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Case Report

Injection of human chorionic gonadotropin (hCG) can cause the luteinized unruptured follicle syndrome

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Summary

Purpose: To demonstrate that the injection of human chorionic gonadotropin (hCG) intramuscularly for purpose of timing of an intrauterine insemination (IUI) can cause an oocyte to fail to rupture from the follicle. *Materials and Methods:* A 33-year-old woman sought help for infertility that seemed related to a male factor problem. The office performed IUI's morning and evenings on weekdays but only in the morning on weekends. The timing of IUI was generally 40 to 48 hours after the initiation of the luteinizing hormone (LH) surge. When a follicle reached a minimum E2 of 200 pg/mL and an ultrasound with at least one follicle of an average of 20 mm, an injection of hCG 10,000 units I.M. was given in the evening on a Thursday or Friday, for an IUI on Saturday or Sunday. Weekday IUI's were based on endogenous LH surge. Ultrasounds were performed on the day of IUI and the next day, if no oocyte was released. Release was considered to have occurred if shrinkage of the follicle by >5 mm took place without the serum P exceeded 2 ng/dL. *Results:* In six natural cycles where IUI was performed Monday-Friday, the peak sera E2 levels reached 368, 334, 337, 465, 365, and 355 pg/mL. Oocyte release was confirmed in all six cycles. There were two cycles where hCG was given for weekend IUI's. In neither cycle was oocyte release demonstrated. Leuprolide acetate also failed to cause oocyte release. *Discussion:* Though hCG injection and GnRH agonists can correct the luteinized unruptured follicle (LUF) syndrome, in some instances, hCG and GnRH agonists can actually cause LUF syndrome.

Key words: Luteinized unruptured follicle syndrome: Human chorionic gonadotropin injection; Gonadotropin releasing hormone agonist; Natural cycle.

Introduction

A subtle, but not uncommon, cause of infertility is the luteinized unruptured follicle (LUF) syndrome where the progesterone (P) rises and exceeds 2 ng/mL without collapse of the follicle by at least 5 mm [1, 2]. Generally LUF is associated with a rise in luteinizing hormone (LH) which is needed for luteinization. Much less commonly, a follicle reaches criteria of maturity, but there is no LH surge and the follicle fizzles without a rise in P. This would not be considered LUF. One of the medical treatments of LUF is to inject 10,000 units of human chorionic gonadotropin (hCG) [3]. The concept is that the follicle has relative resistance to LH and that a pharmacological dosage is needed [3]. Sometimes causing a better endogenous surge of LH and follicle stimulating hormone (FSH) by using a gonadotropin releasing hormone (GnRH) agonist, e.g., leuprolide acetate, proves more effective than hCG alone [4, 5]. Recently, a new treatment with granulocyte colony stimulating factor (G-CSF) has been attempted and has been successful in some difficult cases [6].

Intrauterine insemination (IUI) is frequently performed for mild male factor infertility to allow sperm to reach the uterine cavity at the time of ovulation (rather than 36-40 hours before ovulation at the time of peak cervical mucus quality) or for hostile mucus. Some doctors will perform IUI empirically to help unexplained infertility even with normal semen parameters and normal post-coital tests (although this is not the method of our practice) [7].

Although it was clear that sometimes hCG and/or GnRH agonist were not effective to enable oocyte release, it was not considered that maybe giving hCG can somehow inhibit oocyte release. A case is described, herein, that strongly suggests that at times a bolus of hCG can inhibit oocyte release as can the use of a GnRH agonist.

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Case Report

A 33-year-old woman sought help for infertility that seemed related to a male factor problem. The office performed IUI's morning and evenings on weekdays, but only in the morning on weekends. The timing of IUI was generally 40 to 48 hours after the initiation of the LH surge. She was monitored with ultrasound for follicular size and with a.m. serum LH, estradiol (E2), and P levels.

When a follicle reached a minimum E2 of 200 pg/mL and an ultrasound with at least one follicle of an average of 2 0mm was attained, an injection of hCG 10,000 units I.M. was given in the evening on a Thursday or Friday, for an IUI on Saturday or Sunday morning. Weekday IUI's were based on endogenous LH surge. Ultrasounds were performed on the day of IUI and the next day if no oocyte release. Release was considered to have occurred if shrinkage of the follicle by > 5 mm took place without the serum P exceeding 2 ng/mL.

In six natural cycles where IUI was performed Monday-Friday the peak sera E2 levels reached 368, 334, 337, 465, 365, and 355 pg/mL. Oocyte release was confirmed in all six cycles. There were two cycles where hCG was given for weekend IUI's. In the first cycle, a serum E2 of 211 was reached with a 20-mm follicle. The hCG was given the next day but the follicle on the day of IUI measured 23.3mm and the serum P was 3.3 ng/mL. In the second cycle the hCG was given with a follicle size of 20.6mm and a serum E2 of 288 pg/mL. The LH level on the day of hCG was 7 and 6 mIU/mL. LUF syndrome was confirmed with serum P exceeding 2 ng/mL. In one cycle for a weekend IUI, leuprolide acetate 1 mg every 12 hours x 3 also failed to release an oocyte when given with a 335 pg/mL serum E2 and a follicle size of 22.6 mm.

Discussion

This is the first report of the possibility that taking hCG may cause LUF. The case emphasizes that treating physicians giving hCG should not assume that the oocyte will release from the follicle. Ultrasounds to check oocyte release should be performed 36-40 hours after hCG. This case emphasizes even more to allow the oocyte to release naturally from the follicle if possible. HCG injection (or leuprolide 1mg x3 dosages) should be limited to cycles where clear release was not seen in the prior natural cycles or where timing of an IUI requires triggering release at a certain time. The explanation for this observation is not known. Possibly the supranormal level of hCG (which has biological action similar to LH), or the supranormal levels of LH reached with GnRH agonists as a trigger, down-regulates the LH receptor. Possibly, though the follicle appeared mature, certain events needed for oocyte release had not been attained, and perhaps these same factors contribute to the initiation of the LH surge. Thus interfering with an hCG or leuprolide trigger may attempt to release an oocyte from a follicle that "was not fully ripened".

The hypothesis of why GnRH agonists sometimes work when hCG fails is that hCG fails to induce an FSH surge which may also be important in oocyte release by effects on prostaglandins and converting plasminogen to plasmins [4, 5, 8]. Yet, to add some confusion, sometimes LUF may occur if the level of FSH is too high in the late follicular phase, possibly by causing down-regulation of the FSH receptor [9].

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