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In-vitro maturation of oocytes vs in-vitro fertilization with a gonadotropin-releasing hormone antagonist for women with polycystic ovarian syndrome: can superiority be defined?

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ABSTRACT

Objective: Patients with polycystic ovarian syndrome (PCOS) are at increased risk of ovarian hyperstimulation syndrome (OHSS) in controlled ovarian hyperstimulation cycles. Interventions to reduce the risk of OHSS in these patients include in-vitro fertilization (IVF) with a gonadotropin-releasing hormone (GnRH) antagonist, and retrieval of immature oocytes followed by in-vitro maturation (IVM). The aim of this study was to compare the outcomes of IVM and IVF-GnRH antagonist protocols in women with PCOS undergoing assisted reproductive technology.

Study design: Retrospective cohort study. Records of women with PCOS who underwent IVM or IVF-GnRH antagonist protocols between 2010 and 2011 were reviewed. In total, there were 61 IVM cycles and 53 IVF-GnRH antagonist cycles. The treatment protocols were compared in terms of the number of oocytes retrieved, dose of gonadotropin administrated, fertilization rates, quality of embryos, pregnancy, and delivery and abortion rates.

Results: The number (mean ± standard deviation) of mature oocytes did not differ significantly between the two groups (7.11 ± 5.7 vs 8.16 ± 5.07 for the GnRH antagonist group and the IVM group, respectively; $p = 0.38$). The average dose of gonadotropin (1938 IU ± 838 IU/cycle vs 118 ± 199 IU/cycle; $p < 0.001$), fertilization rate (77% vs 60%; $p < 0.001$) and high-quality embryo rate (58.8% vs 48.3; $p < 0.001$) were significantly higher in the GnRH antagonist group compared with the IVM group. Pregnancy rates (40% vs 25%; $p = 0.08$), livebirth rates per pregnancy (71% vs 53%; $p = 0.265$) and abortion rates (10% vs 27%; $p = 0.17$) were comparable.

Conclusions: The IVM protocol can be an alternative for infertile women with PCOS who wish to prevent the potential adverse effects of gonadotropin treatment. Prospective studies are needed to compare the outcomes of these two treatment protocols.

Introduction

Up to 20% of subfertile women have polycystic ovarian syndrome (PCOS) [1]. These women are extremely sensitive to stimulation by gonadotropins, and are at significantly higher risk of developing ovarian hyperstimulation syndrome (OHSS) [2].

Many OHSS prevention strategies have been adopted for high-responder patients in order to avoid complications. Withholding gonadotropins in women who exhibit a high response to oestradiol before follicles reach full maturation (coasting), or suspending the administration of gonadotropins, can be an option for decreasing the risk of OHSS. However, although these approaches reduced the number of cancellations and complications, the success rate was also reduced [3]. Follicular aspiration and freezing the resulting embryos or cycle cancellation have also been suggested [4,5].

Recently, in in-vitro fertilization with a gonadotropin-releasing hormone (GnRH) antagonist, the use of a GnRH agonist to trigger ovulation instead of human chorionic gonadotropin (hCG) was found to reduce OHSS dramatically and overcome the complications induced by stimulation [6,7]. Another option is the retrieval of immature oocytes from small antral follicles in an unstimulated or minimally stimulated cycle, followed by in-vitro maturation (IVM) [8,9].

Both IVM and IVF-GnRH antagonist protocols are acceptable for women with PCOS [10]. However, reported pregnancy rates are inconsistent. Some authors have reported a higher pregnancy rate

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for the IVF-GnRH antagonist protocol compared with the IVM protocol [8,9], and others have reported comparable results [11,12]. Use of the IVM protocol in women with PCOS eliminates the risk of OHSS and reduces the cost of treatment [11]. Use of the IVF-GnRH antagonist protocol may yield a higher pregnancy rate but a higher incidence of OHSS.

The aim of this study was to compare the clinical outcomes (including pregnancy and livebirth rates), cycle parameters and OHSS of IVM and IVF-GnRH antagonist protocols for subfertile women with PCOS undergoing assisted reproductive technology (ART) at a single IVF unit.

Materials and methods

All women with PCOS who underwent IVF-GnRH antagonist or IVM protocols at Hillel Yaffe Medical Centre, IVF Unit, Israel between January 2010 and December 2011 were reviewed retrospectively. PCOS was diagnosed in accordance with the Rotterdam criteria [13]. The institutional review board approved this study.

IVF-GnRH antagonist protocol

A fixed antagonist protocol was performed as described previously [14]. Gonal-F (Merck Serono Pharmaceuticals, Ltd.), Puregon (MSD Pharmaceuticals, Ltd.) or Menopur (Ferring Pharmaceuticals, Germany) was commenced on Day 2–3 of menses or induced bleeding. On Day 6 of ovarian stimulation, cetrorelix acetate (Merck Serono Pharmaceuticals Ltd.) 0.25 mg/day was added. Ovulation induction by subcutaneous 250 μg recombinant hCG (Ovitrelle, Merck Serono S.A Geneva, Switzerland) was administrated when two or more follicles reached a diameter of 17 mm. Oocyte retrieval was conducted under ultrasound guidance 34–36 h later. Insemination or intracytoplasmic sperm injection was performed according to semen quality. Embryo transfer was conducted between Days 2 and 3 under ultrasound guidance. Luteal phase support with 200 mg daily vaginal progesterone (Endometrin, Ferring Pharmaceuticals, Germany) was commenced 1 day after oocyte retrieval.

IVM protocol

The IVM protocol was performed in an unstimulated cycle, as described by Vitek et al. [15], or a cycle with minimal gonadotropin stimulation. All patients had a baseline transvaginal ultrasound scan on Day 2–3 of menses. The unstimulated group was treated with 4 mg/day of micronized 17β-oestradiol (Estrofem, Novo-Nordisk, Dublin, Ireland), started during menses. In the stimulated IVM group, 150 IU gonadotropin was administered on Day 3 of menses for 3 days. A second ultrasound scan was performed between Days 6 and 10 to assess endometrial thickness and the development of follicles up to 12–14 mm. When endometrial thickness exceeded 6 mm or a follicle reached a diameter of 10–14 mm, hCG priming with 375 μg recombinant hCG (Ovitrelle, Merck Serono S.A Geneva, Switzerland) was administered 38 h before oocyte retrieval, as suggested by Son et al. [16]. Transvaginal-ultrasound-guided oocyte retrieval was performed under general anaesthesia using a 19-gauge needle (Swemed, Goteborg, Sweden) with an aspiration pressure of 80–90 mm Hg (7.5 kPa). Oocytes were placed in oocyte maturation medium (SAGE Media Cooper Surgical Company, USA), and maturity was assessed by trained embryologists 6, 24–30 and 48 h after retrieval. Intracytoplasmic sperm injection was used for mature oocytes on the day of retrieval and for immature oocytes when they reached maturity, 1 or 2 days after retrieval. Embryo transfer was performed on Days 2–3 under ultrasound guidance. Each patient received luteal support with 300 mg daily vaginal progesterone (Endometrin, Ferring Pharmaceuticals, Germany) and 4 mg oestradiol valerate (Proginova, Bayer, New Zealand).

All women underwent a serum pregnancy test 14 days after embryo transfer. Pregnant women underwent a transvaginal ultrasound examination 2 weeks later. Clinical pregnancy was defined as the presence of an intrauterine gestational sac with fetal heart activity.

Data collection

Demographic data including age, diagnosis of infertility, basal hormonal levels and antral follicle count were collected. The dose of gonadotropin used, number of follicles, endometrial thickness during treatment, number of mature and immature oocytes retrieved, fertilization rate, number of embryos transferred, implantation rate, pregnancy rate and pregnancy outcome (in those who conceived) were recorded. Data are reported as mean ± standard deviation unless otherwise indicated.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Shapiro–Wilks test was used to evaluate the distribution of the data. Comparisons were analysed using Student's *t*-test or Mann–Whitney *U*-test as appropriate. Proportions were compared using Chi-squared test or Fisher's exact test. $p < 0.05$ was considered to indicate significance.

Results

In total, 1152 ART cycles (1058 IVF-GnRH antagonist cycles and 94 IVM cycles) were evaluated over the study period. Sixty-one IVM cycles and 53 IVF-GnRH antagonist cycles were conducted in 79 women with PCOS. Only those patients treated with the relevant protocols were recruited into the study. There were no other inclusion/exclusion criteria. Demographic characteristics are summarized in Table 1. Age, basal follicle-stimulating hormone,

Table 1
Patient characteristics for in-vitro fertilization (IVF) with a gonadotropin-releasing hormone (GnRH) antagonist and in-vitro maturation (IVM) groups.

Parameters	IVF-GnRH antagonist	IVM	*p*-value
Number of cycles, *n*	53	61	
Age (years)	30.9 ± 4.6	31.8 ± 4.9	NS
Body mass index (kg/m^2)	28 ± 6.8	31.9 ± 6.2	0.002
Basal follicle-stimulating hormone (IU)	5.6 ± 1.4	5.9 ± 4	NS
Basal luteinizing hormone (IU)	6.6 ± 0.4	5.8 ± 4.6	NS
Serial cycle number	2.16 ± 1.04	2.81 ± 1.78	NS

NS: not significant.
Data expressed as mean ± standard deviation unless otherwise indicated.