Reproductive BioMedicine Online (2013) **26**, 378–383

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ARTICLE

Flexible ovarian stimulation in a poor responder: a case report and literature review

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Abstract This article reports on a novel strategy of continuous ovarian stimulation in a poor responder with two oocyte retrievals within the follicular and luteal phases of the same menstrual cycle. It also reviews studies of flexible ovarian stimulation. A patient aged 41 years diagnosed as infertile with low ovarian reserve sought IVF treatment. A minimal ovarian simulation protocol was commenced with use of low-dose urinary FSH (150 IU/day) from day 3, combined with using clomiphene citrate (50–100 mg) when the biggest follicle reached 10 mm in diameter to prevent ovulation. Gonadotrophin-releasing hormone agonist was administered on day 15 when the lead follicles reached 18 mm in diameter. The first ultrasound-guided oocyte retrieval was performed 21 h later; however, no ovum was obtained. Luteal-phase ovarian stimulation was started 2 days later. The second oocyte retrieval was performed 25 h after human chorionic gonadotrophin administration. Finally, one mature oocyte resulting in a cleavage embryo (8-cell, grade 2) was obtained. The case demonstrates that it is feasible to obtain mature oocytes and good embryos from luteal-phase stimulation. Continuous stimulation during the follicular and luteal phase can be a solution for poor ovarian response. Ovarian stimulation may be performed flexibly in special circumstances.

KEYWORDS: follicular phase, follicular waves, luteal phase, oocyte retrieval, ovarian stimulation, poor responder

Introduction

In the last two decades, pregnancy rates for patients undergoing IVF have significantly increased (Bosch and Ezcurra, 2011). One advance responsible for this improvement has been the development of ovarian stimulation. Ovarian hyperstimulation to allow the collection of more follicles was the first approach, then was replaced by ovarian stimulation to reduce the risks and increase the benefits by tailoring the stimulation according to patient characteristics. Presently, individualized ovarian stimulation is proposed and a variety of ovarian stimulation protocols have been developed with varying success. However, due to the heterogeneity of patients undergoing IVF treatment and variety

1472-6483/$ - see front matter
http://dx.doi.org/10.1016/j.rbmo.2012.11.020

of ovarian stimulation protocols, there is no single best approach for all patients (Bosch and Ezcurra, 2011).

Owing to progress and acceptance of IVF, improvements in civil life and adjustments to national child policy, more infertile people are turning to IVF, including poor ovarian responders. There is no uniform definition of poor ovarian response; the Bologna criteria may be a vital step toward adoption, although its applicability needs to be tested through clinical trials (Ferraretti et al., 2011). Many studies have evaluated the use of various ovarian stimulation regimens to improve the outcome of poor responders undergoing IVF treatment. Considering clinical outcomes, emotional stress and costs to patients with poor ovarian reserve, the choice of a minimal stimulation protocol instead of a classic high-dose regimen could be indicated (Revelli et al., 2011). However, patients with poor prognosis have higher cancellation rates, along with lower pregnancy and live birth rates, compared with good-prognosis women. These relatively high cancellation rates is leading clinicians to seek a more efficient strategy (Lamazou et al., 2012).

Recent evidence indicates that there are multiple follicle recruitment waves during a normal menstrual cycle; hence, there are more opportunities to utilize ovarian stimulation (Baerwald et al., 2003a, b). An ongoing pregnancy from two waves of follicles developing during a long follicular phase of the same cycle supports the observations of multiple follicular waves (Bentov et al. 2010). Several researchers have reported that even random-start ovarian stimulation protocols can be performed when there is insufficient time for conventional follicular-phase oocyte retrieval, as in patients with malignant tumours who cannot postpone chemotherapy (Bedoschi et al., 2010; Demirtas et al., 2008; Maman et al., 2011; Nayak and Wakim (2011); Sönmezer et al., 2011; Von Wolff et al., 2009). However, at present, there is, as far as is known, no report on the clinical application in poor responders of multiple follicular waves theory.

Here is reported the case of a patient diagnosed with poor ovarian response. A mature oocyte leading to a good embryo was successfully obtained through luteal-phase ovarian stimulation following failure to retrieve an oocyte by minimal ovarian stimulation in the follicular phase during the same menstrual cycle. In assisted reproductive treatment, satisfactory oocytes or embryos sometimes cannot be obtained as a result of empty follicle syndrome, failure of fertilization in follicular-phase stimulation and poor ovarian response. In these special circumstances, there is often no choice but to restart the next cycle. From the lessons learned by the present case, the multiple follicular waves theory could be utilized to solve these clinical problems. Therefore, this article also reviews the literature and proposes that ovarian stimulation may be performed flexibly in special circumstances.

Case report

Patient history

A 41-year-old woman with a 2-year history of secondary infertility (G3P1A2, spontaneous labour 2 years previously) was seen at the Reproductive Medicine Centre at Xiangya Hospital. Written consent was obtained from the patient for anonymized data only to be used for the purposes of scientific discussion and publication. Examination of her hysterosalpingography showed the right Fallopian tube was obstructed and the left partly unobstructed. Twenty-four hours later, limited contrast medium was diffused into her pelvic cavity. She had regular menstrual cycles. Her partner's semen analysis showed asthenospermia on two occasions. The couple insisted on IVF treatment even though they were advised against it due to low ovarian reserve, i.e. one antral follicle in each ovary was seen at basal vaginal ultrasound scan in September 2011. In addition, there was probably a luteal cyst in the left ovary. Basal hormone status was 24.33 IU/l FSH, 8.63 IU/l LH and 18.03 pg/ml oestradiol on day 2 of the next menstrual phase. Disappointingly, the ultrasound scan showed just one antral follicle in the left ovary on day 3.

The patient was placed on oral desogestrel and ethinylestradiol tablets (Marvelon; Organon, The Netherlands) one pill daily for one cycle. The previously described cyst disappeared. The day-2 hormone concentrations reduced to 14.52 IU/l FSH, 7.40 IU/l LH and 12.86 pg/ml oestradiol. However, one antral follicle in each ovary was seen at basal scan on day 3 of the following cycle, but it was too small to be resolved completely because of two echo-free areas merely 3—4 mm in diameter with a hyper-echo borderline.

Minimal ovarian simulation protocol within the follicular phase

The IVF cycle was started using the minimal ovarian simulation protocol with FSH (Urofollitropin; Livzon Pharmaceutical, China) 150 IU/day from day 3 to day 15. Vaginal ultrasound was performed every 2—3 days from day 3 to day 13, and daily together with blood hormone or urine LH monitoring from day 13 to day 15. Clomiphene citrate (Fertilan; Codal Synto, Cyprus) was administered at 50 mg from day 8 to day 12, then at 100 mg from day 13 when blood LH was 20.04 mIU/ml and follicles reached 15 mm in diameter until day 16. To inhibit the synthesis of prostaglandin oestradiol to prevent ovulation, ibuprofen (Fenbid; SK and F, Tianjing, China), a prostaglandin synthetic inhibitor, was taken 300 mg every 6 h daily from day 14 to day 16.

After 12 days of daily medication, ultrasound monitoring revealed two follicles (14×18 mm and 17×20 mm) in the right ovary and two follicles (8×9 mm and 4×6 mm) in the left ovary. Blood hormone concentrations were 708.00 pg/ml oestradiol, 23.61 IU/l LH and 0.995 ng/ml progesterone. Gonadotrophin-releasing hormone (GnRH) agonist (0.2 mg triptorelin; Ferring) was administered subcutaneously on day 15 at 12.00 hours. Ultrasound-guided aspiration of both follicles in the right ovary was performed with a double-lumen ovum aspiration needle by the transvaginal route at 09.00 hours on day 16. Oocyte retrieval was performed the next morning (about 21 h after GnRH agonist) to avoid ovulation, based on previous experience of poor responder patients. However, no oocyte was retrieved.

At this moment, although the patient was depressed and wanted to drop out, she was persuaded to try luteal ovarian stimulation because two small follicles (8×9 mm and 4×6 mm) remained in the left ovary.