Comparison of the ongoing pregnancy rate of first frozen-thawed embryo transfer cycles in women undergoing IVF using progestin primed ovarian stimulation versus GnRH antagonist protocol

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Abstract

Objective To compare the pregnancy outcomes of first frozen-thawed embryo transfer in women undergoing IVF using progestin primed ovarian stimulation (PPOS) versus GnRH antagonist protocol. Design Retrospective cohort study. Setting Tertiary-care academic medical center. Population/Sample 382 infertile women with normal ovarian reserve underwent IVF. Methods Women were allocated to PPOS group (n=184) or GnRH antagonist group (n=198) at the discretion of the attending physicians. Main outcome measures The primary outcome was the ongoing pregnancy rate of first FET cycles. Results Both groups had almost comparable demographic and cycle stimulation characteristics. The ongoing pregnancy (34.0 % (49/114) vs 42.3% (52/123), P=0.166, RR=0.81(0.59-1.09)), clinical pregnancy (38.2% (55/144) vs 44.7% (55/123), P=0.281, RR=0.85 (0.64-1.14)) and implantation (29.5% (75/254) vs 31.6% (68/215), P=0.623, RR=0.93 (0.71-1.22)) rates were comparable between the PPOS group and the antagonist group respectively. In order to control the difference in demographic and index stimulated IVF cycle characteristics, a multivariate logistic regression revealed that only the stimulation protocol and number of embryos replaced were significant factors in predicting the ongoing pregnancy. Conclusion The use of medroxyprogesterone during ovarian stimulation is effective in blocking the LH surge, and does not affect the number of oocytes collected in the woman with normal ovarian reserve. However,developmental potential of embryos originating from this regimen seems to be affected compared to those from the antagonist group.

ORIGINAL ARTICLE

Comparison of the ongoing pregnancy rate of first frozen-thawed embryo transfer cycles in women undergoing IVF using progestin primed ovarian stimulation versus GnRH antagonist protocol

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Objective

To compare the pregnancy outcomes of first frozen-thawed embryo transfer in women undergoing IVF using progestin primed ovarian stimulation (PPOS) versus GnRH antagonist protocol.

Design

Retrospective cohort study.

Setting

Tertiary-care academic medical center.

Population/Sample

382 infertile women with normal ovarian reserve underwent IVF.

Methods

Women were allocated to PPOS group (n=184) or GnRH antagonist group (n=198) at the discretion of the attending physicians.

Main outcome measures

The primary outcome was the ongoing pregnancy rate of first FET cycles.

Results

Both groups had almost comparable demographic and cycle stimulation characteristics. The ongoing pregnancy (34.0 % (49/114) vs 42.3% (52/123), P=0.166, RR=0.81(0.59-1.09)), clinical pregnancy (38.2% (55/144) vs 44.7% (55/123), P=0.281, RR=0.85 (0.64-1.14)) and implantation (29.5% (75/254) vs 31.6% (68/215), P=0.623, RR=0.93 (0.71-1.22)) rates were comparable between the PPOS group and the antagonist group respectively. In order to control the difference in demographic and index stimulated IVF cycle characteristics, a multivariate logistic regression revealed that only the stimulation protocol and number of embryos replaced were significant factors in predicting the ongoing pregnancy.

Conclusion

The use of medroxyprogesterone during ovarian stimulation is effective in blocking the LH surge, and does not affect the number of oocytes collected in the woman with normal ovarian reserve. However,developmental potential of embryos originating from this regimen seems to be affected compared to those from the antagonist group.

Tweetable abstract

A retrospect study showed comparable ongoing pregnancy in the group of using progestin primed ovarian stimulation (PPOS) versus GnRH antagonist protocol in their first FET cycles. However, a multivariate logistic regression indicated a higher ongoing pregnancy rate with the antagonist protocol.

Keywords:PPOS, GnRH antagonist, IVF, frozen-thawed embryo transfer, ongoing pregnancy

Introduction

Ovarian stimulation is a crucial step in assisted reproduction and the aim is to produce multiple follicles with the use of gonadotropins. The rapid rise of oestrogen can induce a positive feedback that gives rise to LH surge[1]. However, premature LH surge can cause early ovulation and affect oocyte quality and embryo development resulting in a low pregnancy rate. Therefore, how to inhibit the early onset LH surge becomes

the core issue in the process of ovulation stimulation[2,3]. Efforts to minimize the occurrence of a premature LH surge have mainly relied on the use of GnRH agonist (GnRHa) and antagonist [3]. Down-regulation of GnRHa promotes follicle synchronization, with the consequences being increased procedure complexity, higher cost, and greater risk of ovarian hyperstimulation syndrome (OHSS)[4,5]. GnRH antagonists produce rapid LH suppression with no initial flare effect [6]. A Cochrane meta-analysis showed similar pregnancy outcomes in both protocols (Al-Inany, et al. 2011). Moreover, the use of the GnRH agonist trigger in the antagonist regimen can reduce the incidence of OHSS [7, 8]. Up to now, GnRH antagonist protocol has become the most popular regimen in the great majority of assisted reproduction centers worldwide.

In 2015, progestin-primed ovarian stimulation (PPOS) was proposed[9]. In this new protocol, progestin is used as an alternative to GnRH analog or antagonist to suppress a premature LH surge during the follicular phase. Moreover, progestin has the advantage of being administered orally and is more patient friendly. Furthermore, to avoid a low response of the hypothalamic pituitary ovarian (HPO) axis, a double trigger with GnRHa and a low dose of hCG (1000 IU) was used to induce final oocyte maturation without increasing the risk of moderate or severe OHSS[10]. This new regimen of ovarian stimulation has been proven to effectively prevent a premature LH surge and does not compromise oocyte competence in cycles followed by embryo cryopreservation[9, 11]

However, in most trials, the efficacy and reproductive outcomes of PPOS regimen were compared to short GnRH agonist protocol, which is now rarely used in many assisted reproduction programs. One randomized trial[12] compared use of medroxyprogesterone versus a GnRH antagonist on the number of mature oocytes retrieved in oocyte donation cycles. Though no differences were found in the number of mature oocytes between the two groups, the clinical pregnancy rate was 31% versus 46% (P = 0.006) and the ongoing pregnancy rate 27% versus 40% (P = 0.015) for medroxyprogesterone and GnRH antagonists, respectively. This suggests a possible impairment of oocyte quality when medroxyprogesterone is used in ovarian stimulation. However, the oocyte recipients were not randomized. There is scarcity of information comparing the pregnancy outcomes between PPOS and antagonist protocol.

The aim of this retrospective study is to compare the efficacy of PPOS regimen and GnRH antagonist protocol in terms of pregnancy outcomes in first frozen embryo transfer (FET) cycles.

Methods

Study design and participants

A retrospective study of infertile women with normal ovarian reserve attending the Assisted Reproduction clinic, Shanghai First Maternity and Infant Hospital for IVF from January 2018 to December 2018 was undertaken. Ethical approval was not required for the retrospective analysis.

Women were included if they fulfilled the following inclusion criteria: (i) less than 40 years of age; (ii) having indications for IVF; (iii) regular menstrual cycles over the previous 3-month period (25–35 days in duration); (iv) antral follicle count (AFC) of more than 5 on menstrual cycle day 2–3, and basal serum FSH concentration of no more than 10 IU/L. Women were excluded if they had: (i) diagnosis of polycystic ovarian syndrome, (ii) an abnormal uterine cavity shown on hysterosalpingogram or hysteroscopy, (iii) moderate or severe endometriosis, (iv) use of donor eggs/sperm, (v) preimplantation genetic testing for aneuploidy, (vi) rescue intracytoplasmic sperm injection (ICSI) or half ICSI or (vii) antagonist cycles with fresh embryo transfer.

Women were offered either progestin-primed ovarian stimulation protocol (PPOS group) or antagonist protocol (antagonist group) at the discretion of the attending physicians or subject to the wishes of the couple.

Ovarian stimulation

Women started their IVF with ovarian stimulation using either PPOS or antagonist protocols. For the PPOS protocol, on Day 2-3 of the menstrual cycle, human menopausal gonadotrophin (hMG) (Lebaode, Lizhu, China) or recombinant FSH (Puregon, Organon, Dublin, Ireland or Gonal F, Merck Serono S.p.A,

Modugno, Italy) was given at 150–225 IU per day based on the AFC count, age of women and previous ovarian response, according to the standard operating procedures of the centre. Medroxyprogesterone MPA (MPA, 10 mg/d, Shanghai Xinyi Pharmaceutical Co., China) was also given on the same day afterwards. Ovarian response was monitored by serial transvaginal scanning with or without hormonal monitoring. Further dosage adjustments were based on the ovarian response at the discretion of the clinicians in charge. For the antagonist protocol, antagonist 0.25mg daily (Orgalutran, Organon, Dublin, Ireland) was given from the 6th day of ovarian stimulation until the day of ovulation trigger.

When three leading follicles reached [?]18 mm in diameter, triptorelin (0.1 mg; Decapeptyl, Ferring Pharmaceuticals, Netherlands) and hCG (2000 IU; Lizhu Pharmaceutical Trading Co., China) or Ovidrel 250 microgram (Merck Serono S.p.A., Modugno, Italy) were given to trigger final maturation of oocytes. Oocyte retrieval was performed around 36 hours later.

Fertilization and embryo evaluation

Semen samples were prepared by the swim-up procedure. About 2 hours after oocyte retrieval, each oocyte was inseminated with approximately 20,000–30,000 motile spermatozoa. If total number of motile sperm was $<10^5$ after washing or normal morphology was <4%, intracytoplasmic sperm injection (ICSI) was performed. Oocytes were decoronated and checked for the presence of two pronuclei to confirm fertilization. Embryos were graded on day 3 after retrieval as grade one to grade six according to the evenness of each blastomere and the percentage of fragmentation[13]. Embryos of 6-8 cells and of grade one or two were regarded as top quality embryos. Some non-top-quality embryos were placed in extended culture until they reached the blastocyst stage.

Cryopreservation and frozen-thawed embryo transfer (FET)

All the day 3 top quality embryos and good-morphology Day 5 or 6 blastocysts were cryopreserved using a vitrification protocol. Women in both groups would undergo frozen–thawed embryo transfer (FET) at least 2 months after the stimulated cycle if they had at least one frozen embryo. FETs were carried out in natural cycles for ovulatory women and in clomiphene induced or hormone replacement cycles for anovulatory women. Vitrification was performed with MediCult Vitrifification Cooling (Origio, Denmark) using ethylene glycol, propylene glycol, sucrose as cryoprotectant. Embryos were vitrified one by one at room temperature. For the warming procedure following vitrification, the straw was cut and the capillary was pulled from the straw out of the liquid nitrogen, and immediately warmed one by one using MediCult Vitrification Warming (Origio, Denmark). After warming, embryos were transferred to a culture dish for evaluation and further embryo development. Only embryos with more than 50% of blastomeres present after thawing were transferred in FET cycles. Up to two embryos or blastocysts were transferred in each FET cycle.

Luteal phase support was given by vaginal or intramuscular progesterone at the discretion of the attending physicians. A urine pregnancy test was carried out 2 weeks after the transfer. Those with a positive urine pregnancy test were scanned after 2 weeks to identify the number and presence of a gestation sac with a fetal pole. All pregnant women were contacted or traced for the pregnancy outcomes after delivery or miscarriage.

Outcomes

Only the pregnancy outcomes from the first FET cycle were recorded in this study, and were followed up until June 2019. The primary outcome was the ongoing pregnancy rate and the secondary outcomes included incidence of premature LH surge (LH [?]10 IU/l), clinical pregnancy, miscarriage, multiple pregnancy, ectopic pregnancy and implantation rates. Clinical pregnancy was defined as the presence of at least one gestational sac on ultrasound at 6 weeks. Ongoing pregnancy was the presence of at least one fetus with fetal pulsation on ultrasound beyond 10 weeks. Fertilization rate was the percentage of zygotes with two visible pronuclei among inseminated (IVF) or matured (ICSI) oocytes. Miscarriage rate was defined as the number of miscarriages before 20 weeks divided by the number of women with positive pregnancy test. Multiple pregnancy was defined as a pregnancy with more than one gestational sac detected on ultrasound at 6 weeks. The implantation rate was calculated as the number of gestational sacs seen on scanning divided by the number

of embryos replaced.

Statistical analyses

One sample of the Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. Continuous variables were given as mean ± SD if normally distributed, and as median (interquartile range) if not normally distributed. Statistical comparison was carried out by Student's t-test, Mann–Whitney U-test for continuous variables and chi-square test for categorical variables, where appropriate. And logistic regression analysis was used to analyse factors predicting the ongoing pregnancy rate. Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS Inc., Version 24.0, Chicago, USA). The two-tailed value of $P<0.05$ was considered statistically significant.

Results

Out of 382 women who met the selection criteria, 184 women used the PPOS protocol and 198 women used the antagonist protocol. One woman in the PPOS group and one woman in the antagonist group had premature ovulation. Oocytes were not obtained in two women in the antagonist group. No transferrable embryos were available in 13 women in the PPOS group and 25 women in the antagonist group. During the study period, 26 women in the PPOS group and 47 women in the antagonist group did not undergo FET. Therefore, 144 women in the PPOS group and 123 women in the antagonist group completed their first FET and were included for analysis (Figure1).

Demographic and index stimulated IVF cycle characteristics

No significant differences were found between the two groups with regard to age of women, basal AFC, basal FSH level, number of first IVF cycles, duration of infertility, body mass index, cause of infertility, proportion of primary infertility and proportion of ICSI (Table 1).

The starting dose, total hMG/FSH dose and serum estradiol/LH levels on the day of hCG in the PPOS groups was higher than that in the antagonist group. There was no difference in duration of stimulation between the two groups. Two women in the PPOS groups experienced premature LH surge while none was seen in the antagonist group. No patient experienced moderate or severe OHSS during the study. (Table 1)

No differences were found in number of oocytes obtained, the fertilization rate, cleavage rate, blastocyst formation rate, number of good quality embryos and number of embryos frozen between the two groups. (Table 1)

Pregnancy Outcomes in FET Cycles

During the study, 144 women in the PPOS group and 123 women in the antagonist group complete their first FET. Method of endometrial preparation was different between the two groups. A higher proportion of women used mild stimulation in the PPOS group, while more patients underwent natural cycles in the antagonist group. The number of top quality of embryos after thawing, number of embryos transferred, and endometrial thickness were similar between two groups (Table 2).

Both groups showed comparable ongoing pregnancy, clinical pregnancy, implantation rates, miscarriage, multiple pregnancy and ectopic pregnancy rates. A multivariate logistic regression using the enter method by the women's age, duration of infertility, stimulation protocol (PPOS / antagonist), insemination method, antral follicle count, basal FSH level, FSH/HMG dosage / duration, serum estradiol levels on the day of hCG, number of oocytes obtained, endometrial thickness, methods of endometrial preparation, number of (top quality) embryos replaced revealed that only the stimulation protocol (OR=2.277, 95% CI: 1.009-5.138) and number of embryos replaced (OR=3.245, 95% CI: 1.259-8.366) predicted the ongoing pregnancy rate of IVF (Table 3). The result of multivariate analysis showed the pregnancy outcome in the antagonist group was favored.

Discussion

Main findings

In the present study, we found that the ongoing pregnancy rate was similar in the PPOS group and the antagonist group. In order to control for the differences in the demographic and index stimulation cycle characteristics, a multivariate logistic regression was performed and indicated the stimulation protocol was one of the factors predicting the ongoing pregnancy rate of IVF. Our results were in agreement with that of a previous study [12]which showed lower pregnancy rates in recipients of oocytes from the MPA group compared to that from the antagonist group.

Interpretation

The results of the study suggest that the PPOS regimen is probably not as good as the antagonist protocol in term of the pregnancy outcomes of FET and indicated that the embryos originating from the PPOS protocol may have a reduced development potential to those from the antagonist group. While most researches indicate that elevated progesterone levels on trigger day do not have a negative impact on the FET results of stimulated cycles using PPOS[9, 11, 14], there are some reports of a negative effect of elevated progesterone on oocyte quality [15, 16] and cumulative live birth rate per retrieval cycle [17]. The reasons for this possible impairment are still unknown. Studies in animal experiments showed that oocyte competence was regulated by progesterone-responsive genes[18,19]. Differences in the expression of OCT-4 and MATER in bovine oocytes with diverse progesterone concentration was found by Urrego et al. (2015) and indicated that lower progesterone concentration could increase bovine oocyte developmental competence in vitro by up-regulating MATER and OCT-4 gene expression[20].

Progesterone is a steroid hormone and is responsible for preparing the endometrium for uterine implantation of the fertilized egg. On the other hand, progesterone is known to have an inhibitory effect on ovulation by blocking the LH surge[21,22]. Its inhibitory effect on ovulation has been at the base of the design of progestin-only contraceptives, which suppress follicular growth and thus inhibit ovulation after a sustained administration. Progesterone priming seems to slow the LH pulse frequency, augments the pulse amplitude and reduces the mean plasma LH concentrations compared with those in untreated women in some studies[23,24] .

No significant difference was found in the incidence of premature LH surge and premature ovulation in the PPOS group compared with the antagonist group, but LH level on HCG day were significantly lower in the antagonist group indicated progesterone can be used as an alternative to GnRH antagonist for suppressing premature LH surges during ovarian stimulation in IVF cycles, but the effect is weaker compared with the antagonist. However, we also found that the PPOS protocol may lead to stronger pituitary suppression and thus may require a higher dosage of gonadotrophin than that of the conventional ovarian stimulation protocol [9]. No patient experienced moderate or severe OHSS in both group during the study,owning to both protocols is applicable for the use of a GnRHa for ovulation trigger or co-trigger by GnRHa and a low dose of hCG and freezeing all embryos.

In PPOS, freezing of all embryos and FET in subsequent cycles are required. Some situations in which fresh embryo transfer are not required such as fertility preservation, oocyte donation or preimplantation genetic testing, PPOS may be used as a first-line treatment[25,26]. The potential harmful effects of the hormonal environment on endometrial receptivity are therefore avoided. Other patients who can benefit from this protocol are those at risk of OHSS since for these patients there is very frequently the application of the "freeze-all" strategy, and triggering can be exerted by the GnRH agonist, which helps to avoid early-onset OHSS.

Other advantages over the use of a progestin are oral administration, easier access and more control over LH concentrations[10]. PPOS is also more patient-friendly as fewer injections are required and medroxyprogesterone is much cheaper compared to antagonist[12]. However, our study showed the total amount of stimulation with FSH/HMG was higher in PPOS protocol, the total cost related to medicine is therefore comparable between the two protocols. The cost-effectiveness of progestins compared with GnRH antagonists has been studied in a recent article by Evans and colleagues[27], but this study was only limited to planned freeze-only cycles and to high-responder patients for whom a "freeze only" is likely and the risk of OHSS is high. Since

many women with normal ovarian reserve are suitable for fresh embryo transfer in antagonist protocols, the extra cost produced by embryo cryopreserved–thawed, and delayed transfer in the PPOS protocol should be considered.

Current evidence about the safety of MPA use in ovarian stimulation is limited, and MPA was contraindicated in human pregnancy[28]. The long-term safety for children conceived with ovarian stimulation using MPA is still under investigation. In contrast, GnRH antagonist has been extensively used worldwide for IVF treatment. Our data also demonstrated that antagonist administration produced a comparable number of top-quality embryos and pregnancy outcomes are better compared with MPA. For long-term safety considerations, GnRH antagonist is safer than medroxyprogesterone during ovarian stimulation.

Strengths and weaknesses

Different from previous study,[12] patients in our study used their own oocytes, and perhaps this is a more appropriate model for comparing the pregnancy outcomes, and can control for all potential confounding factors. However, our study is limited by its retrospective design, a small sample size and reporting ongoing pregnancy rates. Some imbalanced characteristics were found in this study and logistic regression analysis was carried out for controlling the basis. Cancellation or postponement of FET was different in the two groups. Hence, reproductive results should be interpreted with caution. Further randomised trials with adequate sample size would be needed to confirm these findings. The comparison of cumulative outcomes after one IVF cycle has not been performed between two groups.

Conclusion

The use of medroxyprogesterone during ovarian stimulation is effective in blocking the LH surge, and does not affect the number of oocytes collected in the woman with normal ovarian reserve. A multivariate logistic regression indicated a higher ongoing pregnancy rate with the antagonist protocol, when compared with the PPOS protocol.

Disclosure of interests

The authors declare no conflict of interest. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

HC and ZQC were involved in the study design, execution and analysis, critical discussion and final approval of the manuscript. MXC and JPP were involved in execution and acquisition of the data. MZ contributed to execution and the analysis of the data. EHYN and KML were involved in the study design, critical discussion and revision of the manuscript. XMT was involved in supervising and coordinating the study, and final approval of the manuscript. The final manuscript and order of authorship have been approved by all authors.

Details of ethics approval

Ethical approval was not required for this retrospective analysis.

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