IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 20, Issue 7 Ser.8 (July. 2021), PP 25-29
www.iosrjournals.org

Pretreatment with Transdermal Testeosterone Gel in Poor Responders and Their IVF Outcomes.

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Abstract:
Introduction - *The poor response to ovarian stimulation among women undergoing IVF is of great concern in reproductive medicine. The reported incidence of poor response varies from 9% to 26%.Certain modalities have been tested through randomized trials to improve the response to gonadotropin stimulation and thus reproductive outcomes such as transdermal testosterone and DHEA, and the duration of the treatment. The present study focused on the intervention of transdermal testosterone administration, which achieves powerful systemic androgenization and subsequently, a greater action of FSH.*
Aims and Objectives - *We performed a study to investigate the effect of pretreatment with transdermal testosterone gel on controlled ovarian stimulation and analyzed their IVF outcomes with regard to the ovarian morphology in poor responders.*
Materials and methods - *Total of 50 women were taken for this study. They were categorized into control group, post 2 week treatment and one month treatment groups. A 12.5mg of transdermal testosterone gel was applied daily for 15 days and one month in the previous cycle of stimulation.*
Results - After 14 days of TTG pretreatment a significant increase of antral follicle count and a decrease in mean follicular diameter was noticed. The total dose of FSH administered for controlled ovarian stimulation was also seen to be decreased in all groups. The no.of oocytes retrieved and mature oocytes were higher after the pretreatment with TTG. The clinical pregnancy rate and live birth rate were increased only in the one month TTG pretreatment group than the control group.
Conclusion - *The data demonstrated that TTG treatment for one month increases antral follicle count and ovarian stromal blood flow, therefore improving the ovarian response to controlled ovarian stimulation and IVF outcomes in poor responders undergoing either IVF or ICSI.*
Keywords :*IVF , TRANSDERMAL TESTOSTERONE GEL, POOR RESPONDERS , CONTROLLED OVARIAN STIMULATION.*

Date of Submission: 02-07-2021 Date of Acceptance: 16-07-2021

I. Introduction

There are many causes for infertility but by far the most complicated and challenging one, as been proved to be poor ovarian reserve for an infertility specialist. In the past years, many theories has been formulated to define poor ovarian reserve but the most significant and simplified classification of them all is the BOLOGNA criteria and the POSEIDON criteria.

These criteria's helped us formulate a concept of prognosis for the management of the patient undergoing assisted reproductive technologies. It was mainly based on the patients age, antral follicle count and the antimullerian hormone levels . Based on which they were categorized into group 1 and 2 as the suboptimal responders and group3 and 4 as the low responders. The suboptimal responders had a good prognosis verus the low responders had a poor prognosis. Basically this categorization helped in personalized treatments, providing a better success rates of the IVF cycles.

Poor ovarian response to controlled ovarian hyperstimulation (COH) remains a major problem in assisted reproduction. Although no clear definition has been agreed, poor ovarian response in the context of in vitro fertilization (IVF) treatment is usually defined as failure to achieve ≥3 oocytes or a certain estradiol concentration in response to ovarian stimulation.

A variety of stimulation regimes have been used for the management of low responders in the post.Most prevalent regimes for treating them at present are GnRH agonist and GnRH antagonist protocols ,unfortunately none of these protocols has been effective in improving ovarian response and IVF outcomes in poor responders.

Reproductive plans are often delayed and the proportion of patients with POR has become massive. Different pharmacological approaches have been proposed to improve the outcomes of IVF treatment but none

have been established with certainty. In recent decades, there has been an increased interest in the role of androgen supplementation while undergoing IVF.

Androgens and their ovarian receptors have been shown to play an important role in ovarian physiology and follicular growth by numerous studies. Recently, clinicians have attempted to improve the ovarian response in poor ovarian responders by using androgens or androgen modulators prior to in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) treatment.

Thereafter, a series of studies of patients with POR reported that dehydroepiandrosterone (DHEA) supplementation not only improves oocyte yield but also positively affects the egg and embryo quality and IVF pregnancy rate (PR).

In primate ovary, androgens stimulate early stages of follicular growth and primate experiments suggest that androgens may influence the responsiveness of ovaries to gonadotropins and may amplify the effects of FSH on the ovary.

Hence this study of small group of patients with poor ovarian response were taken and a randomizied clinical trial was conducted with transdermal testosterone gel , to see the effects of it in poor responders and their IVF outcomes.

II. Methods and materials :

Total of Fifty poor responders fulfilling the Bologna criteria were taken for this study. We did a randomized prospective, controlled single blind study. The study was conducted at an IVF Unit at an hospital for women health , Chennai , from 02/2019 until 11/2019. Patients were allocated to either testosterone pretreatment with 12.5mg of transdermal testosterone gel for 30 days or 15 days or no pretreatment, according to a computer-generated randomization list. Physicians and embryologists involved in oocyte retrieval and embryo culture were not aware of patient allocation. Patients could participate in the study only once.

Inclusion criteria :
Patients had to fulfill at least two of the three Bologna criteria :

(i) advanced maternal age (≥40 years) or any other risk factor for POR,
(ii) a previous POR (≤3 oocytes with a conventional stimulation protocol),
(iii) an abnormal ovarian reserve test (i.e. AFC < 5–7 follicles or AMH < 0.5–1.1 ng/ml).

Exclusion criteria :

(i) body mass index (BMI) of ≥32 kg/m^2
(ii) endometriosis stage III-IV,
(iii) history of previous ovarian surgery,
(iv) endocrine or metabolic disorders
(v) use of sperm from testicular sperm extraction,
(vi) fine needle aspiration or cryopreservation.

All patients underwent a long follicular protocol with GnRH agonist 3.75 mg depot, starting on the first day of the menstrual cycle, followed by daily injections of GnRH antagonist 0.1 mg, if necessary. In the testosterone group, a daily dose of 12.5 mg of testosterone gel was applied transdermally onto the inner arm daily, for 30 days or 14 days.

Ovarian stimulation with FSH (Gonal-F) was started depending on the antral follicular count. Patients in the no pretreatment group underwent the same protocol without receiving, however, testosterone pretreatment. Triggering of final oocyte maturation was performed using 250 µg of recombinant HCG (Ovitrelle), as soon as at least two follicles reached 20 mm in diameter or if this was not possible, when the maximum number of follicles were present. Oocyte retrieval was performed by ultrasound-guided transvaginal follicular aspiration 36 h after HCG administration. Intracytoplasmic sperm injection was performed in all patients. A maximum of 2 embryos were transferred in women less than 40 years of age and a maximum of 3 embryos were transferred in women more than 40 years of age on either day 3 or day 5 of in vitro culture.

Luteal phase was supported by administration of micronized progesterone starting on the day of oocyte retrieval and continued up to the day of pregnancy test or in case of a positive test until the twelfth week of pregnancy.

All patients were tested for Sr Testosterone, Sr FSH, Sr LH, DHEA, SHBG(sex hormone binding globulin) and AMH . patient eligible for testosterone treatment were those with SHBG value less than 80 nmol/L , Testosterone less than normal range and DHEA within normal range.

All hormones were tested pre treatment.

The outcome measures included the no.of antral follicles, oocyte count , no .of mature m2 oocyte, fertilization rate and no.of cancelled cycles. Fertilization rate was calculated by the no.of fertilized oocytes . embryo quality was assessed by the morphological criteria based on the assessment of stages of embryo and the quality of blastomeres along with their degree of fragmentation. Clinical pregnancy was assessed by the presence of intrauterine sac.

III. Results :

All 50 patients were divided into 2 groups:

1. 25 patients with pre treatment of transdermal testosterone for 2 weeks and
2. 25 patients with pre treatment of transdermal testosterone for 4 weeks.

The main baseline characteristics of all patients were very similar including the hormonal levels, age, BMI , duration and reason of infertility .A significant improvement was reached in the hormonal levels such as in testosterone and DHEA counts. No difference was detected in AMH,LH,FSH levels. However, there was an increase in the AFC between the groups noted, which increased the oocyte count and quality of the oocyte. Total no of Mature M2 oocytes retrieved in group 2 was more than that of group 1 , group 1 was more than that of patient with no pretreatment. The analysis showed an improvement of the fertilization rate in the study group . In the TTG pretreatment , 2 cycles was canceled before embryo transfer, because in 1 cycle no oocytes were obtained in spite of a follicular aspiration for oocyte retrieval. In 1 out of 50 cycles in which oocyte retrieval was performed, no oocyte was obtained and in 1 out of 50 cycles there was thin endometrium for which the cycles were canceled. There was no significant difference in overall cycle cancellation rate between the TTG pretreatment groups. Total days and dose of recombinant FSH required for COS were significantly lower in the TTG pretreatment group. The duration of administration of GnRH antagonist administration was shorter in the TTG pretreatment group. The embryo implantation rate was higher in the TTG pretreatment group. The clinical pregnancy rates per cycle initiated and per cycle ET were higher in the TTG pretreatment group. The live birth rate per cycle initiated was higher in the TTG pretreatment group. No patient reported any local or systematic side effects with the transdermal treatment of testosterone application.

IV. Discussion:

This was a prospective randomized study to evaluate the effectiveness of pretreatment for 4 weeks and 2 weeks with transdermal testosterone gel for low responder before undergoing icsi cycles with Gnrh antagonist protocol. This study showed that pretreatment with TTG can increase AFC, no of oocytes retrieved, no of fertilized oocytes and grade 1 &2 embryos and the clinical pregnancy rates. It also showed that the days and amount of rhFSH required for follicular maturation can be reduced in low responders prior to ICSI cycles. Pretreatment of poor ovarian responders with androgen(testosterone) or androgen-modulating agents (letrozole) has been a popular topic for debate for many years, with one other systematic review already published in this area. Experimental studies (5–7) demonstrated that treatment with testosterone increased FSH receptor expression in granulosa cells, promoting the initiation of primordial follicle growth and improving the number of growing preantral and small antral follicles in rhesus monkeys. These studies suggested that androgen treatment may amplify the effects of FSH in the ovaries. There was also a positive correlation between serum testosterone level and the number of oocytes retrieved. females with higher baseline levels of testosterone required a lower FSH dose, a shorter duration of ovarian stimulation and were more likely to achieve a pregnancy than females with lower testosterone levels.

Poor ovarian responders taking IVF/ICSI treatment often face a high risk of cycle cancellation due to few oocytes or good quality embryos being obtained. Thus, the number of oocytes retrieved, clinical pregnancy rate and the live birth rate per cycle initiated were the primary outcomes to be considered when evaluating the curative effect of any treatment. The current study demonstrated that pretreatment with transdermal testosterone was able to effectively improve the clinical outcomes of poor ovarian responders.

The results confirmed the effectiveness of transdermal testosterone in improving the ovarian reactivity of poor ovarian responders. The current systematic review provided evidence that pretreatment with transdermal testosterone prior to IVF/ICSI cycles may improve the clinical outcomes of poor ovarian responders.

A potential role of androgens in folliculogenesis has been suggested by several authors. However, the positive effect of increasing the androgen availability in the ovary and its precise biological role, particularly among women with poor ovarian reserve remain to be clarified.

This potential stimulatory role of androgens in follicle cell proliferation and basal follicular growth has been investigated in both animal and human models. In rodents, treatment with testosterone or dihydrotestosterone led to alterations in the cell cycle of granulosa cells and follicular atresia. Conversely, studies in primates showed that treatment with testosterone resulted in a marked increase in the number of

growing follicles and the proliferation of granulosa and thecal cells, as well as a reduction in granulosa cell apoptosis.

Interestingly, this latter group revealed the selective colocalization of the mRNA of androgen receptor and FSH receptor within the growing follicles. They demonstrated a significant positive correlation between these two receptors at the mRNA level in individual follicles and observed increased levels of FSH receptor mRNA in granulosa cells after androgen supplementation. Recently, observed a response in women that was consistent with these findings. These data suggest that androgens enhance follicle responsiveness to FSH, particularly in early antral stages of folliculogenesis, and could to some extent explain the hypersensitivity to gonadotropin stimulation observed in women with polycystic ovarian syndrome.

Taking into consideration that granulosa cells express androgen receptors at early stages of folliculogenesis and that these stages of follicle maturation occur weeks to months before ovulation, it would be reasonable to assume that prolonged androgen supplementation would be associated with an increased pool of follicles available for gonadotropin stimulation and thus a larger pool of the oocytes available for retrieval, although side effects should also be considered. This assumption would involve particularly the two drugs that exert their effects through systemic androgenization, i.e. testosterone and DHEA, and that have been tested among poor responders and analysed in previous meta-analyses, which appear to improve reproductive outcomes.

Apart from this, if it is assumed that androgens have this synergistic effect with FSH on folliculogenesis, the pretreatment of poor responders with androgens during an IVF cycle could not only enhance the number of growing follicles but could also reduce the dose of exogenous FSH required. Interestingly, the results from this meta-analysis show that women pretreated with transdermal testosterone required significantly lower amounts of FSH compared with the control group (RR −461.96, 95% CI −611.82 to −312.09), which in turn, could facilitate adherence to gonadotropin administration and thus improve reproductive outcomes.

Despite this possible increased sensitivity to FSH observed among women in the intervention group, no differences were detected in the number or quality of oocytes retrieved, the fertilization rate or the concentrations of estradiol reached during gonadotropin stimulation, although these results showed some level of heterogeneity ($I^2 \geqslant 25\%$). Conversely, the clinical pregnancy rate and clinical pregnancy per embryo transferred were greater among women that were pretreated with transdermal testosterone compared with the control group (RR 2.07, 95% CI 1.13 to 3.78 and RR 1.72, 95% CI 0.91 to 3.26, respectively). However, when the clinical pregnancy rate was adjusted per embryo transferred, differences among the two groups were not statistically significant. These results must nonetheless be interpreted with caution, since original data regarding the total number of embryos transferred was not published and thus clinical pregnancy per embryo transferred was calculated from secondary variables.

The current study has several potential limitations that need to be considered.

In conclusion, there is evidence from randomized controlled trials to support the use of transdermal testosterone prior to ovarian stimulation in women who are considered poor responders, and this treatment has shown to significantly improve live birth rates and reduce the doses of FSH required for ovarian stimulation. The exact subgroup of poor responders who would benefit from this treatment still needs to be identified. However, the result should be interpreted with caution because of the small number of trials and their clinical heterogeneity. Although trends in all parameters appear to favour testosterone supplementation, further investigations are needed to confirm these findings.

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