RBM ONLINE

ELSEVIER

Article

A retrospective analysis of ovarian stimulation with letrozole in women undergoing artificial insemination by donor

XJ Sun [a], L Jiang [a], LC Ji [a], R Nie [a], H Chen [b], L Jin [a], GJ Zhu [a], K Qian [a,]*

[a] *Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, Wuhan, China*

[b] *Department of Rehabilitation Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*

Dr Qian is Associate Professor of Obstetrics and Gynaecology at the Huazhong University of Science and Technology, China. He has been a clinician and researcher at the Assisted Reproductive Technologies Centre since 2005. His research interests include assisted reproductive technologies, endometrium receptivity and stem cell.

KEY MESSAGE

Adding gonadotrophins to letrozole improves the clinical outcome of artificial insemination by donor.

A B S T R A C T

The aim of this retrospective study was to determine the clinical pregnancy rate in women undergoing letrozole ovarian stimulation and artificial insemination by donor (AID). Between 2012 and 2015, 130 natural cycles, 939 letrozole cycles and 130 letrozole plus gonadotrophin cycles were conducted. Letrozole cycles were divided into three groups according to LH concentration on the day of HCG administration (LH <10 mIU/ml and follicle size ≥18 cm; LH ≤10 to <20 mIU/ml; and LH ≥20 mIU/ml). Pregnancy rates were 17.3%, 22.4% and 26.8%, respectively ($P = 0.012$). In women given 10 mIU/ml LH or more, logistic regression identified oestradiol (OR 1.002, 95% CI, 1.000 to 1.004, $P = 0.029$) and leading follicle size (OR 0.861, 95% CI, 0.772 to 0.960, $P = 0.007$) as significant predictive factors of pregnancy rate; the higher the oestradiol and the smaller the follicles, the better the pregnancy rate. The pregnancy rate was significantly higher in the letrozole plus gonadotrophin group than the letrozole group ($P = 0.04$). Better pregnancy rates can be achieved if LH surge occurs before HCG administration, especially with higher oestradiol and lower follicle size; treatment with letrozole plus gonadotrophin was significantly more effective than letrozole alone in AID.

* Corresponding author.
E-mail address: qiankun1129@sina.com (K. Qian).

http://dx.doi.org/10.1016/j.rbmo.2017.01.008

Please cite this article in press as: X.J. Sun, L. Jiang, L.C. Ji, R. Nie, H. Chen, L. Jin, G.J. Zhu, K. Qian, A retrospective analysis of ovarian stimulation with letrozole in women undergoing artificial insemination by donor, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.01.008

Introduction

Letrozole, a highly selective aromatase inhibitor, inhibits the aromatization of androgens into oestrogens, which releases the hypothalamic–pituitary axis from the negative oestrogenic feedback, leading to increased follicular growth (Mitwally and Casper, 2001). Transient inhibition of aromatase with letrozole results in ovulation induction with no apparent adverse effect on endometrial thickness or pattern at mid-cycle compared with clomiphene citrate (Fisher et al., 2002). The disadvantages of clomiphene citrate include detrimental effect on cervical mucus, endometrial thickness and overall pregnancy outcome (Fisher et al., 2002; Fujii et al., 1997). Several clinical studies have suggested that letrozole could be used as an alternative to clomiphene citrate in ovulation induction (Al-Omari et al., 2004; Fisher et al., 2002; Mitwally and Casper, 2001).

The administration of HCG at mid-cycle, mimicking the endogenous LH peak, determines final follicular maturation. Premature HCG trigger may result in follicular atresia, and delayed HCG trigger can occur after ovulation has already taken place (O'Herlihy et al., 1982). The timing of triggering of ovulation is critical. Many techniques are used to detect ovulation, including ultrasound, measurement of LH in the plasma and urine to detect the LH surge, and serum oestradiol level in the late follicular phase (Odem et al., 1991; Palatnik et al., 2012; Vermesh et al., 1987). Even though a wide variation exists in the level of LH at its peak, the LH surge is a reliable indicator of timing of ovulation (Garcia et al., 1981).

The use of gonadotrophin may have a beneficial effect on the endometrium, embryo development and pregnancy rates (Barroso et al., 2006; Goswami et al., 2004; Healey et al., 2003). A recent randomized trial by Diamond *et al.* (2015) showed that ovarian stimulation with gonadotrophin results in a significantly higher pregnancy rate but with higher frequency of multiple gestation compared with letrozole. It has recently been suggested that letrozole plus FSH achieved a higher pregnancy rate than letrozole alone in intrauterine insemination (IUI) (Wang and Zheng, 2015).

The aim of this retrospective study was to evaluate the clinical pregnancy rate of letrozole for ovarian stimulation and to compare the effect between letrozole and letrozle plus gonadotrophin protocol in women undergoing artificial insemination by donor (AID).

Materials and methods

Study population

Our retrospective analysis included patients attending an academic reproductive medicine centre between December 2012 and December 2015. This study was approved by the Institutional Review Board at Huazhong University of Science and Technology, Wuhan City, China, on 26 March 2015 (Institutional Review Board reference number TJ-C20150313).

Indications for AID were mostly non-obstructive azoospermia and a few cases of obstructive azoospermia and severe oligo-asthenoterato-zoospemia. A careful history was taken of all participants, along with a general and gynaecologic examination. The inclusion criterion from this study were as follows: women with normal uterine cavity and at least one tubal patency confirmed by hysterosalpingography or laparoscopy; women with baseline FSH 10 mIU/ml or less or aged 38 years or younger; women with body mass index (BMI) of 16 kg/m^2 or less or 28 kg/m^2 or more; women who had an endometrial lining 6 mm or over on HCG day; oestradiol on HCG day 100 pg/ml or over; normal prolactin and thyroid stimulation hormone levels; and natural cycles and ovarian stimulation with letrozole alone or letrozole combined with gonadotrophin.

Study procedures

Artificial insemination by donor took place in cycles using letrozole for ovarian stimulation (the first-line treatment used in this centre) or with clomiphene citrate or gonadotrophin. Insemination also took place in the natural cycles. On the basis of the above criteria, this study included 130 natural cycles with serum LH 30 mIU/ml or more on HCG day (93 patients), 939 letrozole cycles (556 patients) and 130 letrozole and gonadotrophin cycles (90 patients). The 130 natural cycles and the 130 cycles with serum LH 30 mIU/ml or more on HCG day in the letrozole group were matched for age baseline FSH and LH.

Most women undergoing AID were physically normal, and some patients with polycystic ovary syndrome (n = 42), anovulation (n = 10), endometriosis (n = 13) and diminished ovarian reserve (n = 4) were also included in this study. Letrozole (Jiangsu Hengrui Medicine Co., Ltd.; Lianyungang, China) was given in a dose of 2.5–5 mg per day for 5 days starting on days 3 or 5 of the menstrual cycle. All patients gave informed consent to using letrozole as an off-label medication for ovulation induction. Gonadotrophin injections were given in the form of HMG (Menotrophin for Injection, Livzon Pharmaceutical Group Inc., Guangzhou, China) or uFSH (Urofollitropin for Injection, purified, Livzon Pharmaceutical Group Inc., Guangzhou, China) after day 9 of the menstrual cycle every 2 days. The starting dose was 75 IU. The dose and duration were adjusted according to follicle response. The adjustment was flexible. In general, gonadotrophin was given after taking letrozole if the follicle size was less than 8 cm. Monitoring in every cycle included day 3–5 baseline serum LH and FSH levels. From cycle day 10 onward, ovarian ovulation was monitored regularly with a transvaginal ultrasound to determine leading diameter of growing follicles. This was recorded along with endometrial thickness, serum LH and oestradiol. The blood samples were drawn between 08:00 and 09:00.

If the LH was less than 10 mIU/ml with follicle diameters 18 mm or over, or the LH was 10 mIU/ml or over, HCG 4000 IU (HCH for Injection, Livzon Pharmaceutical Group Inc., Guangzhou, China) was given to induce ovulation. To minimize the adverse effects of ovarian stimulation, HCG was withheld if more than three follicles with a mean diameter of 15 mm or wider were detected, or more than five follicles with a mean diameter wider than 10 mm were detected. Double IUI per cycle was carried out 24–36 h later after HCG administration, using cryopreserved semen by donors. The selection criteria for donors were as follows: age 22–45 years; anonymous volunteers and presenting in a healthy state (free from hepatitis B virus, hepatitis C virus, human immunodeficiency virus, syphilis, gonorrhoea, mycoplasma, chlamydia and transmissible genetic disorders); and good sperm quality with minimum concentration of 60×10^6 per ml, progressive motility of 60% and normal morphology of 30%. Luteal support was given as 40 mg dydrogesterone tablets per day (Duphaston, Abbott Biologicals B.V., Netherlands) for 2 weeks after AID.

Patients were instructed to obtain a quantitative serum HCG measurement 2 weeks after the insemination if they did not menstruate. If the result was positive, patients were scheduled for a transvaginal ultrasound at about 4–5 weeks after the insemination to confirm pregnancy location and cardiac activity.

Please cite this article in press as: X.J. Sun, L. Jiang, L.C. Ji, R. Nie, H. Chen, L. Jin, G.J. Zhu, K. Qian, A retrospective analysis of ovarian stimulation with letrozole in women undergoing artificial insemination by donor, Reproductive BioMedicine Online (2017), doi: 10.1016/j.rbmo.2017.01.008