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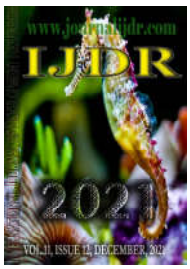

RESEARCH ARTICLE OPEN ACCESS

THE EFFECTIVENESS OF TRANSDERMAL TESTOSTERONE GEL 1% (ANDROGEL) FOR POOR RESPONDERS UNDERGOING IN VITRO FERTILIZATION

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ABSTRACT

Aim: To investigate the effectiveness of transdermal androgel before using controlled ovarian stimulation on patient undergoing IVF. **Objective:** To investigate the effectiveness of treatment with transdermal testosterone gel (TTG) 1%(androgel) before ovarian stimulation (COS) using GnRH antagonist in low responders undergoing IVF/intracytoplasmic sperm injection (ICCSI)s **Design:** prospective randomized controlled trial. **Setting:** Aarogya hospital (IVF CLINIC) Delhi/ vaishali. **Study:** A total of 60 low responder, who were defined as patient 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 in a previous failed IVF/ICSI cycle from 1.1.17 to 31.3.18 (15 months). **Intervention(s):** Patient were randomized into TTG pretreatment group and control group. Fot TTG pretreatment group, 12.5mg TTG were applied daily for 21 days in the cycle preceding COS for IVF. **Main outcome measure(s):** COS result and IVF outcome. **Result:** There were no differences in patients characteristics between the two group. Total dose of FSH used were significantly fewer in the TTG pretreatment group than in the control group. The number of oocytes retrieved, mature oocytes, fertilized oocytes, and good quality embryos were significantly higher in the TTG pretreatment group. Embryos implantation rate and clinical pregnancy rate per cycle 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).

Citation: ***Anjali Chaudhary, Umesh Varma, Aditya Varma and Kanika Gupta.*** "The effectiveness of transdermal testosterone gel 1% (androgel) for poor responders undergoing in vitro fertilization*", International Journal of Development Research*, 11, (12), 52850-52855.

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 (2,3). It is one major challenge to treat poor response in assisted reproduction .It has been demonstrated in a number of studies the androgel stimulates the early stage of follicular growth, increasing in the ovarian response to follicle stimulation hormone (FSH). It help increase the number of eggs, obtained embryos and pregnancy rate. Many studies have evidenced that androgel can improve poor response.Our 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 embryos implantation rate among poor responders using topical androgel prior to ovarian stimulation.

MATERIALS AND METHODS

Sample Selection: Sixty patients were selected in the study. The criterion for selection was that these patient have either history or probability of poor ovarian response by antral follicle count (AFC<5-7 follicles) or anti-mullerian hormone (AMH) <1.26ng/ml). Those with systemic pathology, uterus and ovarian disease, and those applying for ovum were excluded.

Study design: the selected 60 patients were randomly categorized into two group: (i) group I included 30 patients, prescribed to use 12.5mg androgel 1% gel prior of ovarian stimulation from day 6th of the previous to day 2nd of the stimulated menstrual period, and (ii) group 2nd includes the remaining 30 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 from day 6th FSH.

Once there were at least two follicles of more than 17mm size, the patients were to use HCG to stimulate ovulation (inj ovitrelle 250). The ova were obtained by means of aspiration under ultrasound guidance about 34-35hrs after HCG injection. 2-3 embryos were transferred into the uterus on D3.Luteal support was provided by administering 90mg vaginal progesterone gel (crinone gel 8 %) from day of ET.

The studied indicators include:

1. Number of follicles on the day of HCG injection
2. Number of over-17mm sized follicles on the day of HCG injection
3. Number of oocyte aspired
4. Number of M ll oocyte
5. Number of fertilized ova
6. Number of embryos, the emrbyo quality
7. Number of embryos transferred
8. Chemical pregnancy rate
9. Embryo implantation rate
   Fourteen days after embryo transfer, patient were to test the blood B-HCG:
   - Biochemical pregnancy: by 14 days after embryo transfer, b-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 embryo transferred.

Average age	32.7±3.42	33.4±2.96	0.25
Infertility duration (years)	5.2±3.91	6.1±3.52	0.67
AMH (ng/ml)	0.82±0.46	0.86±0.46	0.13
FSH (MIU/ML)	9.8 ±4.1	10.1±3.7	0.35
LH (MIU/ML)	5.5±1.2	4.9±2.1	0.22
E2 (PG/ml)	49.1±14.6	42.2±20.3	0.46
AFC (antral follicle count) (follicle)	5.8±1.7	5.9 ± 1.6	0.17
FSH injection days	9.2±0.6	9.9±0.7	0.11
Total FSH dose (MIU/ml)	1680 ± 341.6	1722±362.1	0.41
Average FSH dose (MIU/ml)	186.6±50.8	191.3±62.7	0.54
Days of GnRH antagonist	4.4±0.8	4.9±1.2	0.00
Uterus lining on the day of HCG	9.2±1.8	9.0 ± 1.45	0.24
The number of 14- to <17-mm sized follicles	3.1 ± 1.9	2.9±2.0	0.59
The number of ≥17-mm sized follicles	5.2 ±1.7	4.8±2.1	0.2
The number of post aspiration oocytes	5±1.6	4 ± 1.1	0.00
Number of grade I & II embryos	2.2±1.4	1.3±0.8	0.00
The number of embryos	4.1±1.6	2.5 ± 1.1	0.00
The number of embryos transferred	2.6±0.6	2.1±0.8	0.00
The number of frozen embryos	1.8±0.3	0.5±0.3	0.00

Clinical and preclinical characteristics of the two groups

- **Result** $\frac{result\ (x \pm sd)}{group1 \qquad group2 \qquad p}$

Statistical analysis: The study was conducted from 1.1.17 to 31.3.18. Values were expressed as mean +_ SD. A student t test was used to compare the mean value. 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 window, version 11.0 (SPSS, Chicago, IL). Androgel 1% gel: drug information and usage- Androgel 1% gel is manufactured by basins healthcare (Brussels, Belgium). Ingredients; testosterone 50mg, which is natural testosterone, 100% biologically similar to testosterone secreted by human body. Packaging: 01 packet of 30 gels, each 5g gel contain 50g testosterone. Usage: the gel in applied on the inner upper arms (dry, clean, and intact skin), it should be used at night. The dosage is a quarter of a gel, which is approximately 12.5mg testosterone. The patient must take the full gel into a syringe and apply a quarter of the amount the skin, then leave it to dry in 3-5 min. Hand washing is required after applying the gel. Side effects: Possible adverse effect to TTG include acne, facial hair growth voice deepening, and skin irritation on application sites. Long – term effect of TTG remain unknown, in the parents study, TTG, medication was well tolerated by all patient.

RESULTS

Clinical and preclinical characteristics of the two groups were similar in age, duration of the infertility, basic endocrine test result, 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. The average numbers of both 14-17mm sized follicles (3.1+/-1.9) and over -17mm sized follicle (5.2+/-1.7) in group 1st were higher than those in group 2nd (2.9+\-2.0)and (4.8+/-2.1 respectively). Of which the number of over 17mm sized follicles of group 1st of was found higher than that of group 2nd which statistical significance (p<0.05). M 2nd oocytes accounted for the most in both groups, with 163 oocytes (89.6%) in group I and 118 oocytes (81.3%) in group 2nd the number of M 1st oocytes was 15 in group 1 (8.2%) and 21 in group 2nd (14.4%) the number of both M1&M 2oocytes in group 1st were higher than those in group 2nd statistical significance (p-<0.05). the number of germinal vesicle (GV) oocytes was the least, with 4 oocytes (2.2%) in group 1st and 6 oocytes (4.1 %) in group 2nd . however, there was no significantly statistical between the two group in terms of the number of GV IVF result shows that there statistically significant differences between two group in terms of the number of post aspiration ooccytes the number of embryos. Embryos transferred and frozen embryos (p<0.05). The embryo implantation rate in group 1st and 2nd was 16.47% (14/85) and 9.7% (7/72), respectively. The number of clinical pregnancy cases in group 1st 10/30 (33.3 %) while that in group 2nd was only 6/30 (20%) cases. The embryos implantation rate and clinical pregnancy rate in group 1st were found statistically higher than those in group 2nd (p<0.05).

Table 2. Classification of matured oocytes

$\frac{result - n(\%)}{group\ 1 \qquad group\ 2 \qquad p}$

Indictor:

MII (metaphase 2)	163 (89.6%)	118 (81.3%)	0.02
MI (metaphase 1)	15 (8.2%)	21 (14.4%)	0.04
GV (germinal velcle)	4 (2.2%)	6 (4.1%)	0.35
Total	182	145	-

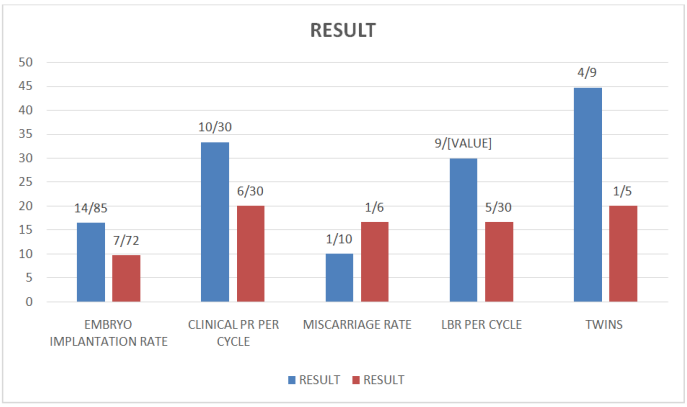
DISCUSSION

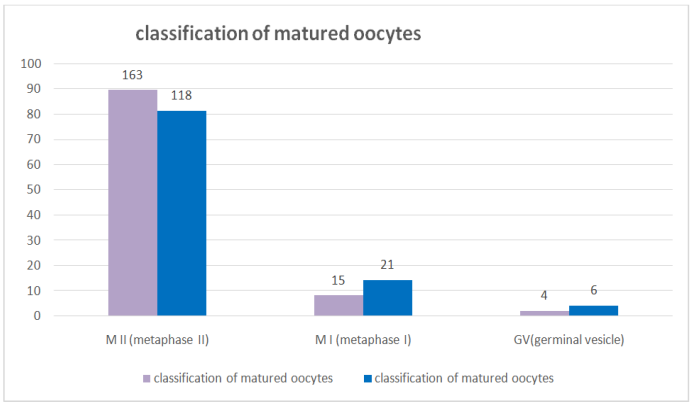
The study aimed to evaluate the effectiveness of transdermal androgel on follicles, embryos and IVF result of low ovarian responders; therefore, patient selected to participate in the study were those with characteristics affecting their ovarian response, such a age, cause of infertility, AMH test result , FSH, LH,E2, AFC , 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 ofclinical and preclinical characteristic prior to intervention

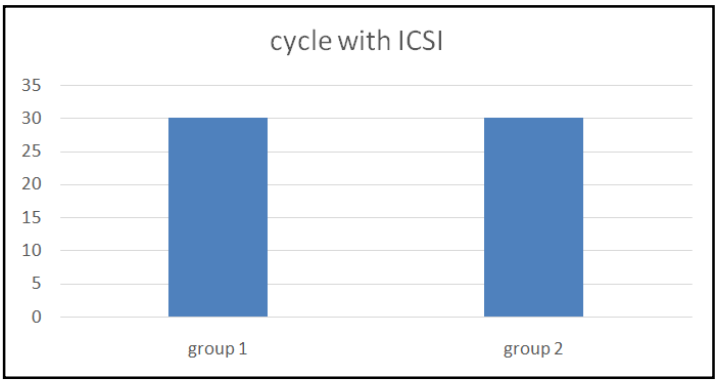
The result of ovarian periods of the two group in the study were evaluated by using the following: the number of follicles observed by ultrasound on the day of HCG injection, the number of oocytes obtained after aspiration, the rate of matured oocytes, the number

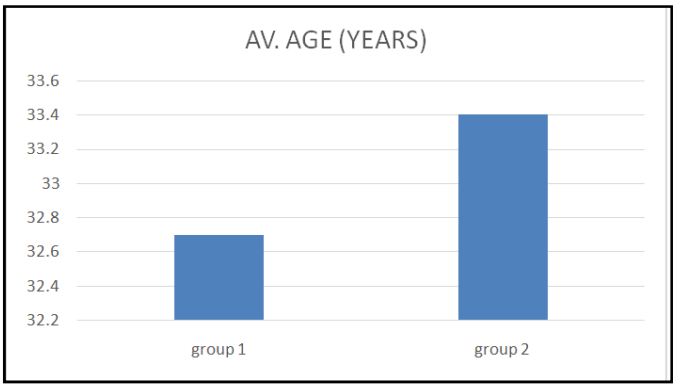
Table 3. Comparison of controlled ovarian stimulation result and IVF/ICSI outcome

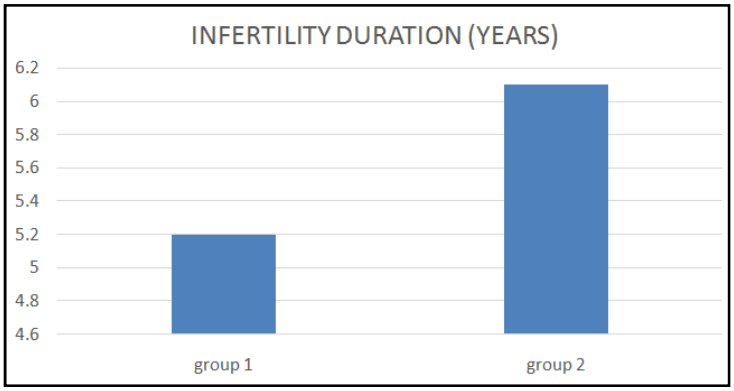
	(GROUP I)	GROUP I %	GROUP II	GROUP II %	P VALUE
Embryo implantation rate	14/85	16.47	7/72	9.7	.019
Clinical PR per cycle	10/30	33.3	6/30	20	.04
Miscarriage rate	1/10	10	1/6	16.6	NS[a]
LBR per cycle	9/30	30	5/30	16.6	.057[a]
Twin PR per clinical pregnancy	4/9	44.7	1/5	20	NS[a]

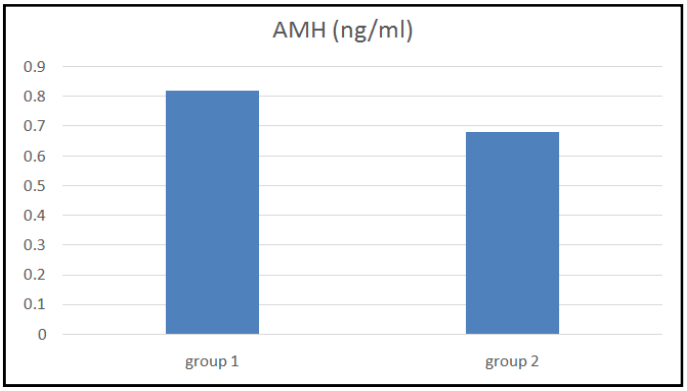








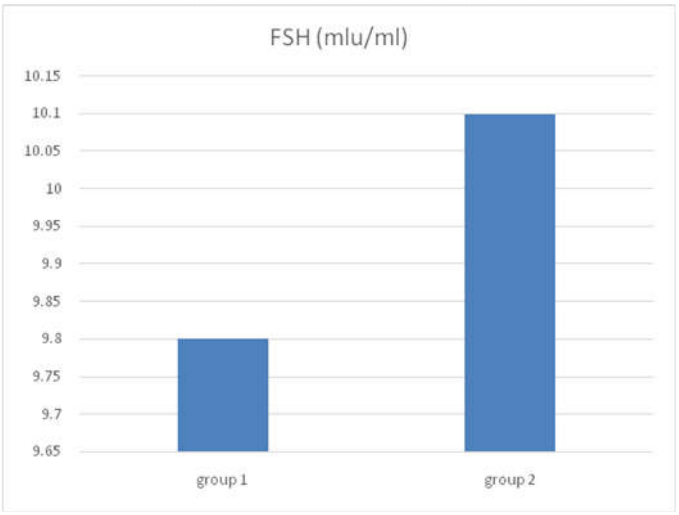


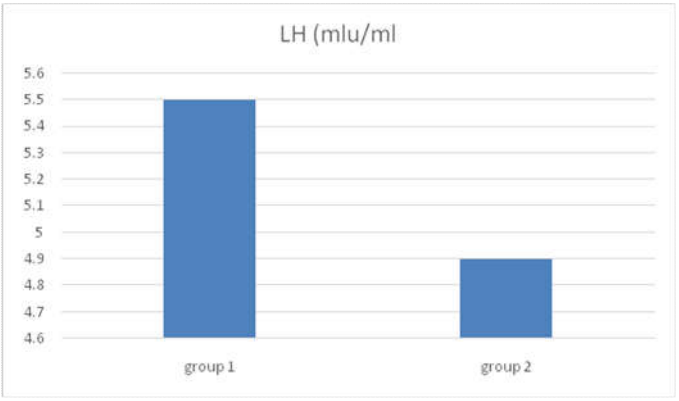


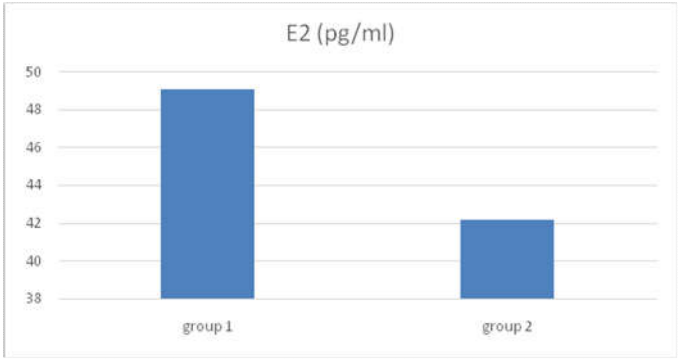
of obtained embryos, and the number of transferred embryos and frozen embryos, it was revealed that all of those indicators were found higher in group I, which was prescribed to use transdermal androgel prior to ovarian stimulation, than in group 2nd which did not use transdermal by pregnancy rate and embryo implantation rate was statistically significantly higher in group I than in group 2nd.

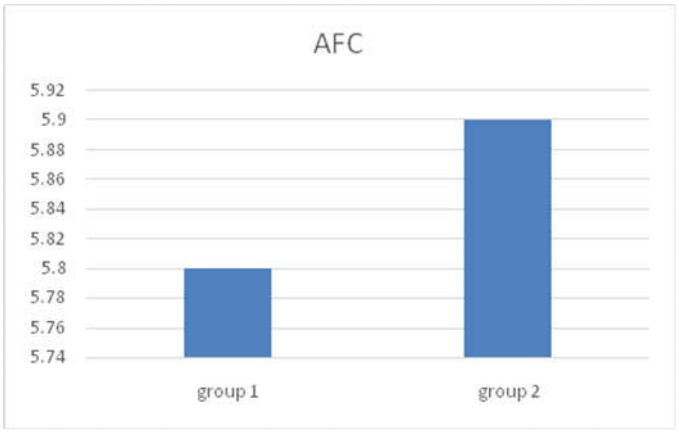
LITERATURE

These result 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 20ug/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 transdremal testosterone gel before controlled ovarian stimulation by two group, one prescribed with transdermal testosterone (group 1st) and the other not (group 2nd). It was found that the both the number of obtained oocytes and the number of embryos and clinical pregnancy in group I was also higher than those in group 2nd, with statistical significance for the latter ($p<0.05$). Nagels et al. study the impact for androgelon 1496 reproduction assisted woman with low ovarian response the result showed that low responders using testosterone prior to treatment could have higher pregnancy rate and survival rate. [7] nagels et al. continued studying further and androgel, conforming the positive impact of androgel on low ovaries responders[8].

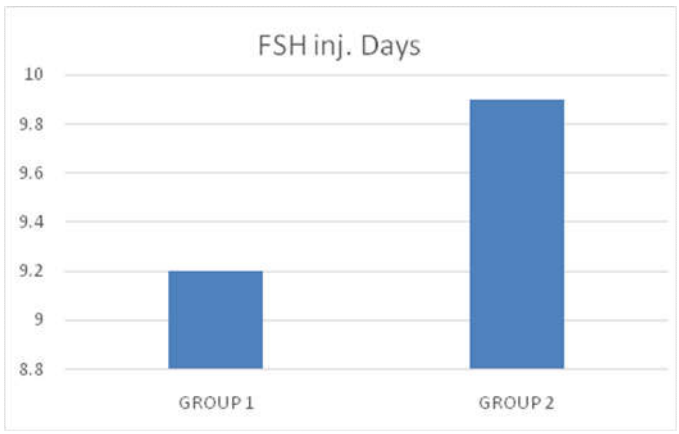


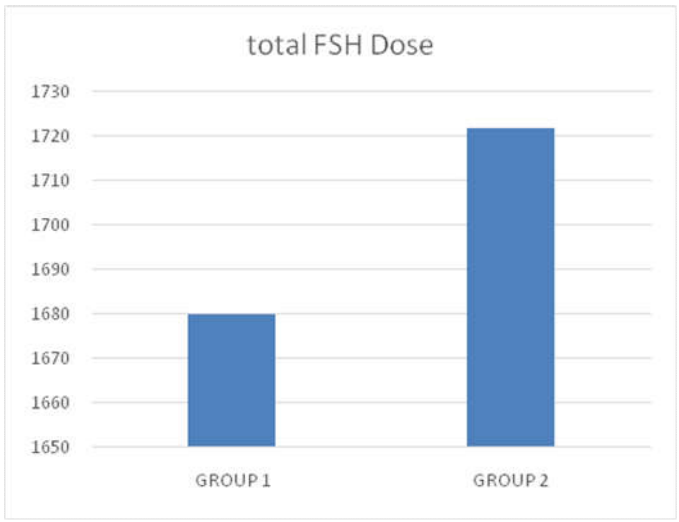


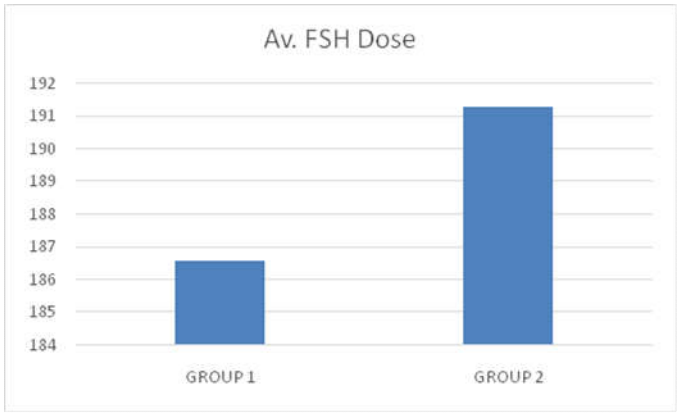


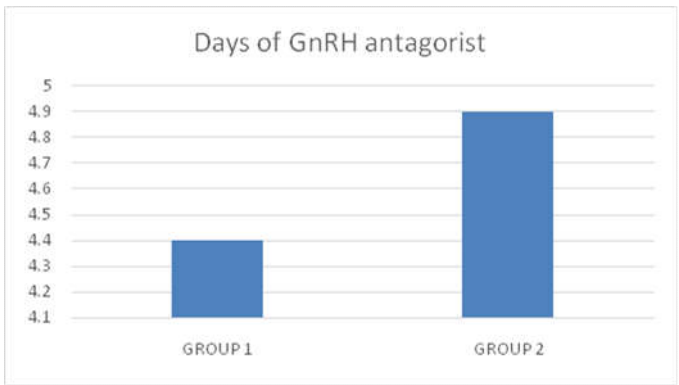


Fabregues et al. applied randomized clinical trial to study the impact of impact of transdermal on 62 women with history of canceled period due to low ovarian response. It was concluded that testosterone could improve the ovarian response with FSH increase that number of obtained eggs, and decrease the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

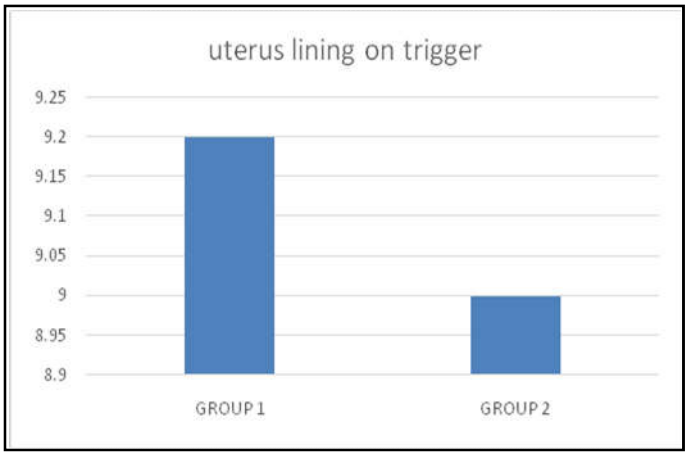


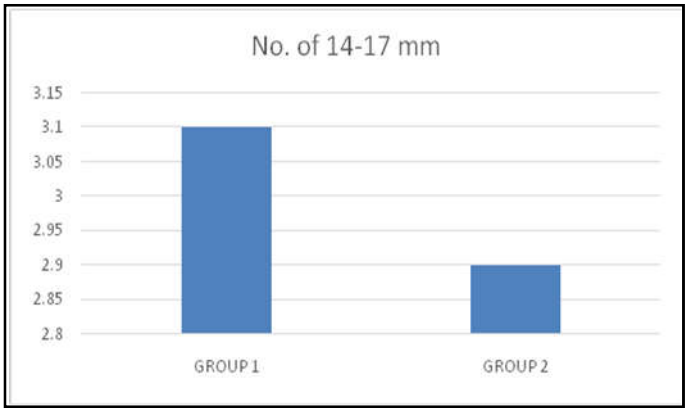


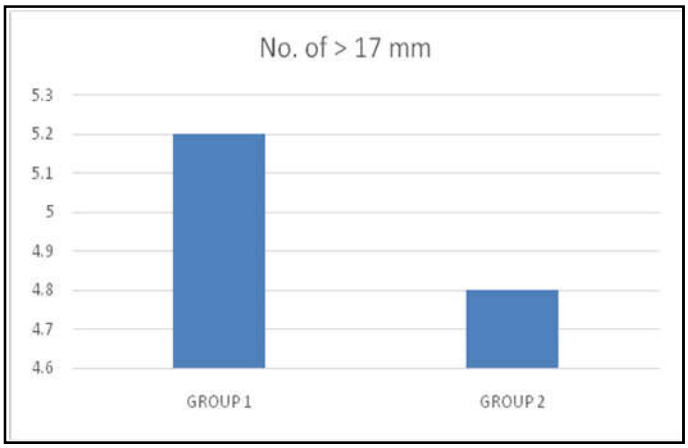


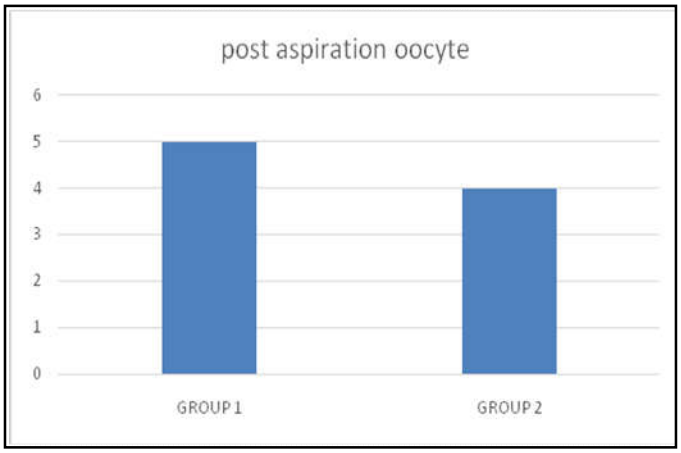


It was demonstrated in various studies that only secondary follicles with the largest number of FSH receptors could continue to grow into dominant ones that ovulate. Other secondary follicles would degrade due to the lack of FSH.

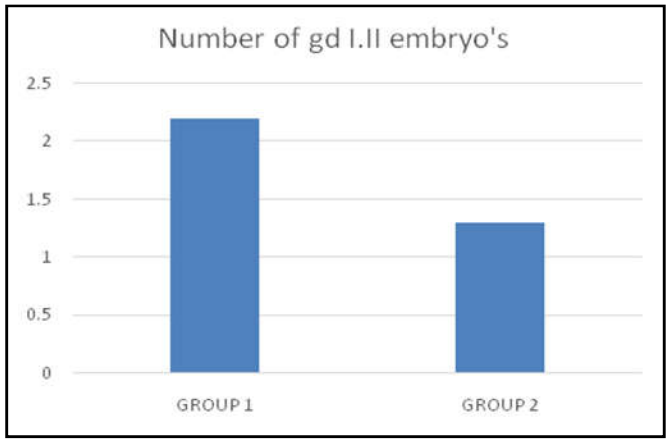


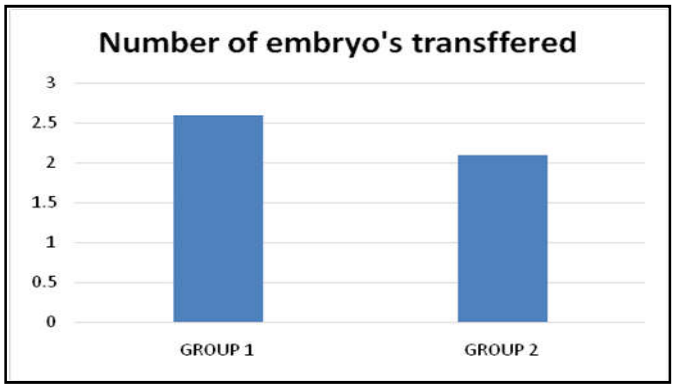


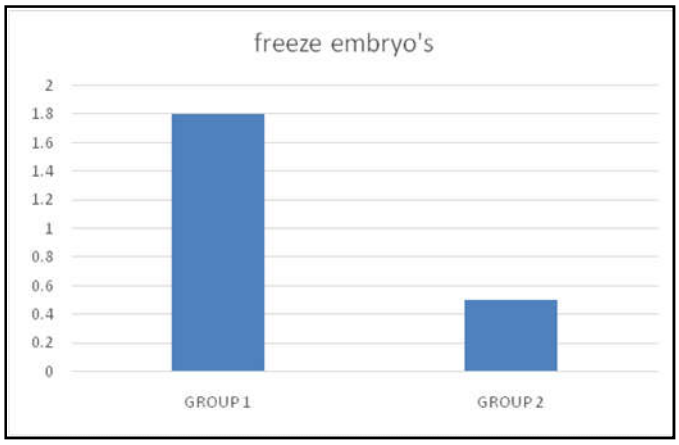




The supplement of androgel before ovarian stimulation could improve the impact of FSH on the ovary [9,10] which when increase the number of follicles overcoming FSH selection step, increasing the number of dominant follicles of ovulate, and improving pregnancy rate.







CONCLUSION

In conclusion, the study result showed the using transdermal androgel prior to ovarian stimulation could increase the number of oocytes and embryos, the rate of pregnancy, and embryo implantation among IVF patient with low ovarian response. However larger studies with standardized method will be needed for confirmation of our conclusion . In contrast to oral androgel therapy, percutaneous route does not produce supraphysiological hepatic concentrations of the steroid, because first – pass metabolism in the liver is prevented. Therefore, androgel treatment using TTG is mostly safe. Moreover application of TTG is easy, convenient, and cost effective. The management for low responders with diminished ovarian reserve is still a challenge, although many studies have been under taken to seek a method of efficient COS for infertile woman with reduced ovarian reserve. Although oocyte donation is a very successful alternative treatment for infertile woman with diminished ovarian reserve, effort must be made to maximize each patients potential to use her own oocytes.

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