Stimulation of the young poor responder: comparison of the luteal estradiol/gonadotropin-releasing hormone antagonist priming protocol versus oral contraceptive microdose leuprolide

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Objective: To evaluate in vitro fertilization (IVF) cycle outcomes in young poor responders treated with a luteal estradiol/gonadotropin-releasing hormone antagonist (E_2/ANT) protocol versus an oral contraceptive pill microdose leuprolide protocol (OCP-MDL).
Design: Retrospective cohort.
Setting: Academic practice.
Patient(s): Poor responders: 186 women, aged <35 years undergoing IVF with either E_2/ANT or OCP-MDL protocols.
Intervention(s): None.
Main Outcome Measure(s): Clinical pregnancies, oocytes retrieved, cancellation rate.
Result(s): Patients in the E_2/ANT group had a greater gonadotropin requirement (71.9 ± 22.2 vs. 57.6 ± 25.7) and lower E_2 level (1,178.6 ± 668 vs. 1,627 ± 889), yet achieved similar numbers of oocytes retrieved and fertilized, and a greater number of embryos transferred (2.3 ± 0.9 vs. 2.0 ± 1.1) with a better mean grade (2.14 ± .06 vs. 2.7 ± 1.8) compared with the OCP/MDL group. The E2/ANT group exhibited a trend toward improved implantation rates (30.5% vs. 21.1%) and ongoing pregnancy rates per started cycle: 44 out of 117 (37%) versus 17 out of 69 (25%).
Conclusion(s): Poor responders aged <35 years may be treated with the aggressive E_2/ANT protocol to improve cycle outcomes. Both protocols remain viable options for this group. Adequately powered, randomized clinical comparison appears justified. (Fertil Steril® 2011;95:592–5. ©2011 by American Society for Reproductive Medicine.)

Key Words: Estrogen priming, IVF failure, GnRH antagonist, poor responder

Poor responders pose a major challenge in assisted reproduction and represent a considerable portion of the infertility population, with a prevalence ranging from 9% to 24% (1). The "poor responder" was initially described by Garcia et al. (2), who defined such patients as achieving a peak estradiol (E_2) level <300 pg/mL after standard in vitro fertilization (IVF) stimulation. Additional clinical characteristics have been employed for diagnosis in poor responders, including elevated basal follicle-stimulating hormone (FSH) levels (3), previous IVF cycle cancellation (4), high gonadotropin requirements (5), a reduced number of follicles (6), and few oocytes at retrieval (7).

Young poor responders (YPR), those aged less than 35 years, are a unique subgroup. For these patients, age confers better oocyte quality and thus improved pregnancy outcomes as compared with older patients who have a poor response. Generally, aggressive stimulation protocols are used as an attempt to improve outcomes in this population. The goal of treatment for poor responders is to enhance follicular recruitment leading to an increase in the number of mature follicles, matures oocytes, and embryos. Specific protocols are typically employed in an effort to optimize follicular responsiveness to gonadotropins and to counteract some of the natural phenomena inherent in the selection of a dominant follicle. However, these patients still suffer a high rate of cycle cancellation and potential implantation failure. Thus, the ideal protocol to maximize stimulation outcomes has yet to be established. We compared outcomes for two commonly used protocols for poor responders, the luteal E_2 patch/gonadotropin-releasing hormone (GnRH) antagonist protocol and the oral contraceptive pill (OCP) microdose leuprolide protocol (8–11).

The luteal E_2 patch/GnRH antagonist protocol aims to synchronize follicular growth by decreasing antral follicle heterogeneity and specifically counteracting luteal follicular recruitment, leading to a dominant follicle (12). Luteal E_2 administration has been shown to suppress the early FSH rise during the late luteal phase, resulting in a reduction in size of antral follicles and improved homogeneity of early antral follicles. Similarly, use of an antagonist in the luteal phase was found to reduce antral follicle size and follicular heterogeneity through prevention of the luteal FSH rise (12–14).

Dragisic et al. (14) first described a novel protocol incorporating both transdermal E_2 and a GnRH antagonist in the luteal phase followed by gonadotropin stimulation and an adjunctive GnRH antagonist. This study demonstrated superior outcomes in patients undergoing stimulation with the luteal E_2 patch/GnRH antagonist protocol when compared with outcomes in previous cycles. Patients

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were found to have a decreased cancellation rate, an increased number of oocytes retrieved and fertilized, and an increased number of embryos transferred.

Since the early 1990s, poor responders have commonly been treated with an OCP-microdose leuprolide protocol (8, 9). It retains the advantages of standard flare protocols, primarily by using the initial rise of gonadotropins in response to GnRH administration. Additionally, the "microdose" of leuprolide minimizes the suppressive effects of GnRH agonist down-regulation on endogenous gonadotropin secretion. The pretreatment with oral contraceptive pills mitigates corpus luteum rescue and an early follicular phase progesterone rise, which could have detrimental effects on the endometrium and oocyte quality (9).

Our study evaluated cycle outcomes, specifically in young poor prognosis patients who were undergoing IVF with either the luteal E_2 patch/GnRH antagonist protocol (E_2/ANT) or a standard protocol of OCP-microdose leuprolide (OCP-MDL).

MATERIALS AND METHODS

Patients

Patients were included if they were age <35 years and poor responders, as defined by one or more of the following criteria: [1] history of previously canceled cycles, [2] poor response to stimulation (<3 dominant follicles or E_2 <500 pg/mL), or [3] basal follicle-stimulating hormone (FSH) levels >12 mIU/mL (follicular female range: 3.0–14.4 mIU/mL). The study included 186 patients who underwent controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF) at the Center for Reproductive Medicine at Weill Cornell Medical College from January 2004 to January 2008. Charts were reviewed for patients undergoing their first stimulation cycle at our center with either the E_2 patch or OCP-MDL protocol. The patients in our practice were assigned to either protocol based on the primary physician's choice. Some patients may have had cycled previously with one of these protocols at another institution, although this information was not specifically documented. The institutional review board at Weill Cornell Medical College approved this study.

Treatment Protocols

Luteal E_2 patch/GnRH antagonist protocol A total of 117 women underwent controlled ovarian hyperstimulation (COH)/IVF with the luteal E_2 patch/GnRH antagonist protocol. As previously described by Dragisic et al. (14), these patients self-monitored with a home urinary ovulation predictor kit. On day 10 after the luteinizing hormone (LH) surge, patients applied one 0.1-mg transdermal E_2 patch (Climara, estradiol transdermal patch; Bayer Healthcare Pharmaceutical, Wayne, NJ) and changed the patch every other day. On the second day after the application of the E_2 patch, patients began daily subcutaneous injections with 0.25 mg of ganirelix acetate (Antagon; Organon Pharmaceuticals, West Orange, NJ) for 3 days. Patients then presented to the IVF center on day 2 of their menses for measurement of their baseline FSH, LH, and E_2 levels and ultrasound examination (antral follicle count, endometrial thickness).

Patients remained on the last E_2 patch for a total of 7 days unless the patch fell off earlier. On day 2, patients were started on 450–600 IU of gonadotropins, either FSH (Follistim; Organon Pharmaceuticals, West Orange, NJ; or Gonal-F; EMD-Serono, Inc., Rockland, MA), human menopausal gonadotropin (hMG, Menopur; Ferring Pharmaceuticals, Tarrytown, NY), or a combination of both, employing a step-down protocol. Ganirelix acetate was initiated daily when one of the following criteria was met: [1] cycle day 7 of the stimulation, [2] the presence of at least one lead follicle >13 mm, or [3] E_2 level exceeding 300 pg/mL. Gonadotropin dosing was based on each patient's basal antral follicle count, day-3 FSH testing, body mass index (BMI), and prior response. As these patients were identified as poor responders, they underwent stimulation with higher doses of gonadotropins. As per standard practice, we routinely use a combination of both FSH and hMG, especially in poor responder patients.

TABLE 1

Patient characteristics.

Characteristic	OCP-MDL (n = 69)	E_2/ANT (n = 117)	*P* value
Age (y)	32 ± 2.6	32 ± 2.4	NS
RD3 FSH (mIU/mL)	12.9 ± 9.7	12.2 ± 5.7	NS
BMI	23.3 ± 4.2	23.2 ± 4.2	NS
No. of prior attempted cycles	2.3 ± 1.9	1.6 ± 1.5	<.05

Note: Results are reported as mean ± standard deviation. ANT = gonadotropin-releasing hormone antagonist; BMI = body mass index; E_2 = estradiol; FSH = follicle-stimulating hormone; NS = not statistically significant; OCP-MDL = oral contraceptive pill microdose leuprolide RD3 = random day 3.

Shastri. Young poor responder: luteal E_2 vs. OCP-MDL. Fertil Steril 2011.

OCP-microdose leuprolide protocol There were a total of 69 patients included in the OCP-MDL group. These patients received 21 days of OCP pretreatment (Desogen; Organon Pharmaceuticals). On the second day after discontinuing the OCP (designated cycle day 1), patients presented for baseline FSH, LH, E_2 measurements and ultrasound examination. On cycle day 2, patients initiated subcutaneous injections of 0.2 cc of leuprolide acetate (40 μg/0.2 cc), twice daily. On cycle day 4, patients began gonadotropin stimulation, 450–600 IU of FSH (Follistim; Organon Pharmaceuticals; or Gonal-F; EMD-Serono) and/or hMG (Menopur; Ferring Pharmaceuticals) with continuation of the 0.2 cc twice daily of leuprolide acetate throughout the cycle.

IVF Procedure

In both groups, human chorionic gonadotropin (hCG) was administered when two or more lead follicles reached 17 mm mean diameter by transvaginal ultrasound. Oocytes were harvested by transvaginal ultrasound-guided follicular puncture 35 to 36 hours after hCG administration. Conventional oocyte insemination or intracytoplasmic sperm injection (ICSI) was performed as indicated. The highest morphologic grade embryos were transferred into the uterine cavity 3 to 5 days after retrieval. Patients received luteal support with 50 mg IM progesterone daily, which was initiated the day after oocyte retrieval. Progesterone was continued until a negative pregnancy test or until the gestational age of 7 to 9 weeks with confirmational ultrasound for patients with a positive pregnancy test.

Outcome Measures and Statistical Analysis

The primary outcome measures included clinical pregnancy rates, number of oocytes retrieved, and cancellation rate. Secondary outcome measures included cycle length, total dose of gonadotropins (ampules), number of mature oocytes, number of embryos transferred, and implantation rate.

Paired *t* tests were used to compare parameters between the two stimulation protocols, and the chi-square test was used to compare differences in categorical values of outcomes. $P<.05$ was considered statistically significant. Data are presented as the mean ± standard deviation (SD).

RESULTS

Of the 186 patients deemed poor responders included in this analysis, 69 patients were treated with the OCP-MDL protocol, and 117 with the E_2/ANT protocol. Table 1 describes the patient characteristics of the two groups.

Baseline characteristics including mean age (32 ± 2.6 vs. 32 ± 2.4 years), random day-3 FSH levels (12.9 ± 9.7 vs. 12.2 ± 5.7 mIU/mL), and BMI (23.3 ± 4.2 vs. 23.2 ± 4.2) were similar