The effect of transdermal testosterone gel pretreatment on controlled ovarian stimulation and IVF outcome in low responders

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Objective: To investigate the effectiveness of treatment with transdermal testosterone gel (TTG) before controlled ovarian stimulation (COS) using GnRH antagonist multiple-dose protocol (MDP) in low responders undergoing IVF/intracytoplasmic sperm injection (ICSI).
Design: Prospective randomized controlled trial.
Setting: University-affiliated infertility clinic.
Patient(s): A total of 110 low responders, who were defined as patients who failed to produce $\leq$3 follicles with a mean diameter of $\geq$16 mm with the result that $\leq$3 oocytes were retrieved despite the use of a high gonadotropin dose (>2,500 IU) in a previous failed IVF/ICSI cycle.
Intervention(s): Patients were randomized into TTG pretreatment group or control group. For TTG pretreatment group, 12.5 mg TTG were applied daily for 21 days in the cycle preceding COS for IVF.
Main Outcome Measure(s): COS results and IVF outcome.
Result(s): There were no differences in patients' characteristics between the two groups. Total dose and days of rhFSH used were significantly fewer in the TTG pretreatment group than in the control group. The numbers of oocytes retrieved, mature oocytes, fertilized oocytes, and good-quality embryos were significantly higher in the TTG pretreatment group. Embryo implantation rate and clinical pregnancy rate per cycle initiated also were significantly higher in the women pretreated with TTG. No patient reported adverse effects attributed to TTG use.
Conclusion(s): TTG pretreatment might be beneficial in improving both response to COS and IVF outcome in low responders undergoing IVF/ICSI. (Fertil Steril® 2011;95:679–83. ©2011 by American Society for Reproductive Medicine.)

Key Words: Transdermal testosterone gel, controlled ovarian stimulation, IVF, low responders

Controlled ovarian stimulation (COS) has contributed to improving the pregnancy rate of women who undergo in vitro fertilization (IVF) by increasing the number of developing follicles and oocytes. However, low responders who are characterized by a diminished ovarian reserve (1) fail to respond adequately despite the maximal dose of gonadotropins administered. A variety of stimulation regimes have been used for the management of low responders. The most prevalent regimes for treating them at present are GnRH agonist low-dose long protocol (2, 3), GnRH agonist flare-up regimes (4, 5), and GnRH antagonist protocols (6–8). Unfortunately, none of these protocols has been especially effective in improving ovarian response in low responders.

In the primate ovary, androgens stimulate early stages of follicular growth (9–11), and primate experiments suggest that androgens may influence the responsiveness of ovaries to gonadotropins and may amplify the effects of FSH on the ovary. In a small series of five patients with documented poor response to high doses of gonadotropins, supplemental DHEA treatment improved response to ovarian stimulation even after controlling for gonadotropin dose (12). This preliminary report was confirmed by Barad and Gleicher (13). DHEA 75 mg/d was given to 25 women with significantly diminished ovarian reserve, and this treatment increased the oocyte yield and embryo quality. In 2009, a randomized clinical trial demonstrated that pretreatment with transdermal testosterone patch decreased the percentage of cycles with low response in low responder IVF patients (14). Recently, clinical trials to investigate the effects of androgen supplementation for low responders have been attempted, but results have been limited. Androgen priming using transdermal testosterone gel (TTG) for women with diminished ovarian reserve has not been reported. Androgen treatment using topically applied testosterone gel has been proven to be convenient and effective in aging or hypogonadal men (15, 16). Therefore, this prospective randomized study was performed to assess the effectiveness of treatment with TTG before COS using GnRH antagonist multiple-dose protocol (MDP) in low responders undergoing IVF/intracytoplasmic sperm injection (ICSI).

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MATERIALS AND METHODS

Patients

Our prospective randomized study was performed at a university-based infertility clinic at the Asan Medical Center, Seoul, South Korea. The study

TABLE 1

Patient characteristics.

	TTG pretreatment	Control	*P* value
No. of patients	55	55	
Age of patients (y)	37.8 ± 3.0	37.9 ± 2.9	NS[a]
Age of husbands (y)	42.8 ± 4.0	42.4 ± 4.3	NS[a]
Infertility duration (mo)	53.1 ± 23.4	50.2 ± 24.5	NS[a]
BMI (kg/m^2)	21.7 ± 2.4	21.9 ± 2.1	NS[a]
No. of nullipara (%)	29 (72.5%)	27 (67.5%)	NS[b]
No. of patients with AFC ≤5	36 (90.0%)	34 (85.0%)	NS[b]
AFC	4.2 ± 0.8	4.4 ± 1.1	NS[a]
Basal FSH (IU/L)	8.9 ± 0.9	9.0 ± 1.1	NS[a]
Basal LH (IU/L)	5.2 ± 1.1	5.1 ± 1.0	NS[a]
Basal E_2 (pg/mL)	51.3 ± 15.3	49.7 ± 12.3	NS[a]
Basal T (ng/mL)	0.2 ± 0.1	0.2 ± 0.1	NS[a]
Basal free T (pg/mL)	0.3 ± 0.1	0.4 ± 0.1	NS[a]

Note: Values are mean ± SD. AFC = antral follicle count; BMI = body mass index; NS = not significant; TTG = transdermal testosterone gel.

[a] Student *t* test.

[b] Chi-square test.

Kim. Testosterone gel for low responders. Fertil Steril 2011.

population consisted of 110 low responders who had undergone 110 IVF/ICSI cycles between March 2005 and January 2009. Low responder was defined as patients who failed to produce ≤3 follicles with a mean diameter of ≥16 mm with the result that ≤3 oocytes were retrieved despite the use of a high gonadotropin dose (>2,500 IU) in a previous failed IVF/ICSI cycle. The Institutional Review Board of the University of Ulsan College of Medicine, Asan Medical Center, approved the study, and each of the patients provided written informed consent. Patients were randomly allocated into TTG pretreatment group (n = 55) or control group (n = 55) by the use of sealed envelopes and a computer-generated list. The sequence of allocation to the two groups was provided to the investigating physicians, and randomization was performed as planned according to the randomization list order.

All of the patients had regular ovulatory cycles (duration 21–35 days). They were in good health with normal thyroid, hepatic, and renal functions, and they had experienced spontaneous onset of puberty and normal sexual development. None of subjects had ever taken any infertility medications (clomiphene and/or gonadotropins) within the preceding 3 months.

Ovarian Stimulation Protocols

All of the patients received estrogen-progesterone (E-P) pretreatment using E_2 valerate (Progynova; Bayer Schering Pharma, Berlin, Germany) 1 mg/d and norethindrone (Primolut; Bayer Schering Pharma) 5 mg/d for 21 days in the cycle preceding COS. For the TTG pretreatment group, once daily application of 12.5 mg TTG (Testo gel 1%; Laboratories Besins International, Paris, France) with a 1.25 mg/d nominal delivery rate of testosterone was started from sixth day of E-P pretreatment and continued for 21 days. The application was administered in the morning by the patient onto clean dry healthy skin over both upper arms. The gel was simply spread on the skin gently as a thin layer. Ovarian stimulation was commenced the day after last testosterone gel application.

GnRH antagonist MDP was used for COS in all subjects. Five days after discontinuation of E-P pretreatment, ovarian stimulation was commenced using recombinant human FSH (rhFSH; Gonal-F; Merck Serono, Geneva, Switzerland) 300 IU/d after establishing ovarian and uterine quiescence by using transvaginal ultrasound. The dose of rhFSH was adjusted every 3–4 days according to ovarian response. When the lead follicle reached 13-14 mm in average diameter, GnRH antagonist cetrorelix (Cetrotide; Merck Serono) 0.25 mg/d was started and continued daily up to the day of hCG injection. Recombinant hCG (rhCG; Ovidrel; Merck Serono) 250 μg was administered subcutaneously to induce follicular maturation when ≥1 follicles reached a mean diameter of ≥18 mm.

In both groups, transvaginal ultrasound–guided oocyte retrieval was performed 36 hours after hCG injection, and one to four embryos, after IVF or ICSI, were transfered into the uterus on the third day after oocyte retrieval. Luteal support was provided by administering 90 mg vaginal progesterone gel (Crinone gel 8%; Merck Serono) once daily from the day of oocyte retrieval. Pregnancies were confirmed by rising serum β-hCG concentrations and transvaginal ultrasonographic evidence of a gestational sac. Measurement of β-hCG was performed by radioimmunoassay using an hCG MAIA-clone kit (Serono Diagnostics, Woking, U.K.); interassay and intraassay variances were <10% and <5%, respectively.

Outcome Measures

The primary efficacy end point was the number of mature oocytes retrieved. Secondary efficacy variables included total amount and days of rhFSH administered, numbers of fertilized oocytes and good-quality embryos, implantation rate, clinical pregnancy rate per cycle, and live birth rate per cycle. Clinical pregnancy was defined as the presence of a gestational sac by ultrasonography, whereas miscarriage rate per clinical pregnancy was defined as the proportion of patients who failed to continue development before 20 weeks of gestation in all clinical pregnancies. Live birth was defined as the delivery of a fetus with signs of life after 20 completed weeks of gestational age.

Statistical Analysis

Values were expressed as mean ± SD. A Student *t* test was used to compare the mean values. Chi-square test and Fisher exact test were used for the comparisons of fraction. Statistical significance was defined as $P<.05$. All analyses were performed using the SPSS statistical package for Windows, version 11.0 (SPSS, Chicago, IL).

RESULTS

There were no differences in the ages of patients and spouses, duration of infertility, body mass index, antral follicle count (AFC), and basal endocrine profile between the TTG pretreatment and control groups (Table 1).

The TTG pretreatment and control groups each consisted of 55 cycles initiated, corresponding to 55 patients. In the TTG pretreatment group, 1 cycle (1.8%) was canceled before embryo transfer (ET), because no oocytes were obtained despite a follicular

TABLE 2

Comparison of controlled ovarian stimulation results and IVF/ICSI outcome.

	TTG pretreatment	Control	*P* value
No. of cycles initiated	55	55	
No. of cycles retrieved	55	54	
No. of ET cycles	54	53	
No. of cycles canceled	1 (1.8%)	2 (3.6%)	NS[a]
No. of cycles with ICSI	17 (42.5%)	16 (41.0%)	NS[a]
On stimulation day 1			
Serum T (ng/mL)	1.9 ± 0.4	0.3 ± 0.2	<.001[b]
Serum free T (pg/mL)	1.0 ± 0.3	0.4 ± 0.2	<.001[b]
AFC	5.0 ± 1.1	4.3 ± 1.1	.026[b]
Days of rhFSH	9.6 ± 1.1	10.5 ± 1.6	<.001[b]
Total dose of rhFSH	2,552.3 ± 397.2	3,000.8 ± 449.8	<.001[b]
Days of GnRH antagonist	4.5 ± 0.8	5.3 ± 1.5	.001[b]
No. of follicles on hCG day			
14 to <17 mm	2.7 ± 1.4	1.4 ± 0.7	<.001[b]
≥17 mm	4.2 ± 1.4	2.7 ± 1.0	<.001[b]
EMT on hCG day (mm)	9.8 ± 1.2	9.9 ± 1.4	NS[b]
No. of oocytes retrieved	5.4 ± 1.9	3.8 ± 1.4	<.001[b]
No. of mature oocytes	4.6 ± 1.7	3.2 ± 1.2	<.001[b]
No. of fertilized oocytes	4.3 ± 1.7	3.0 ± 1.2	<.001[b]
No. of grade I, II embryos	1.9 ± 1.0	1.3 ± 0.8	.001[b]
No. of embryos transfered	2.6 ± 0.9	2.6 ± 0.7	NS[b]
Embryo implantation rate (%)	14.3 (20/140)	7.2 (8/138)	.019[a]
Clinical PR per cycle initiated (%)	30.9 (17/55)	14.5 (8/55)	.041[a]
Clinical PR per ET (%)	31.5 (17/54)	15.1 (8/53)	.045[a]
Miscarriage rate (%)	11.8 (2/17)	12.5 (1/8)	NS[a]
Live birth rate per cycle initiated (%)	27.3 (15/55)	12.7 (7/55)	.057[a]
Twin PR per clinical pregnancy (%)	17.6 (3/17)	0 (0/8)	NS[a]

Note: Values are mean ± SD. EMT = endometrial thickness; ET = embryo transfer; ICSI = intracytoplasmic sperm injection; PR = pregnancy rate; other abbreviations as in Table 1.

[a] Chi-square test or Fisher exact test.

[b] Student *t* test.

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aspiration for oocyte retrieval. In the control group, 1 cycle (1.8%) was canceled before oocyte retrieval owing to no follicular development. In 1 out of 54 cycles in which oocyte retrieval was performed (1.9%), no oocytes were obtained. Overall in the control group, 2 out of 55 cycles initiated (3.6%) were canceled before ET because no oocytes were available. There was no significant difference in overall cycle cancellation rate between the TTG pretreatment and control groups (Table 2).

Both serum T and free T levels on ovarian stimulation day 1 were significantly higher in the TTG pretreatment group than in the control group (both $P<.001$; Table 2). Total days and dose of rhFSH required for COS were significantly fewer in the TTG pretreatment group than in the control group (both $P<.001$). Duration of GnRH antagonist administration was also shorter in the TTG pretreatment group ($P=.001$). The numbers of oocytes retrieved, mature oocytes, fertilized oocytes, and grade I or II embryos were significantly higher in TTG pretreatment group than those in control group ($P<.001$, $P<.001$, $P<.001$, and $P=.001$, respectively). Embryo implantation rate (14.3%) was significantly higher in the TTG pretreatment group than in the control group (7.2%; $P=.019$). The clinical pregnancy rates per cycle initiated and per cycle ET were also significantly higher in the TTG pretreatment group than in the control group ($P=.041$ and $P=.045$, respectively). Live birth rate per cycle initiated was higher in the TTG pretreatment group, with a borderline significance ($P=.057$). However, miscarriage rate was similar in both groups (Table 2). No patients reported any systemic or local adverse effects attributed to the use of TTG.

DISCUSSION

This is the first prospective randomized study to evaluate the effectiveness of treatment with TTG before COS using GnRH antagonist MDP in low responders undergoing IVF/ICSI. This study demonstrated that TTG pretreatment can increase the numbers of oocytes retrieved, fertilized oocytes, and grade I or II embryos and the clinical pregnancy rate as well as reduce the amount of rhFSH required for follicular maturation in low responders undergoing IVF/ICSI.

In rhesus monkeys, treatment with dehydrotestosterone (DHT) or testosterone augments follicular FSH receptor expression in granulosa cells, promotes initiation of primordial follicle growth, and increases the number of growing preantral and small antral follicles (9–11). These studies suggested that androgen treatment may amplify the effects of FSH on the ovary. Besides these experimental data, several clinical data have implied positive effects of androgens on follicular recruitment and development. Fratarelli and Peterson (17) evaluated androgen levels in 43 normo-ovulatory women before IVF treatment and observed that patients who had low levels of testosterone after down-regulation required a higher FSH dose and a longer duration of ovarian stimulation and were less likely to achieve a pregnancy than patients with higher baseline testosterone levels.

Barbieri et al. (18) observed that testosterone levels decreased significantly with advancing age and that there was a positive correlation between serum testosterone and the number of oocytes retrieved.

Howles et al. (19) suggested that in women with diminished ovarian reserve who undergo assisted reproductive technology treatment, boosting intraovarian androgens might increase the number of follicles available to enter the recruitment stage as well as the process of follicle recruitment itself. A preliminary study by Casson et al. (12) and a case-control study by Barad and Gleicher (13) demonstrated that oral medication with DHEA improves the ovarian response to COS in women with diminished ovarian reserve. The beneficial effect of androgen treatment on the ovarian response was also observed by Fábregues et al. (14). In their randomized trial, transdermal testosterone patch used for 5 days before gonadotropin treatment decreased the percentage of cycles with low response in low responders undergoing IVF. So far, there are limited data on androgen treatment for augmenting the ovarian response to COS in low responders; moreover, androgen treatment using TTG for low responders has not been reported.

In the present randomized study, the clinicians managing the subjects were not blinded. The lack of blinding of the investigators may have influenced the study results. However, considering that (a) the study population was homogeneous on the basis that all patients received IVF treatment at our infertility unit, (b) the subjects were randomized by the use of sealed envelopes and computer-generated list, (c) this randomized method was verified by a statistician, and (d) the ovarian response to gonadotropin was clearly evaluated using transvaginal ultrasonogram by one investigator, any potential bias related to the unblinded design of our study seems to be insignificant.

We used TTG for androgen supplementation in low responders undergoing IVF/ICSI. Androgen treatment using topically applied testosterone gel has already been proven to be convenient as well as effective in aging or hypogonadal men (15, 16). The percutaneous absorption of testosterone ranges from ~9% to ~12% of the applied dose. Following percutaneous absorption, testosterone diffuses into the systemic circulation at relatively constant concentrations during the 24-hour cycle, and this transdermal delivery system maintains stable serum T levels within narrow ranges with little intra- and intersubject variation. Because 5-alpha-reductase enzymes are present in the skin, serum DHT concentrations followed those of serum T, and more DHT might be converted from the TTG applied over a larger surface area (16). The biologic impact of increased DHT levels after TTG application is unclear in folliculogenesis.

We determined to use TTG at a dose of 12.5 mg/d for a 1.25 mg/d delivery rate of testosterone on the basis of experimental data in primates by Vendola et al. (10, 11). In the present study, TTG at a dose of 12.5 mg/d was administered for 21 days in the cycle preceding COS. We had performed a preliminary study on the ovarian features after 2, 3, and 4 weeks of TTG treatment in low responders undergoing IVF/ICSI. In that preliminary study, after 2 weeks of TTG treatment, AFC, mean follicular diameter (MFD), and resistance index (RI) value of the ovarian stromal artery (OSA) were similar to those just before TTG treatment (baseline values). However, both 3 weeks and 4 weeks of TTG pretreatment resulted in a significant increase of AFC and significant decreases of MFD and RI value of OSA compared with baseline values. Therefore, we chose to use TTG for 21 days (minimal days that caused significant changes in AFC, MFD, and RI value of OSA).

Possible adverse effects of TTG include acne, facial hair growth, voice deepening, and skin irritation on application sites. Long-term effects of TTG remain unknown, and we should closely monitor the potential of long-term adverse effects such as dyslipidemia. However, in the present study, TTG medication was well tolerated by all patients. Any systemic or local adverse effects by TTG have not been reported, and miscarriage rates were similar between the TTG pretreatment and control groups. Also, any major or minor congenital anomalies of neonates were not found in the TTG pretreatment group as well as the control group.

In contrast to oral androgen therapy, the percutaneous route does not produce supraphysiological hepatic concentrations of the steroid, because first-pass metabolism in the liver is prevented. Therefore, androgen treatment using TTG is mostly safe. Moreover, application of TTG is easy, convenient, and painless.

The management for low responders with diminished ovarian reserve is still a challenge, although many studies have been undertaken to seek a method of efficient COS for infertile women with reduced ovarian reserve. Although oocyte donation is a very successful alternative treatment for infertile women with diminished ovarian reserve, efforts must be made to maximize each patient's potential to use her own oocytes.

In conclusion, this study suggests that androgen pretreatment with TTG improves the ovarian response to COS and the clinical pregnancy rate with fewer doses and days of rhFSH used, and thus it can be a cost-effective and patient-friendly treatment option to maximize the ovarian potential of low responders undergoing IVF/ICSI. Larger studies with standardized methods will be needed for confirmation of our conclusions.

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