Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: http://www.tandfonline.com/loi/igye20

The effectiveness of transdermal testosterone gel 1% (androgel) for poor responders undergoing in vitro fertilization

Hang Thi Doan, Lam Hoang Quan & Tung Thanh Nguyen

To cite this article: Hang Thi Doan, Lam Hoang Quan & Tung Thanh Nguyen (2017): The effectiveness of transdermal testosterone gel 1% (androgel) for poor responders undergoing in vitro fertilization, Gynecological Endocrinology, DOI: 10.1080/09513590.2017.1332586

To link to this article: http://dx.doi.org/10.1080/09513590.2017.1332586

Published online: 31 May 2017.

GYNECOLOGICAL ENDOCRINOLOGY, 2017
https://doi.org/10.1080/09513590.2017.1332586

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The effectiveness of transdermal testosterone gel 1% (androgel) for poor responders undergoing *in vitro* fertilization

Hang Thi Doan, Lam Hoang Quan and Tung Thanh Nguyen

Centre for Human Reproduction and Embryology, Millitary Medical University, Hanoi, Vietnam

ABSTRACT

The study was conducted on 110 poor responders undergoing *in vitro* fertilization (IVF) from October 2015 to July 2016 at the IVF Center of Millitary Medical University, Vietnam. Its aim is to investigate the effectiveness of transdermal androgel before using controlled ovarian stimulation on patients undergoing IVF. A prospective, descriptive study was conducted to compare between the group of patients who used testosterone gel and the group of those who did not in terms of the following indicators: the number of oocytes retrieved, MII oocytes, fertilization rate, number of embryos, pregnancy rate, and embryo implantation rate. The number of oocytes retrieved, number of embryos, pregnancy rate, and embryo implantation rate of the group of patients using transdermal androgel before Controlled Ovarian Stimulation (COS) were found higher than those of the control group, with statistical significance. The use of androgel before stimulating ovarian can improve the responsiveness of poor responders when undergoing IVF.

ARTICLE HISTORY
Received 4 April 2017
Revised 14 April 2017
Accepted 16 May 2017
Published online 31 May 2017

KEYWORDS
Androgel; *in vitro* fertilization; poor responder

Introduction

In vitro fertilization (IVF) is so far an effective method in assisted reproduction with success rate of 35–40% [1]. In the process of ovarian stimulation, poor response is a probable obstacle accounting for 9–24% of the total number of IVF cases [2,3]. It is one major challenge to treat poor response in assisted reproduction, with a variety of proposed solutions yet none is proved dominant. Meanwhile, androgel supplementation is currently of much concern. It has been demonstrated in a number of studies that androgel stimulates the early stages of follicular growth, increasing the ovarian response to Follicle Stimulation Hormone (FSH). Subsequently, it helps increase the number of eggs, obtained embryos, and pregnancy rate. Many studies conducted worldwide has evidenced that androgel can improve poor response. No study, however, has been reported in Vietnam. This research, hence, was carried out with aim to evaluate the number of post-aspiration oocytes and matured ovum, fertilization rate, number of embryos, pregnancy rate, and embryo implantation rate among poor responders using topical androgel prior to ovarian stimulation.

Methods

Sample selection

One hundred and ten patients were selected in this study. The criterion for selection was that these patients have either history or probability of poor ovarian response (antral follicle count [AFC] < 5–7 follicles or Anti-Mullerian Hormone [AMH] ≤ 1.26 ng/ml). Those with systemic pathology, uterus and ovarian disease, and those applying for ovum were excluded.

Study design

The selected 110 patients were randomly categorized into two groups: (i) Group I included 55 patients, prescribed to use 12.5 mg Androgel 1% Gel prior to ovarian stimulation from day 6th of the previous menstrual period to day 2nd of the stimulated menstrual period, and (ii) Group II includes the remaining 55 patients, not prescribed to use Androgel 1% Gel prior to ovarian stimulation.

The two groups were then treated by stimulating ovary, following the GnRH antagonist protocol. Their follicles were subsequently monitored on ultrasound since day 6th FSH. Once there were at least two follicles of more than 17 mm size, the patients were to use hCG (human chorionic gonadotropin) to stimulate ovulation (Pregnyl, Organon 5,000 IU or 10,000 IU). The ova were obtained by means of aspiration under ultrasound guidance about 35–40 h after hCG injection.

The studied indicators include:

- Number of follicles on the day of hCG injection
- Number of over-17 mm sized follicles on the day of hCG injection
- Number of oocyte aspired
- Number of MII oocyte
- Number of fertilized ova
- Number of embryos, the embryo quality
- Number of embryos transferred
- Biochemical pregnancy rate
- Clinical pregnancy rate
- Embryo implantation rate

Fourteen days after embryo transfer, patients were appointed at the Center to test the blood ß-hCG:

- Biochemical pregnancy: by 14 days after embryo transfer, ß-hCG > 25 mIU/ml.
- Clinical pregnancy: An amniotic sac could be seen in the uterus by ultrasound by 4–5 weeks after embryo transfer.
- Embryo implantation rate is the rate between the number of embryo implanted and the number of embryos transferred.

Data collected in the study were processed by using medical statistical techniques on SPSS 18.0 for Windows (SPSS Inc.,

CONTACT Hang Thi Doan hangdt166@gmail.com Centre for Human Reproduction and Embryology, Millitary Medical University, Hanoi, Vietnam

Chicago, IL). The continuous variants were demonstrated by mean and standard deviation. Student's t test was used to compare quantitative variants and χ^2 test was used to compare qualitative variants. A result is considered statistically significant if its p values are less than 0.05. The study was conducted from September 2015 to June 2016.

Androgel 1% gel: drug information and usage

Androgel 1% Gel is manufactured by Besins Healthcare (Brussels, Belgium). Ingredients: Testosterone 50 mg, which is natural testosterone, 100% biologically similar to testosterone secreted by human body. Packaging: 01 packet of 30 gels, each 5 g gel contains 50 mg testosterone. Usage: The gel is applied on the inner upper arms (dry, clean, and intact skin), or on shoulders or abdomen skin if the inner upper arm skin is not qualified. It should be used at night, after bath. The dosage is a quarter of a gel, which is approximately 12.5 mg testosterone. The patients must take the full gel into a syringe and apply a quarter of the amount on skin, then leave it dry in 3–5 min before taking on clothes. The remaining gel is discarded. Hand washing is required after applying the gel. It is noted not to contact with other people on the applied skin.

Results

Clinical and preclinical characteristics of the two studied groups showed no difference, suggesting that the two groups were similar in age, duration of infertility, basic endocrine test results, the AFC, the number of FSH injection days, the total dose of FSH, average FSH dose, the uterus lining on the day of hCG injection (Table 1).

The average numbers of both 14–17 mm sized follicles (2.1 ± 1.9) and over-17 mm sized follicles (4.5 ± 1.7) in group I were higher than those in group II (1.9 ± 2.0 and 2.6 ± 2.1, respectively). Of which, the number of over-17 mm sized follicles of group I was found higher than that of group II, with statistical significance ($p < 0.05$) (Table 1).

MII oocytes accounted for the most in both groups, with 225 oocytes (89.6%) in group I and 145 oocytes (81.9%) in group II. The number of MI oocytes was 21 in group I (8.4%) and 25 in group II (14.1%). The numbers of both MI and MII oocytes in group I were higher than those in group II, with statistical significance ($p < 0.05$). The number of germinal vesicle (GV) oocytes was the least, with 5 oocytes (2%) in group I and 7 oocytes (4%) in group II. However, there was no significantly statistical difference between the two groups in terms of the number of GV (Table 2).

IVF results showed that there were statistically significant differences between two groups in terms of the number of post-aspiration oocytes, the number of embryos, embryos transferred, and frozen embryos ($p < 0.05$) (Table 1).

No patient in group I was canceled period, while 3 ones in group II (5.5%) were due to the lack of follicle or embryo formed from follicles. Therefore, the number of periods, in which embryos were transferred in group I, was 55 periods (100%), while that in group II was 52 periods (94.5%). The embryo implantation rate in group I and group II was 14.1% (21/149) and 6.1% (9/147), respectively. There were 12 biochemical pregnancy cases in group I (21.8%) and 5 ones in group II (9.6%). The number of clinical pregnancy cases in group I was 12 (20%), while that in group II was only 4 cases (7.7%) because there was one case observed without gestational sac, making hCG decrease gradually to negative level for pregnancy (Table 3).

With p values greater than .05, there was no statistically significant difference between the two studied groups in terms of the rate of canceled period, the rate of period with transferred embryos, and the rate of biochemical pregnancy. Meanwhile, the embryo implantation rate and clinical pregnancy rate in group I were found statistically higher than those in group II ($p < 0.05$).

Discussion

The study aimed to evaluate the effectiveness of transdermal androgel on follicles, embryos, and the IVF result of low ovarian responders; therefore, patients selected to participate in the study were those with characteristics affecting their ovarian response, such as age, cause of infertility, AMH test results, FSH, Luteinizing Hormone (LH), E2, AFC observed by ultrasound on day 2 of the menstrual period, total FSH dose, average FSH dose, and uterus lining on the day of hCG injection. With random sampling, the study ensures similarity between the two groups in terms of clinical and preclinical characteristics prior to intervention (Table 1).

The results of ovarian stimulated period of the two groups in the study were evaluated by using the following indicators: the number of follicles observed by ultrasound on the day of hCG injection, the number of oocytes obtained after aspiration, the

Table 1. Clinical and preclinical characteristics of the two groups.

	Result ($\bar{X}$ ±SD)		
Indicator	Group 1 ($n = 55$)	Group 2 ($n = 55$)	p
Average age	38.7 ± 3.42	39.4 ± 2.96	0.25
Infertility duration (years)	6.8 ± 3.91	7.1 ± 3.52	0.67
AMH (ng/ml)	0.82 ± 0.46	0.86 ± 0.54	0.13
FSH (mIU/ml)	10.5 ± 7.1	9.8 ± 3.7	0.35
LH (mIU/ml)	5.6 ± 1.3	4.8 ± 2.2	0.22
E2 (pg/ml)	43.5 ± 20.6	38.1 ± 22.3	0.46
AFC (antral follicle count) (follicle)	5.6 ± 2.9	6.2 ± 1.7	0.17
FSH injection days	9.3 ± 0.7	9.5 ± 0.6	0.11
Total FSH dose (mIU/ml)	2897 ± 341.6	2932 ± 362.1	0.41
Average FSH dose (mIU/ml)	283.5 ± 78.9	292.6 ± 76.4	0.54
Uterus lining on the day of hCG injection	11.2 ± 2.1	10.7 ± 2.8	0.29
The number of 14- to <17-mm sized follicles	2.1 ± 1.9	1.9 ± 2.0	0.59
The number of ≥17-mm sized follicles	4.5 ± 1.7	2.6 ± 2.1	0.00
The number of post-aspiration oocytes	4.5 ± 1.6	3.1 ± 1.1	0.00
The number of embryos	3.8 ± 1.6	2.5 ± 1.1	0.00
The number of embryos transferred	2.6 ± 0.7	2.2 ± 0.8	0.00
The number of frozen embryos	1.1 ± 0.3	0.5 ± 0.3	0.00

Table 2. Classification of matured oocytes.

	Results – n (%)		
Indicator	Group 1	Group 2	p
MII (metaphase II)	225 (89.6)	145 (81.9)	0.02
MI (metaphase I)	21 (8.4)	25 (14.1)	0.04
GV (germinal vesicle)	5 (2.0)	7 (4.0)	0.35
Total	251	177	–

Table 3. Ovarian response in ovarian stimulated period.

	Group 1 ($n = 55$)		Group 2 ($n = 55$)		
Characteristic of ovarian response	n	%	n	%	p
Rate of canceled period	0/55	0	3/55	5.5	0.23
Rate of period with transferred embryos	55/55	100	52/55	94.5	0.23
Rate of embryo implantation	21/149	14.1	9/147	6.1	**0.04**
Biochemical pregnancy rate	12/55	21.8	5/52	9.6	0.09
Clinical pregnancy rate	12/55	21.8	4/52	7.7	**0.04**

Bold values signifies $p = 0.04 < 0.05$.

rate of matured oocytes, the number of obtained embryos, and the number of transferred embryos and frozen embryos. It was revealed that all of those indicators were found higher in group I, which was prescribed to use transdermal androgel prior to ovarian stimulation, than in group II, which did not use transdermal androgel before stimulating ovary. The ovarian response, demonstrated by pregnancy rate and embryo implantation rate, was statistically significantly higher in group I than in group II (Table 3).

These results are similar to those in some research conducted previously. For example, the research by Balasch and Francisco studied patients with history of low ovarian response but normal basic FSH, of which 25 patients were prescribed to use transdermal testosterone with a dose of 20 μg/kg/day, 5 days before using FSH. It was concluded that transdermal testosterone could improve the pregnancy rate in low ovarian responders with normal basic FSH [4]. Kim et al. [5] discovered the impact of transdermal testosterone gel before controlled ovarian stimulation by studying the IVF results of 110 low responders categorized into two groups, one prescribed with transdermal testosterone (Group I) and the other not (Group II). It was found that both the number of obtained oocytes and the number of embryos in group I were higher than those in group II. Besides, the percentage of transferred embryos and clinical pregnancy in group I was also higher than those in group II, with statistical significance for the latter ($p < 0.05$) [5].

Ono et al. compared the concentration of testosterone in a group of endometriosis patients with that in the control group. It was observed that the testosterone concentration in endometriosis patients was lower than that in the control group, which might be a cause of ovarian failure. Hence, androgel might be effective for patients with decreased ovarian reserve [6]. Nagels et al. studied the impact of androgel (DHEA 25 mg tablet) on 1496 reproduction assisted women with low ovarian response. The results showed that low responders using DHEA or testosterone prior to treatment could have higher pregnancy rate and survival rate [7]. Nagels et al. continued studying further on androgel, confirming the positive impact of androgel on low ovarian responders [8].

Fabregues et al. applied randomized clinical trials to study the impact of transdermal testosterone on 62 women with history of canceled period due to low ovarian response. It was concluded that testosterone could improve the ovarian response with FSH, increase the number of obtained eggs, and decrease the number of low responding periods [1].

It was demonstrated in various studies that only secondary follicles with the largest number of FSH receptors could continue to grow into dominant ones that ovulate. Other secondary follicles would degrade due to the lack of FSH. The supplement of androgel before ovarian stimulation could improve the impact of FSH on the ovary [9,10], which then increase the number of follicles overcoming FSH selection step, increasing the number of dominant follicles to ovulate, and improving pregnancy rate.

In conclusion, the study results showed that using transdermal androgel prior to ovarian stimulation could increase the number of oocytes and embryos, the rate of pregnancy, and embryo implantation among IVF patients with low ovarian response.

Disclosure statement

The authors report no conflict of interest.

References

1. Fabregues F, Penarrubia J, Creus M, et al. Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial. Hum Reprod 2009;24:349–59.
2. Venetis CA, Kolibianakis EM, Talatzi TB, et al. Evidence-based management of poor ovarian response. Ann NY Acad Sci 2010;1205:199–206.
3. Lan VTN. Đáp úng kém với kích thích buồng trúng [Low response with ovarian stimulation]. Reprod Health Mag 2003;5:8–9.
4. Balasch J, Francisco F. Pretreatment with transdermal testosterone may improve ovarian response to gonadotrophins in poor responder IVF patients with normal basal concentrations of FSH. Hum Reprod 2006;21:1884–93.
5. Kim CH, Howles CM, Lee HA. The effect of transdermal testosterone gel pretreatment on controlled ovarianstimulation and IVF outcome in low responders. Fertil Steril 2011;95:679–83.
6. Ono YJ, Tanabe A, Nakamura Y, et al. A Low-testosterone state associated with endometrioma leads to the apoptosis of granulosa cells. PLoS One. 2014;9:e115618.
7. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) in women undergoing assisted reproduction. Cochrane Database Syst Rev 2012;3:CD009749.
8. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) in women undergoing assisted reproduction. Cochrane Database Syst Rev 2015;11:CD009749.
9. Humaidan P, Ejdrup Bredkjer H, Bungum L, et al. GnRH agonist (buserelin) or hCG for ovulation induction in GnRH antagonist IVF/ICSI cycles: a prospective randomized study. Hum Reprod 2005;20:1213–20.
10. Walters KA, et al. Role of androgens in normal and pathological ovarian function. Hum Reprod 2015;149:R193–218.