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CASE REPORT

Ovarian hyperstimulation syndrome following the sole administration of injectable gonadotropin-releasing hormone agonist (triptorelin) for the pituitary down-regulation and in vitro fertilization treatment: report of two cases

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Abstract This report is to illustrate two cases of ovarian hyperstimulation syndrome following the sole administration of injectable mid-luteal gonadotropin-releasing hormone agonists (triptorelin) for pituitary down-regulation. Both women underwent egg retrieval, and despite the transfer of good quality embryos, no pregnancy was achieved. The possible mechanism and management of the condition were discussed.

Keywords Gonadortopin-releasing hormone agonist · Ovarian hyperstimulatio syndrome · In vitro fertilization

Introduction

Gonadotropin-releasing hormone agonists (GnRH-a) are now used widely in the controlled ovarian stimulation for in vitro fertilization (IVF) treatment. Because of their initial flare-up effect, they have been used successfully for the first time in 1989 by Lanzone et al. to induce an endogenous luteinizing hormone (LH) peak, follicular maturation and to provoke follicular rupture in cycles stimulated with clomiphene citrate [1]. The following years showed an encouraging use of GnRH-a for the same purpose in cycles stimulated with the various types of drugs for the IVF treatment [2]. Recently, several cases of ovarian hyperstimulation syndrome (OHSS) following the sole administration of GnRH-a have been reported in women who underwent IVF treatment [3–9]. This phenomenon was seen after using different protocols (early follicular or mid-luteal phase), different preparations (short-acting and long-acting) and the different routes of administration of the GnRH-a (intranasal, subcutaneous and intramuscular) [6]. In these different cases, the egg collection from the multifollicles with subsequent successful development of embryos has been reported [4, 6, 8, 9]. Unfortunately, to date, no successful pregnancy was reported. This condition may recur in subsequent administrations of GnRH-a [6]. We report two cases of OHSS following the sole administration of injectable mid-luteal GnRH-a (triptorelin) for pituitary down-regulation.

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Case 1

A 35-year-old woman presented to the IVF clinic with a history of 8 years of primary infertility. Her infertility work-up including hormonal profile, diagnostic laparoscopy and hysterosalpingography was normal. The husband seminal fluid analysis also was within normal limits. Her menstrual cycles were regular. She underwent four cycles of ovulation induction with husband/intrauterine insemination (AIH/IUI) without conception. So, the patient was advised for IVF/intracytoplasmic sperm injection (ICSI) treatment due to unexplained infertility. She received long luteal GnRH analog Triptorelin 3.75 mg (Decapeptyl: Ipsen, Paris; France) on day 21 of the current menstrual cycle for pituitary down-regulation before commencing controlled ovarian stimulation for IVF treatment and embryo transfer. The patient was instructed to present on the following second or third menstrual cycle or 2 weeks without menses following the GnRH-a administration. Fifteen days after GnRH-a administration, the transvaginal

examination revealed 12 follicles measuring 16–19 mm in both ovaries with endometrial thickness of 8.6 mm and no ascites. Laboratory investigations revealed negative pregnancy test, estradiol levels of 13,460 pmol/L, FSH of 0.9 U/L, LH of 1.7 U/L and progesterone of 7.1 ng/mL. The patient complained of nausea and abdominal bloating. Based on these findings, the diagnosis of OHSS was made. The decision was taken to continue the IVF treatment, and ten eggs were retrieved of which seven were fertilized and the best three embryos (two grade 1 and one grade 2) were transferred. Progesterone pessaries were used for luteal phase support. Two weeks after embryo transfer, serum b-HCG was requested and was negative.

Four months later, the same patient underwent another cycle of IVF treatment, where she received the same protocol. Similarly, the patient had no menses 2 weeks after the GnRH-a administration. Again, the pregnancy test was negative and the laboratory investigations showed estradiol levels of 11,885 pmol/L, FSH of 0.8 U/L, LH of 1.1 U/L and progesterone level of 6.9 ng/mL. Transvaginal ultrasonography revealed endometrium of 9.1 mm and 11 follicles measuring 15–20 mm. Seven eggs were collected and three good quality embryos were transferred and the same luteal phase support medication was described. Twelve days after ET, the patient experienced vaginal bleeding and the pregnancy test was negative.

Case 2

A 26-year-old woman referred to the IVF clinic because of 5 years of unexplained infertility. The infertility work-up was normal. The patient received the luteal long-acting triptorelin 3.75 mg for pituitary down-regulation. Two weeks after the administration, the patient presented with lower abdominal heaviness. The transvaginal ultrasonogrphy showed bilateral ovarian follicles nine in number measuring 15–21 mm with moderate amount of free fluid in the cul-de-sac, and endometrium of 9.3 mm. Estradiol level was 9,765 pmol/L. The gonadotropins were low (FSH = 0.8 U/L and LH = 1.3 U/L). The pregnancy test was negative. Decision was taken to continue the IVF treatment, and five eggs were retrieved of which three fertilized. Three days after retrieval, two embryos of good quality were transferred. Progesterone pessaries were described for luteal phase support. Two weeks later, the pregnancy test was negative.

Discussion

Ovarian hyperstimulation syndrome following the sole administration of GnRH-a is extremely rare and the underlying pathophysiology of which remains unclear. It has been reported that the incidence of functional ovarian cysts is increased following the GnRH-a administration in the IVF cycles. The incidence of 9.5% was reported [10]. The precise mechanism by which these cysts are formed is unknown. Possible explanations include the initial transient flare up effect of the GnRH agonist on gonadotropins [11], and insufficient suppression of the circulating gonadotropins to hypophysectomy levels [12]. In contrast to these studies, the patients in our report had suppressed levels of FSH and LH, making the stimulatory effect of these gonadotrophins unlikely. This observation is in agreement with previous case reports [4, 8, 9]. Recently, the direct ovarian stimulation by the GnRH-a has been suggested. In a retrospective study, Parinaud et al. [4] evaluated 1,075 IVF cycles. In spite of the suppressed levels of gonadotrophins, the paradoxical ovarian stimulation with GnRH analogs was observed in 8.7% of cases. The authors hypothesized that the certain effect is probably due to a variation in the expression of ovarian GnRH receptors. However, the GnRH receptor mRNA has been demonstrated in the human ovary and granulosa-lutein cells [13]. Moreover, the occurrence of this condition follows the different preparations and routes of GnRH-a in two women suffering from primary infertility and the recurrence in one woman supporting the hypothesis of the direct effect on the ovary.

In the two present cases, no pregnancy was achieved despite the transfer of good quality embryos and the adequate endometrium. This observation is consistent with the previous reports where no pregnancy occurred in similar cases, but no data were available regarding the quality of embryos and the endometrial thickness [4, 6, 8, 9]. Common finding in our case reports and the previous reports is the high levels of E2 at the time of diagnosis. It has been found that this aberrant rise in serum E2 after GnRH agonist down-regulation may cause imperfect pituitary suppression of bioactive gonadotropins, with subsequent effects on oocyte quality and implantation [14]. Moreover, in a prospective randomized study, Andersen et al. [15] reported reduced implantation rate in women who received GnRH-a versus human chorionic gonadotropin (HCG) for ovulation induction. The authors concluded that GnRH-a induces corpus luteum insufficiency that is responsible for the low implantation rate in the GnRH agonist-treated group. The two women in this report received progesterone for luteal phase support making this hypothesis unlikely. The activation of the endocrine–paracrine pathway has also been suggested as another mechanism by which ovarian hyperstimulation may affect the IVF results [14].

To date, there is no optimal management of recurrence of this condition because of the small number of reported case. In a similar case, Weissman et al. [6] reported that the same condition recurred in a subsequent cycle despite the

preventive pretreatment with an oral contraceptive pills. More recently, successful outcome was reported only in one case that was managed with GnRH antagonist with low dose human menopausal gonadotropin in the subsequent cycle [9].

In summary, the ovarian hyperstimulation after the sole administration of GnRH agonist is a rare condition that may recur in following cycles. The true incidence and recurrence rate are difficult to calculate because of the rarity of this condition. The direct ovarian stimulation by the GnRH agonist is the possible mechanism of the occurrence of the OHSS. The optimal management of this condition is still unclear because of the paucity of data.

Conflict of interest We ensure you that we do not have any conflict of interest and this paper is not supported by any organization.

References

1. Lanzone A, Apa R, Fulghesu AM et al (1989) LH surge induction by GnRH-agonist at the time of ovulation. Gynecol Endocrinol 3:213–220
2. Gonen Y, Balakier H, Powell W, Casper RF (1990) Use of gonadotropin-releasing hormone agonist to trigger follicular maturation for in vitro fertilization. J Clin Endocrinol Metab 71:918–922
3. Yeh J, Barbieri RL, Ravnikar VA (1989) Ovarian hyperstimulation associated with the sole use of leuprolide for ovarian suppression. J In Vitro Fertil Embryo Transf 6:261–263
4. Parinaud J, Cohen K, Oustry P, Perineau M, Monrozies X, Reme JM (1992) Influence of ovarian cysts on the results of in vitro fertilization. Fertil Steril 58:1174–1177
5. Droesch K, Barbieri RL (1994) Ovarian hyperstimulation syndrome associated with the use of the gonadotropin-releasing hormone agonist leuprolide acetate. Fertil Steril 62:189–90
6. Weissman A, Barash A, Shapiro H, Casper RF (1998) Ovarian hyperstimulation following the sole administration of agonistic analogues of gonadortophin releasing hormone. Hum Reprod 13:3421–3424
7. Letterie GS (2000) Ovarian hyperstimulation caused by a gonadotropin agonist. Am J Obstet Gynecol 183:747
8. Khalaf Y, Anderson H, Taylor A, Braude P (2000) Two rare events in one patient undergoing assisted conception: empty follicle syndrome and ovarian hyperstimulation with the sole administration of gonadotropin-releasing hormone agonist. Fertil Steril 73:171–172
9. Brett S, Yong PYK, Thong KJ (2001) Ovarian hyperstimulation after the sole use of a gonadotrophin-releasing hormone agonist (Nafarelin) as a complication of in vitro fertilization treatment. J Assist Reprod Genet 18:353–356
10. Qublan HS, Amarin ZO, Tahat YA, Smadi ZS, Kilani M (2006) Ovarian cyst formation following GnRH agonist administration in IVF cycles: incidence and impact. Human Reprod 21:640–644
11. Feldburg D, Ashkenazi J, Dicker D, Yeshaya A, Goldman GA, Goldman JA (1989) Ovarian cyst formation: a complication of gonadotropin-releasing hormone agonist therapy. Fertil Steril 51:42–44
12. Jenkins JM, Davies DW, Anthony F, Wood P, Gadd SG, Waston RH, Masson GM (1992) The detrimental influence of functional ovarian cyst during in-vitro fertilization cycles. Human Reprod 7:776–780
13. Minaretzis D, Jakubowski M, Mortola JF, Pavlou SN (1995) Gonadotropin-releasing hormone receptor gene expression in human ovary and granulose-lutein cells. J Clin Endocrinol Metab 80:430–434
14. Penzias AS, Lee G, Seifer DB, Shamma FN, DeCherney AH, Reindollar RH, Jones EE (1994) Aberrant estradiol flare despite gonadotropin-releasing hormone-agonist induced suppression is associated with impaired implantation. Fertil Steril 61:558–560
15. Andersen CY, Humaidan P, Ejdrup HB, Bungum L, Grondahl ML, Westergaard LG (2006) Hormonal characteristics of follicular fluid from women receiving either GnRH agonist or HCG for ovulation induction. Hum Reprod 21:2126–2130