CEOG Clinical and Experimental Obstetrics & Gynecology

Original Articles

Reproductive Biology Section

Detection of a microgonadotropinoma by magnetic resonance imaging performed because of excellent response to controlled ovarian hyperstimulation despite elevated day 3 FSH

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Summary

Purpose: To determine if a better response than anticipated to controlled ovarian stimulation in a woman assumed to have diminished oocyte reserve based on an increased day 3 serum follicle stimulating hormone (FSH) level, could be related to a gonadotropinoma. *Materials and Methods:* Magnetic resonance imaging (MRI) with and without gadolinium contrast was used in a woman who made 21 mature oocytes despite a history of day 3 serum FSH as high as 20 mIU/mL. *Results:* A pituitary microgonadotropinoma was detected. *Conclusions:* The presence of a better response than anticipated to controlled ovarian hyperstimulation (COH) with exogenous gonadotropins despite an increase in day 3 serum FSH should prompt a search for a possible gonadotropinoma.

Key words: Gonadotropinoma; Controlled ovarian hyperstimulation; Follicle stimulating hormone; Early follicular phase.

Introduction

A pituitary tumor secreting follicle stimulating hormone (FSH) and luteinizing hormone (LH) (referred to as a gonadotropinoma) is uncommon but probably underdetected because they frequently will not cause any abnormal symptoms or signs in contrast to pituitary tumors secreting prolactin or ACTH. Some have been detected because they have caused ovarian hyperstimulation in younger women [1].

Recently, a case was described where the gonadotropin cells were replaced by the tumor cells but the excess FSH and LH secreted was not biologically active leading to a false diagnosis of premature ovarian failure [2]. Interestingly, that tumor converted to a very large macroprolactinoma which replaced the gonadotropin cells and following a hypophysectomy, she was able to induce ovulation and achieve a live baby following treatment with exogenous gonadotropins at the age of 40 [2].

One way to consider the diagnosis of a gonadotropinoma in a pre-menopausal woman would by responding better than expected to exogenous gonadotropins despite an elevated day 3 serum FSH when controlled ovarian hyperstimulation (COH) is used for purposes of in vitro fertilization- embryo transfer (IVF-ET). A case exemplifying this caveat is presented.

Case Report

A 27-year-old woman who was evaluated for infertility at another infertility center was told she had diminished oocyte reserve and possibly poor oocyte quality based on an elevated day 3 serum FSH level. They advised her to proceed with IVF-ET immediately because she could soon be depleted of oocytes.

She failed to conceive after her first fresh and two frozen embryo transfer cycles where two embryos were transferred each time with 11 oocytes (eight metaphase II) retrieved. The second IVF-ET cycle using a micro-flare protocol provided 13 oocytes (11 metaphase II) and she conceived and delivered a live baby girl following the transfer of four embryos.

She sought an opinion with our group because of our experience with treating women with diminished oocyte reserve and because she was hoping to find a non-IVF solution for financial reasons. Her previous highest serum FSH was 20 mIU/mL. The couple had been told that the semen analysis of the male partner was perfectly normal but they had not measured antisperm antibodies. In fact, by direct immunobead testing we found that 70% of the sperm had anti-sperm antibodies attached.

Revised manuscript accepted for publication October 2, 2013

A natural cycle investigation revealed that she made a mature follicle without follicle maturing drugs but had an abnormal post-coital test at that time. Thus, the conclusions were that the presence of the anti-sperm antibodies were immobilizing antibodies and intrauterine insemination (IUI) should be performed despite otherwise normal semen parameters [3]. Because these antibodies could also inhibit the attachment of the sperm to the zona pellucida, the sperm was first pre-treated with chymotrypsin-galactose to render the antibodies less biologically potent prior to IUI [4].

Serial sonographic studies found that she released the oocytes and based on her history of high serum FSH levels, despite forming mature follicles naturally, she was treated with vaginal progesterone in the luteal phase [5-7]. She failed to conceive after three IUI cycles with chymotrypsin-galactose treated sperm.

She wanted to try IVF-ET again. In her controlled ovarian hyperstimulation (COH) IVF cycle her day 2 serum FSH was slightly increased at 12 mIU/mL with a serum estradiol (E2) of 25 pg/mL. Normally, with diminished oocyte reserve we recommend mild ovarian hyperstimulation using no more than 150 IU instead of the 300 IU that we use for women with normal oocyte reserve [8, 9]. However, since her antral follicle count seemed quite adequate, and she previously conceived with a regimen using 600 IU of FSH, it was decided to use a conventional protocol of 225 highly purified FSH and 75 LH and 75 FSH combined. Because of a very good response, the dosage was decreased to 225 IU total FSH, then 112.5, and finally 75 IU of FSH.

The peak serum E2 reached 2,668 pg/mL when human chorionic gonadotropin (hCG) 10,000 units were given. There were 22 oocytes retrieved of which 21 were metaphase II. Sixteen of the 21 mature oocytes fertilized following intracytoplasmic sperm injection (ICSI) and two mildly fragmented embryos of six- and eight-cells were transferred on day 3.

Thirteen embryos were cryopreserved – ten at the 2 pronuclear stage and three multi-cells (four, four, and six blastomeres). Six of the two pronuclear embryos were thawed and she transferred ten, eight-, and six-cell embryos but still failed to conceive. Eight more embryos were thawed and she transferred on day 3 an 8 and two seven-cell embryos but failed to conceive again.

She took a six-month break from the infertility before returning for another infertility consult. She was presented the option to consider returning to IUI with chymotrypsin-galactose treated sperm with luteal phase progesterone support or IVF-ET with some extra procedures, e.g., endometrial biopsy during menses, injection of luteal phase leuprolide acetate to stimulate gonadotropin releasing hormone receptors in the endometrium, or infusing the uterus with 500 units of hCG seven minutes before embryo transfer and finally using lower dosage (150 IU) FSH. However, based on her unexpected good response this time to half the dosage of FSH used in her previous infertility center, she was advised to have magnetic resonance imaging (MRI) of her pituitary to see if she may have an FSH secreting micro or macroprolactinoma.

Magnetic resonance of the brain with high-resolution images through the pituitary showed an isolated oval mass within the pituitary gland which showed no enhancement post-contrast. The measurements were 5.95 by 5.4-mm longitudinal by 10.8-mm transverse. As a result it displaced the pituitary infundibulum dorsally. Thus the MRI of the brain with and without gandolinium detected a pituitary microadenoma. Since her serum cortisol and prolactin levels were normal, the conclusion was that this was an FSH secreting gonadotropinoma.

Discussion

In contrast to the previously mentioned case report of the gonadotropinoma that presented as premature menopause, this case presented as a woman with regular menses but she was falsely considered to have diminished oocyte reserve related to increased early follicular phase serum FSH which was related to direct FSH secretion by a gonadotropinoma rather than lack of negative feedback from inhibin B [2].

One explanation to explain the aforementioned case of pseudo-ovarian failure was that either the entire lot of normal gonadotroph cells were replaced by tumor cells secreting immunoreactive FSH and LH, but biologically inactive, or perhaps significant hyperprolactinoma existed (because the tumor may have been a mixed prolactinoma and gonadotropinoma) and the high serum prolactin suppressed endogenous gonadotropins but not from the tumor [2]. Eventually, the gonadotropinoma cells were replaced by the macroprolactinoma and thus the tumor now only made prolactin and not gonadotropins when she reached her late 30's [2].

The present case shows that a woman with FSH secreting gonadotropinoma can still spontaneously ovulate. A woman who responds far better to COH than expected for someone hypothesized to have diminished oocyte reserve based on day 2-3 serum FSH should be considered to possibly have a gonadotropinoma [2].

This condition of gonadotropinoma is probably underdetected in contrast to ACTH and prolactin secreting tumors which produce symptoms. Diagnosis is based on finding increased serum cortisols or prolactin level or inability to suppress cortisol levels with dexamethasone. Occasionally, a minority of gonadotropinomas will present with ovarian hyperstimulation in the absence of exogenous gonadotropin. Recently, Carteto-Branco *et al.* presented one such case and summarized data from previous cases of ovarian hyperstimulation with FSH and LH secreting tumors [1].

Recently, a case was described of a mixed microprolactinoma and gonadotropinima that presented with high prolactin but normal FSH and LH. However, following the lowering of the prolactin level by cabergoline, this allowed the LH and FSH, which were suppressed by the hyperprolactinoma to now increase and cause mild ovarian hyperstimulation [10].

Whereas most macroprolactinomas do not start out as microprolactinomas, it is not clear what is the likelihood of a microgonadotropinoma growing to a macrogonadotropinoma. Thus, one could recommend transphenoidal microadenectomy or careful vigilance and benign neglect, or careful follow-up with MRI examination. The options were presented to this woman and she chose observation with a repeat MRI in six months.

This case exemplifies the importance of considering a gonadotropinoma in any woman with increased day 3 serum FSH who seems to respond much better than anticipated when stimulated with exogenous gonadotropins.

References

[1] Castelo-Branco C., del Pino M., Valladares E.: "Ovarian hyperstimulation, hyperprolactinaemia and LH gonadotroph adenoma". *Reprod. Biomed. Online*, 2009, *19*, 153.
[2] Check J.H.: "Gonadotropinoma presenting as a case of pseudo-ovarian failure changing to macroprolactinoma". *Clin. Exp. Obstet. Gynecol.*, 2013, *40*, 295.
[3] Check J.H.: "Antisperm antibodies and human reproduction". *Clin. Exp. Obstet. Gynecol.*, 2010, *37*, 169.
[4] Bollendorf A., Check J.H., Katsoff D., Fedele A.: "The use of chymotrypsin-galactose to treat spermatozoa bound with antisperm antibodies prior to intrauterine insemination". *Hum. Reprod.*, 1994, *9*, 484.
[5] Check J.H., Nowroozi K., Wu C.H., Adelson H.G., Lauer C.: "Ovulation-inducing drugs versus progesterone therapy for infertility in patients with luteal phase defects". *Int. J. Fertil.*, 1988, *33*, 252.
[6] Check J.H.: "Progesterone therapy versus follicle maturing drugs - possible opposite effects on embryo implantation". *Clin. Exp. Obstet. Gynecol.*, 2002, *29*, 5.
[7] Check J.H.: "Ovulation defects despite regular menses: Part III". *Clin. Exp. Obstet. Gynecol.*, 2007, *34*, 133.
[8] Check J.H.: "Mild ovarian stimulation". *J. Assist. Reprod. Genet.*, 2007, *24*, 621.
[9] Check J.H., Slovis B.: "Choosing the right stimulation protocol for in vitro fertilization-embryo transfer in poor, normal, and hyper-responders". *Clin. Exp. Obstet. Gynecol.*, 2011, *38*, 313.
[10] Garmes H.M., Grassiotto O.R., Fernandes Y.B., Queiroz Lde S., Vassalo J., de Oliveira D.M., Benetti-Pinto C.L.: "A pituitary adenoma secreting follicle-stimulating hormone with ovarian hyperstimulation: treatment using a gonadotropin-releasing hormone antagonist". *Fertil. Steril.*, 2012, *97*, 231.

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