The Follicular Output Rate (FORT) as a method to evaluate transdermal testosterone efficacy in poor responders

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ABSTRACT
Objective: Follicular Output Rate (FORT) is an efficient quantitative and qualitative marker of ovarian responsiveness to gonadotropins. Transdermal testosterone (TT) has been used as adjuvant therapy to gonadotrophins in order to improve ovarian response in poor responders (PR). The aim of this study was to analyze whether TT can improve follicular sensitivity to gonadotropins using FORT.

Methods: This retrospective study, held in a tertiary-care university hospital included 90 PR patients, according to the Bologna criteria. Patients in Group 1 (n = 46) received transdermal application of testosterone preceding gonadotrophin ovarian stimulation under pituitary suppression. In Group 2 (n = 44) ovarian stimulation was carried out with high-dose gonadotrophin in association with minidose GnRH agonist protocol. We analyzed ovarian stimulation parameters and IVF outcomes. We determined antral follicle count (AFC) (3-8 mm) before ovarian stimulation, pre-ovulatory follicle count (PFC) (16-22 mm) and the day of hCG administration. We calculated the FORT using the PFCx100/AFC ratio.

Results: Baseline characteristics and ovarian reserve parameters were similar in both groups. FORT and oocytes retrieved were significantly higher in group 1 vs group 2. There were no significant differences in pregnancy rates. In group 1 there was a significant correlation between FORT and AFC.

Conclusions: This study suggests that the potential beneficial mechanism of TT in poor responder patients may be based on increasing the antral follicle sensitivity to gonadotrophin. FORT is an excellent tool to demonstrate this.

Keywords: Follicular Output Rate, Transdermal testosterone, Poor responder, ovarian stimulation

INTRODUCTION
The management of poor responders (PR) is a major challenge in IVF. Various stimulation regimens and interventions have been proposed for improving pregnancy outcomes in PR. These also include several adjuvant therapies such as androgen supplements (dehydroepiandrosterone and testosterone) and GH (Ubaldí et al. 2014, Ata & Selli, 2015, Kamath et al., 2019). Most of the Randomized Clinical Trials (RCT) evaluating these clinical add-ons had poorly reported methodologies, small sample sizes, or were at risk of bias. The conclusions for almost all the clinical adjuncts is the need for robust, well-designed RCTs to address both clinical and cost-effective parameters of the interventions. Although all of these adjuvant therapies provided promising results in initial studies, their efficacy has not been solidly demonstrated in RCT studies. The challenge in conducting an adequately powered RCT is the sample size. To show an improvement of 5% in LBR with 80% power after an intervention, a sample size of more than 2,000 participants is needed, which would be difficult to recruit even in large centers (Kamath et al., 2019).

According to results obtained in animals, it is possible that androgens exert a facilitating role in follicle responsiveness to FSH, which leads to an increase in the number of growing follicles (Weil et al., 1999; Vendola et al., 1998; 1999). A simple method to evaluate these effects is controlled ovarian hyperstimulation (COH); however, ovarian response to COH is quantitatively influenced by the pretreatment amount of small antral follicles.

To overcome this difficulty, an objective index to assessing antral follicle responsiveness to exogenous FSH, the Follicular Output Rate (FORT) is being developed (Genro et al., 2011; Gallot et al., 2012; Grynberg & Labrosse, 2019). FORT is calculated based on the ratio between the number of preovulatory follicles obtained in response to FSH administration and the preexisting pool of small antral follicles. Hence, in case of androgen pretreatments, FORT constitutes an interesting clinical strategy to check whether the ability of antral follicles to respond to exogenous gonadotropins has been improved (Fanchin et al., 2011).

The aim of this study was precisely to assess whether transdermal testosterone was able to improve FORT in poor responders.

MATERIALS AND METHODS
Patients
This study was performed by a retrospective analysis of our database of women referred to our center for IVF, and was conducted from January 2013 to May 2016 in the Assisted Reproduction Unit of the Hospital Clinic in Barcelona (Spain). Before starting the IVF cycle, the patients were suggested to use Transdermal testosterone (TT) as an adjuvant therapy to ovarian stimulation. Two patients rejected this therapy. Review Board and informed consent was obtained from all individual participants, included in the study (HB-15-EL-LS-C). We recruited 90 poor responder patients according to the Bologna criteria (Ferraretti et al., 2011). All the patients were in good normal thyroid, kidney and hepatic health laboratory results, and they had regular menstruation periods with a 21-35 days duration. None of them had taken any infertility medication in the 3 months prior to the study.

We used the long GnRH agonist protocol in all the patients. Group 1 patients were treated with TT preceding ovarian stimulation with gonadotropins, and Group 2 started ovarian stimulation after ovarian arrest was confirmed. (Fig 1).

FORT was calculated as the ratio of pre-ovulatory follicle count (PFC)(16-22 mm in diameter) on dhCG x 100/small antral follicle (3-8 mm in diameter) count.
Figure 1. Schematic representation protocol

at baseline (ovarian arrest day) (Fig 2). We evaluated
the following study parameters: days of stimulation,
pre-ovulatory follicles on the day of human chorionic
gonadotropin (hCG) administration, number of oocytes
retrieved, number of embryos achieved and transferred.
We also assessed pregnancy outcomes, including clinical
and ongoing pregnancy rates.

There was no perimplantation diagnosis in any of the
cycles

Stimulation regimens

We suppressed the pituitary suppression by s.c.
administration of leuprolide acetate (Procrin; Abbott
Laboratories, Madrid, Spain). This treatment was started
in the midluteal phase of the previous cycle and given 1
mg daily, then reduced to 0.5 mg after ovarian arrest
was confirmed, and continued until the administration of HCG.

Group-1 patients started TT on the day when pituitary
suppression was confirmed and the therapy was continued
for 5 days. Transdermal testosterone treatment was
accomplished on a daily single patch with a 2.5 mg/day
nominal delivery rate of testosterone (Testopatch, Pierre
Fabre Iberica SA, Barcelona, Spain), which was applied to
the thigh at night and removed always at 09:00h in the
morning.

This transdermal delivery system maintains
testosterone levels stable within narrow ranges with little
within - and between - subject variation, providing a highly
controllable and reliable way of delivering testosterone,
and the hormonal dose administered can be modified
according to the patch duration (Buckler et al., 1998; De
Sanctis et al., 1998; Mazer, 2000). We chose to use 20 mg/
kg of testosterone per day for 5 days, based on previous
experimental studies in primates (Vendola et al., 1998;
1999). Thus, in each patient, the patch was applied at
night, supposedly left in place for a predetermined number
of hours in order to provide the desired daily dose of
testosterone (e.g. in a woman weighing 60kg and needing
1,200mg/day, the patch was used for 12h [0.1mg/h delivery
rate 12h, 1.2mg or 1200mg], and applied at 21:00h).

We performed the testosterone therapy according to a
routinely used protocol (Balasch et al., 2006; Fàbregues
et al., 2009; 2019).

In Group 2 gonadotropin therapy started after ovarian
arrest was confirmed. In both groups controlled ovarian
hyperstimulation was performed with 300IU per day of
r-hFSH (Gonal-F, Merck S.A., Madrid, Spain) together
with 75IU HMG (Menopur, Ferring S.A., Madrid, Spain).
The criteria for hCG administration (250mg s.c.Ovitrelle,
Serono S.A.) were the presence of two or more follicles
>18 mm in diameter, with >4 follicles measuring
>14mm in association with a consistent rise in serum E2
centration.

The cycle was cancelled when there were less than
3 follicles with diameter >14 mm after 8-9 days of
gonadotropin therapy, or after 4-5 additional treatment
days without attaining, or the imminent prospect of
attaining, the criteria for hCG administration.

Oocyte aspiration was performed under vaginal
ultrasonography 35-36h after hCG administration. Embryo
grading was recorded according to published criteria
(Veeck, 1999); embryos graded 1 or 2 were considered
of high quality. In both groups, embryo transfer was
performed in the cleavage stage (day 3). The luteal phase
was supported with vaginal micronized progesterone
(600mg/day given at 8h intervals) starting on the day
following oocyte aspiration and continuing either up to
menstruation or, if the patients became pregnant, for at
least the first 3 weeks of pregnancy.

Pregnancy was diagnosed by a positive serum β-hCG
test 12 days after ET. Clinical pregnancy was defined
by observation of a fetal heartbeat using transvaginal
ultrasonography upon 5-6 weeks of gestation.

Statistical analysis

Sample size was based on two previous studies from
our group, showing that: (i) multifollicular development
and oocyte retrieval was obtained in 80% of previously
low responders receiving pretreatment with TT and
gonadotrophin ovarian stimulation as used in patients in
Group 1 (Balasch et al., 2006); and (ii) 46% of patients
having their first cycle of IVF cancelled because of poor
follicular response underwent oocyte retrieval in the
second IVF attempt, when treated according to the
approach used in Group 2 (Peñarrubia et al; 2005). The
sample size required to provide an 80% power to detect
this magnitude of treatment effect between groups was
calculated to be a minimum of 31 patients per group, using
a two-tailed analysis with a detection limit of 5%, to avoid
a type I error in hypothesis testing.
All statistical analyses were performed using the SPSS version 23.0 software (Chicago, IL, USA). We used a t-test to compare the mean values between the two different stimulation protocols. Differences in outcome rates were analyzed using an χ² test or the Fisher’s exact test. P < 0.05 was considered statistically significant. The Spearman’s test was used to determine the correlation between FORT and ovarian reserve parameters in patients treated with TT.

RESULTS

As summarized in Table 1, the groups were similar with respect to age, body mass index (BMI), duration of infertility, infertility causes, antral follicle count (AFC), Anti-Müllerian hormone (AMH) levels and basal FSH and estradiol. There were no reported major side effects after testosterone therapy, and both protocols were well tolerated by all patients.

Table 2 shows stimulation parameters and IVF outcomes, and we found that the number of cancelled cycles was similar in both groups (10.9 vs 22.8 %). The duration of ovarian stimulation was significantly shorter in Group 1 when compared with Group 2 (10.2±0.3 vs 11.5±0.2 days). FORT and number of oocytes retrieved were also significantly higher in Group 1 vs Group 2 (73±4.6 vs 55.6±4.1 %); and (4±0.3 vs 3±0.3), respectively. There were no differences in fertilization, implantation and pregnancy rates in both groups.

When we evaluate the correlations between FORT and ovarian reserve parameters in Group-1 patients, there was a significant correlation with AFC (r=0.41; p=0.001). However, this was not demonstrated with age, basal FSH and AMH levels.

DISCUSSION

To our knowledge, this is the first study to analyze the value of FORT in poor responder patients, and specifically in those who have undergone adjuvant treatment with TT in IVF cycles. The Cochrane review on the role of testosterone pretreatment included four RCTs with poor responders (Nagels et al., 2015). Pooling the RCTs showed that pretreatment with testosterone was associated with improved LBR (OR 2.60; 95% CI, 1.30–5.20; 4 RCTs, n =345). However, a sensitivity analysis removing the studies at high risk of performance bias showed no statistically significant difference in LBR between the testosterone and control groups (OR 2.00; 95% CI, 0.17–23.49; 1 RCT, n = 53). These contradictory results could be explained by the different doses used (10 to 12 mg/daily), the way of application (patches or gel) and the pretreatment length (5 to 21 days) (Massin et al., 2006; Fàbregues et al., 2009; 2019; Kim et al., 2011; Doan et al., 2017). Obviously, only a multicenter randomized study with a large number of patients can definitively clarify the true efficacy of this add-on therapy in ovarian stimulation (Polyzos et al., 2018).

The above notwithstanding, in this study we chose to use TT for 5 days on the basis of studies in primates (Vendola et al., 1999), and also reports from previous clinical studies (Balasch et al., 2006; Fàbregues et al., 2009; 2013; 2019). The effects of T on follicular response appears to be mediated by increasing FSH-receptor activity and by stimulating insulin-like growth factor I (IGF-I) (Weil et al., 1999). In studies in subhuman primates, androgen receptor gene expression correlated with follicle growth, and the T treatment significantly increased granulosa cell (GC) FSH receptor messenger RNA (mRNA) (Vendola et al., 1998). In this line, previous studies have shown that just 5 days of T caused a progressively increased level of circulating IGF-1 throughout the ovarian stimulation for more than a week after TT was discontinued, and it has been suggested that increased levels of IgF1 could amplify the effect of gonadotropins in the ovary (Balasch et al., 2006; Meldrum et al., 2013).

Regardless of the controversy that exists regarding the clinical evidence of the androgen therapy usefulness, it is especially interesting to analyze whether there really is a greater capacity of androgens for the sensitization of follicles to the action of gonadotropins. In this sense, FORT is an excellent method to evaluate it (Fanchin et al., 2011).

Interestingly, the number of pre-ovulatory follicles obtained at the end of controlled ovarian hyperstimulation (COH) is not a reliable reflection of antral follicle sensitivity to FSH, as it is greatly influenced by the number of the

**Figure 2.** Follicular output rate = Ratio of pre-ovulatory follicle count on day hCG x 100/antral follicle count
Table 1. Baseline characteristics of poor-responder IVF patients in Groups 1 (TT) and 2 (No TT)

| Variable                      | Group 1 (n = 46) | Group 2 (n = 44) |
|-------------------------------|------------------|-----------------|
| Age (years)                   | 36.8 ± 0.3       | 37 ± 0.3        |
| BMI (Kg/m²)                   | 24 ± 0.5         | 24.2 ± 0.7      |
| Infertility factor            |                  |                 |
| Male factor (n,% )            | 21 (45.6)        | 18 (40.9)       |
| Unexplained (n,% )            | 11 (23.9)        | 10 (22.7)       |
| Tubal factor (n,% )           | 9 (19.5)         | 10 (22.7)       |
| Endometriosis (n,% )          | 5 (10.8)         | 6 (13.6)        |
| Duration of infertility (years)| 5.8 ± 2.7        | 5.6 ± 2.2       |
| Basal FSH (IU/l)              | 12.3 ± 0.5       | 13.2 ± 0.2      |
| Antral follicle count (n)     | 5.4 ± 0.4        | 5.8 ± 0.3       |
| AMH (ng/ml)                   | 0.7 ± 0.3        | 0.9 ± 0.1       |

Values are mean ± SD. Between group differences all non-significant at a 0.05 level of significance.

Table 2. Ovarian response, ovum retrieval and IVF/ICSI outcomes in Groups 1 and 2

| Variable                          | Group 1 | Group 2 | p-value |
|-----------------------------------|---------|---------|---------|
| Patients with hCG and ovum retrieval (n,% ) | 41 (89.1) | 34 (77.2) | 0.3     |
| Days of ovarian stimulation       | 10.2 ± 0.3 | 11.5 ± 0.2 | 0.01    |
| Pre-ovulatory follicle (16-22mm)  | 4.1 ± 1.2 | 3 ± 0.9   | 0.2     |
| FORT (%)                          | 73 ± 4.6  | 55.6 ± 4.1 | 0.01    |
| No. of oocytes retrieved*         | 4 ± 0.3   | 3 ± 0.3   | 0.04    |
| No. of metaphase II oocytes*      | 4 ± 0.3   | 2.8 ± 1.8 | 0.15    |
| No. of 2PN on day 1*              | 3.9 ± 0.1  | 2.4 ± 0.1 | 0.1     |
| No. of embryos obtained*          | 2.6 ± 0.3  | 1.7 ± 0.1 | 0.29    |
| No of embryos transferred*        | 1.7 ± 0.5  | 1.4 ± 0.4 | 0.28    |
| Implantation rate (%)*            | 28.3      | 22.8     | 0.58    |

Values are mean ± SD. *Values are relative to the number of patients with oocyte retrieval.

Several studies have established FORT groups according to tercile values: low (<42%), average (42-58%) and high (>58%) in order to analyze the effective response to FSH and ovarian follicular competence (Gallot et al., 2012; Tan et al., 2019). According to the data from this study, the observed FORT can be considered medium-high (73 ± 4.6 vs 55.6 ± 4.1), and this is in agreement with previous studies in the sense that with ovarian aging, antral follicles do not lose their aptitude to respond to FSH, and probably reveals a compensating mechanism for preserving ovulatory folliculogenesis. (Gallot et al., 2012).

Table 2. Ovarian response, ovum retrieval and IVF/ICSI outcomes in Groups 1 and 2

Taking into account the homogeneity of the studied groups, the significantly higher FORT in Group 1 vs 2 of the study has special relevance. This could also be related to a shorter duration on the days of stimulation and an increase in the number of oocytes obtained. This data agrees with those obtained in other studies (Gallot et al., 2012; Griesinger et al., 2019).

In accordance with previous studies, a correlation between FORT and antral follicle count was also shown in our study (Gallot et al., 2012); however, with AMH levels we did not find an aspect that was reported in other studies (Genro et al., 2011). It has been speculated that the negative correlation between AMH levels with FORT could be related to the possible inhibitory effect of this hormone with the sensitivity of follicles to FSH. However, this aspect has been suggested in patients with normal ovarian reserve but not in low responders.

TT has been used in poor responders with long GnRH agonist and antagonist protocols, finding no differences in terms of pregnancy rate or live birth rate (Fábregues et al., 2019). In this study, we included patients in whom the long agonist protocol was used based on the study sample size being calculated for this protocol.

The main limitation of this study was its retrospective design and small sample size. However, the poor responder


population according to the Bologna criteria represents only a 5 to 10% of patients in most assisted reproduction clinics, which creates logistic problems when performing a prospective study with sufficient power. Although the patients were not randomized, the two populations had similar baseline characteristics, which made it possible to compare IVF outcomes between the groups.

Obviously, the findings of this study should be confirmed by other groups in larger randomized trials, which could shed light on the specific aspect of the sensitizing effect of TT pre-treatment in COH of poor responder patients according to the Bologna criteria.

**CONCLUSIONS**

Despite moderate evidence regarding the efficacy of TT as an adjuvant treatment in ovarian stimulation, this study suggests that the potential beneficial mechanism of TT in poor responder patients may be based on increasing the antral follicle sensitivity to the action of gonadotrophin treatment. FORT is an excellent tool to demonstrate this.

**CONFLICT OF INTEREST**

The author has no conflict of interest to declare.

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**REFERENCES**

Ata B, Seil E. Strategies for controlled ovarian stimulation in the setting of ovarian aging. Semin Reprod Med. 2015;33:436-48. PMID: 26562286 DOI: 10.1055/s-0035-1567818

Balasch J, Fábregues F, Peñarrubia J, Carmona F, Casamitjana R, Creus M, Manau D, Casals G, Vanrell JA. 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. PMID: 16517559 DOI: 10.1093/humrep/dei052

Besow C, Donato R, Souza T, Chajou R, Genro V, Cunha-Filho JS. Antral follicle responsiveness asayed by follicular output Rate (FORT) correlates with follicles diameter. J Ovarian Res. 2019;12:48. PMID: 31128993 DOI: 10.1186/s13048-019-0522-4

Buckler HM, Robertson WR, Wu FC. Which androgen replacement therapy for women? J Clin Endocrinol Metab. 1998;83:3920-4. PMID: 9814469 DOI: 10.1210/jcem.83.11.5280

De Sanctis V, Vullo C, Urso L, Rigolin F, Cavallini A, Caramelli K, Daugherty C, Mazer N. Clinical experience using the Androderm testosterone transdermal system in hypogonadal adolescents and young men with beta-thalassemia major. J Pediatric Endocrinol Metab. 1998;11:891-900. PMID: 10091163

Doan HT, Quan LH, Nguyen TT. The effectiveness of transdermal testosterone gel 1% (androgel) for poor responders undergoing in vitro fertilization. Gynecol Endocrinol. 2017;33:977-9. PMID: 28562099 DOI: 10.1080/09513590.2017.1332586

Fábregues F, Peñarrubia J, Creus M, Manau D, Casals G, Carmona F, Balasch J. Transdermal testosterone may improve ovarian response to gonadotrophins in low-responder IVF patients: a randomized, clinical trial. Hum Reprod. 2009;24:349-59. PMID: 19054777 DOI: 10.1093/humrep/den428

Fábregues F, Iraola A, Casals G, Creus M, Peralta S, Peñarrubia J, Manau D, Cívico S, Balasch J. IVF results following transdermal testosterone in poor responder patients according Bologna criteria. Hum Reprod. 2013;28:i311-56.

Fábregues F, Solernou R, Ferreri J, Guimerá M, Peralta S, Casals G, Peñarrubia J, Creus M, Manau D. Comparison of GnRH agonist versus luteal estradiol GnRH antagonist protocol using transdermal testosterone in poor responders. JBA Assist Reprod. 2019;23:130-6. PMID: 30614665 DOI: 10.5935/1518-0557.201800990

Fachin R, Frydman N, Even M, Berwanger AL, Gynberg M, Ayoubi JM. Androgens and poor responders: are we ready to take the plunge into clinical therapy? Fertil Steril. 2011;96:1062-5. PMID: 22036049 DOI: 10.1016/j.fertnstert.2011.09.050

Ferraretti AP, La Marca A, Fauser BC, Tarlatzis B, Nargund G, Gianaroli L; ESHRE Working Group on Poor Ovarian Response Definition. ESHRE consensus on the definition of ‘poor response’ to ovarian stimulation for in vitro fertilization: the Bologna criteria. Hum Reprod. 2011;26:1616-24. PMID: 21505041 DOI: 10.1093/humrep/der092

Gallot V, Silva AL, Genro V, Gynberg M, Frydman N, Fachin R. Antral follicle responsiveness to follicle-stimulating hormone administration assessed by the Follicular Output Rate (FORT) may predict in vitro fertilization-embryo transfer outcome. Hum Reprod. 2012;27:1066-72. PMID: 22279090 DOI: 10.1093/humrep/der479

Geno VK, Gynberg M, Scheffer JB, Roux I, Frydman R, Fachin R. Serum anti-Müllerian hormone levels are negatively related to Follicular Rate (FORT) in normocycling women undergoing controlled ovarian hyperstimulation. Hum Reprod. 2011;26:671-7. PMID: 21177311 DOI: 10.1093/humrep/deg361

Griesinger G, Teal V, McCrory Sisk C, Ruman J. Comparison of the follicular output rate after controlled ovarian stimulation with daily recombinant follicle-stimulating hormone versus Corifollitropin alfa. Eur J Obstet Gynecol Reprod Biol. 2019;232:101-5. PMID: 30529793 DOI: 10.1016/j.ejogr.2018.11.002

Grynberg M, Labrosse J. Understanding follicular output rate (FORT) and its Implications for POSEIDON criteria. Front Endocrinol. 2019;10. PMID: 30140828 DOI: 10.3389/fendo.2019.00246

Kamath MS, Mascarenhas M, Frank S, Liu E, Sunkara SK. Clinical adjuncts in in vitro fertilization: a growing list. Fertil Steril. 2019;112:978-86. PMID: 31703943 DOI: 10.1016/j.fertnstert.2019.09.019

Kim CH, Howles CM, Lee HA. The effect of transdermal testosterone gel pretreatment on controlled ovarian stimulation and IVF outcome in low responders. Fertil Steril. 2011;95:679-83. PMID: 20801436 DOI: 10.1016/j.fertnstert.2010.07.1077
Massin N, Cedrin-Durnerin I, Coussieu C, Galey-Fontaine J, Wolf JP, Hugues JN. Effects of transdermal testosterone application on the ovarian response to FSH in poor responders undergoing assisted reproduction technique—a prospective, randomized, double-blind study. Hum Reprod. 2006;21:1204-11. PMID: 16476678 DOI: 10.1093/humrep/dei481

Mazer NA. New clinical applications of transdermal testosterone delivery in men and women. J Control Release. 2000;65:303-15. PMID: 10699290 DOI: 10.1016/S0168-3659(99)00252-7

Meldrum DR, Chang RJ, Giudice LC, Balasch J, Barbieri RL. Role of decreased androgens in the ovarian response to stimulation in older women. Fertil Steril. 2013;99:5-11. PMID: 23122826 DOI: 10.1016/j.fertnstert.2012.10.011

Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev. 2015;CD009749. PMID: 26608695 DOI: 10.1002/14651858.CD009749.pub2

Polyzos NP, Davis SR, Drakopoulos P, Humaidan P, De Geyter C, Vega AG, Martinez F, Evangelou E, Van de Vijver A, Smitz J, Tournaye H, Barri P; T-TRANSPORT Investigators Group. Testosterone for poor ovarian responders: lessons from ovarian physiology. Reprod Sci. 2018;25:980-2. PMID: 27489169 DOI: 10.1177/1933719116660849

Peñarrubia J, Fábregues F, Manau D, Creus M, Carmona F, Casamitjana R, Vanrell JA, Balasch J. Previous cycle cancelation due to poor follicular development as a predictor of ovarian response in cycles stimulated with gonadotrophin-releasing hormone agonist-gonadotrophin treatment. Hum Reprod. 2005;20:622-8. PMID: 15608035 DOI: 10.1093/humrep/deh674

Tan X, Wen Y, Chen H, Zhang L, Wang B, Wen H, Zhang F, Wu Q, Du J. Follicular output rate tends to improve clinical pregnancy outcomes in patients with polycystic ovary syndrome undergoing in vitro fertilization-embryo transfer treatment. J Int Med Res. 2019;47:5146-54. PMID: 31379237 DOI: 10.1177/0300060519860680

Ubaldi F, Vaiareli A, D’Anna R, Rienzi L. Management of poor responders in IVF: is there anything new? Biomed Res Int. 2014;2014:352098. PMID: 25136579 DOI: 10.1155/2014/352098

Veeck LL. An atlas of human gametes and conceptuses: an illustrated reference for assisted reproductive technology. Boca Raton: CRC Press; 1999.

Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgens stimulate early stages of follicular growth in the primate ovary. J Clin Invest. 1998;101:2622-9. PMID: 9637695 DOI: 10.1172/JCI2081

Vendola K, Zhou J, Wang J, Famuyiwa OA, Bievre M, Bondy CA. Androgens promote oocyte insulin-like growth factor I expression and initiation of follicle development in the primate ovary. Biol Reprod. 1999;61:353-7. PMID: 10411511 DOI: 10.1095/biolreprod61.2.353

Weil S, Vendola K, Zhou J, Bondy CA. Androgen and follicle-stimulating hormone interactions in primate ovarian follicle development. J Clin Endocrinol Metab. 1999;84:2951-6. PMID: 10443703 DOI: 10.1210/jcem.84.8.5929