimulated cycles". *Hum. Reprod.*, 1993, 8, 568.

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