

Which is the Best Protocol of Ovarian Stimulation Prior to Artificial Insemination by Donor

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Objective To compare the different ovarian stimulation protocols, clomiphene citrate (CC), letrozole, human menopausal gonadotropin (hMG) only or combined with CC or letrozole in women undergoing artificial insemination by donor (AID).

Methods In this prospective clinical trial, 671 couples prepared for AID cycles were randomly allocated to 6 groups according to receive different protocols for the first time, natural cycle (group A, n=114), CC (group B, n=101), CC and hMG (group C, n=124), letrozole (group D, n=97), letrozole and hMG (group E, n=123) and hMG only (group F, n=112). Outcomes including total dose of hMG, duration of hMG therapy, dominant follicles number, endometrial thickness, rates of clinical pregnancy, miscarriage, ovarian hyperstimulation syndrome (OHSS), multiple pregnancy and cancelation were compared among the 6 groups.

Results The total doses and duration of administered hMG were significantly lower in group C and group E than in group F. Dominant follicle number was significantly less in group A and more in group C than in other groups. Endometrial thickness of group B was significantly lower than that of other groups. Clinical pregnancy rate, multiple pregnancy rate, miscarriage rate, OHSS rate and cancelation rate were not statistically different among the stimulation groups.

Conclusion AID cycles in which both CC and letrozole had been administered may require shorter duration and a lower total gonadotropin dose, while the clinical outcomes were similar.

Key words: intrauterine insemination; clomiphene citrate (CC); letrozole; human menopausal gonadotropin (hMG)

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Intrauterine insemination (IUI) can be accomplished in a natural cycle or with ovarian stimulation. There has been little controversy that ovarian stimulation protocol can improve pregnancy rate in IUI compared with natural cycle^[1], but till now there is no consensus about which protocol is the first choice for inducing ovulation. In the clinic, clomiphene citrate (CC), letrozole (both can combined with gonadotrophin) and gonadotrophin only are used for ovarian stimulation. Gonadotrophin accomplished alone may increase multiple pregnancy rate and ovarian hyperstimulation syndrome (OHSS) rate^[2,3]. So, taking account of cost, comfort and security, CC and letrozole are widely used for ovulation inducing before IUI, which can increase endogenous follicle stimulating hormone (FSH) by inducing estrogen receptors depletion or suppress the production of estrogen. But the benefit of CC and letrozole used before hMG was debated, in the study of Mahani et al.^[4], hMG group had a higher pregnancy rate compared with CC group. But the conclusion of Ibrahim et al.^[5] was just the opposite: the pregnancy rate of CC group was higher than that of hMG group.

For more than four decades, CC is a popular choice for inducing ovulation because of effective and cheap. However it induces estrogen receptor depletion and has anti-estrogenic effect on endometrium, which may be the reason of low pregnancy rate. As an aromatase inhibitor, letrozole has no adverse effect on endometrium. It was reported that letrozole was superior to CC for inducing ovulation in IUI in some studies^[6,7], but others got the opposite results^[8-10]. Artificial insemination by donor (AID) is proposed for couples when infertility is established to be due to severe male factors, AID is the special case of IUI which can avoid some male infertility factors. The purpose of our study was to compare the efficacy of different ovary stimulation protocols in women undergoing AID.

Materials & Methods

Patients and groups

This randomized clinical trial was approved by the Ethics Committee of Ruijin Hospital, Medical School of Shanghai Jiao Tong University. Recruitment was conducted in Reproductive Center of Ruijin Hospital from September 2009 to June 2012. All couples had been unable to conceive for at least 1 year before coming to our IVF center for treatment. The reasons for AID were azoospermia or chromosome abnormality on the male's side. In our study, all females were assessed by hysterosalpingography (HSG) before IUI treatment and had at least one patent tube. Couples were excluded if there were a history of previous assisted reproduction attempts by IUI, IVF or ICSI, women with endometriosis (classification stage III and IV of the American Infertility Society), myoma, endometrial polyps or polycystic ovary syndrome (PCOS)^[11], or contraindication to one of the investigated drugs, persistent ovarian cyst (a cyst of at least 30 mm persisting for longer than 2 months) were excluded. Women with normal ovulation was monitored in nature cycle (group A, $n=114$), women with

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