

Effects of Hormonal Supplements in Women with Poor Ovarian Response Undergoing Assisted Reproductive Technology

Silan Melis BOZAN¹, Gurkan BOZDAG²

Ankara, Turkey

ABSTRACT

Poor ovarian response remains one of the major challenges of assisted reproductive technology. Over the years, various interventions have been proposed to improve reproductive outcomes in poor responders, yet few have been shown to be beneficial. Recent studies indicate that hormonal pretreatments might increase clinical pregnancy rate, live birth rate and the number of oocytes retrieved in women with poor ovarian response undergoing assisted reproductive technology. Areas covered: Following extensive research of the up to date literature, this review aims to cover current considerations and controversies regarding the use of hormonal supplements such as dehydroepiandrosterone, transdermal testosterone and growth hormone. Expert opinion: There is limited data for the validity of using growth hormone and androgens or androgen modulating agents during assisted reproductive technology cycles in women suffering from poor ovarian response. However, there is a need to support the available data with further randomized controlled trials seeking for live birth rate as the primary outcome.

Keywords: Assisted reproductive techniques, Dehydroepiandrosterone, Growth hormone, Poor ovarian response, Transdermal testosterone

Gynecol Obstet Reprod Med 2019;25 (0):00-00 (Article in press)

Introduction

Diminished ovarian reserve (DOR) might be defined as premature loss of primordial follicle than expected for any given age. It's common among women attending infertility clinics with an incidence of 9 - 24% and has been increased in recent years (1). In order to standardize the definition, European Society of Human Reproduction and Embryology Campus Workshop in Bologna proposed a subset of criterion including at least two of the following three features: (1) advanced maternal age (≥ 40 years) or any other risk factor for poor ovarian response (POR); (2) a previous POR (≤ 3 oocytes with a conventional ovarian stimulation protocol); and (3) an

abnormal ovarian reserve test (antral follicle count, AFC $< 5 - 7$ or AMH $< 0.5 - 1.1$ ng/ml). In addition, two episodes of POR after maximal stimulation would be sufficient to define a patient as a poor responder in the absence of advanced maternal age or abnormal ORT (1,2).

Ovarian reserve is an important predictor for ovarian response in assisted reproductive technology (ART) cycles and constitutes a significant challenge in ART. Nevertheless, independent from the combination of diagnostic criterion according to Bologna, poor ovarian responders have high cancellation rates (5%-18% of all IVF cycles) and very low live birth rate (3). There are strategies that have been suggested to improve IVF outcomes in poor responders, such as hormone supplementations as an adjuvant treatment to the stimulation protocols. Numerous studies have been conducted to investigate the clinical results and proposed mechanisms of some hormonal pretreatments such as dehydroepiandrosterone (DHEA), transdermal testosterone and growth hormone (GH). In this study, we aimed to review the available data about these hormonal treatments in women with poor ovarian response undergoing ART cycles.

Dehydroepiandrosterone (DHEA) Supplementation

Dehydroepiandrosterone (DHEA) is an endogenous steroid and originates from the adrenal zona reticularis (%85) and ovarian theca cells (%15) (4). It's a precursor of both estradiol (E2) and testosterone (T) which are required for normal follicular development and fertility (1). DHEA has a promoting effect on follicular development and granulosa cell proliferation by increasing intraovarian androgen concentra-

¹ Hacettepe University, School of Medicine, Ankara, Turkey

² Hacettepe University, School of Medicine, Department of Obstetrics and Gynecology, Ankara, Turkey

Address of Correspondence: Gurkan Bozdag
Hacettepe University, School of Medicine,
Department of Obstetrics and Gynecology,
Sihhiye, 06100, Ankara, Turkiye
gbozdag@hacettepe.edu.tr

Submitted for Publication: 28.02.2019

Accepted for Publication: 20.04.2019

ORCID IDs of the authors:

S.M.B.:0000-0001-6005-5407, G.B.: 0000-0002-6679-9623

Quick Response Code:	Access this article online
	Website: www.gorm.com.tr e-mail: info@gorm.com.tr
	DOI:10.201613/GORM.2019.923

How to cite this article: Bozan SM. and Bozdag G. Effects of Hormonal Supplements in Women with Poor Ovarian Response Undergoing Assisted Reproductive Technology. *Gynecol Obstet Reprod Med* 2018;24(0):00-00

tions. It can also enhance the level of follicular insulin-like growth factor-1 (IGF-1), which promotes folliculogenesis by enhancing the effect of gonadotropin and reducing follicular arrest (2).

There are several studies evaluating the impact of DHEA supplementation in women with POR undergoing ART. In all cases, DHEA was given as a supplement before ovarian stimulation during in-vitro fertilization (IVF) cycle and mostly, the main outcomes were the number of oocytes retrieved, clinical pregnancy and/or live birth rates (2,4,5).

According to systematic review including 21 studies, three trials (n=69) women <36 years had reported significantly increased number of oocytes retrieved after DHEA treatment as a surrogate marker of live birth (WMD 2.38, 95% CI 2.15 - 2.61, $p<0.0001$) (2). In six trials (n=163) included in the same review, there was also increased the number of oocytes retrieved after DHEA treatment (WMD 1.31, 95% CI 0.73 - 1.90, $p<0.0001$) when compared with controls (4). In the same review, analysis of 8 RCTs and 3 case-control studies showed significantly increased pregnancy rates of patients treated with DHEA compared with untreated control groups (RR: 1.53, 95% CI; 1.25 - 1.86, $p<0.0001$). The live birth rate in patients treated with DHEA was significantly higher compared with controls (RR: 1.87, 95% CI 1.22 - 2.88, $p=0.004$) (2).

According to Artini et al., DHEA might decrease the level of hypoxia-inducible factor-1 (HIF-1) and improve the number of mature oocytes retrieved from selected follicles significantly when compared with controls (0.50 ± 0.52 vs. 0.08 ± 0.29 , $p=0.018$) (6). Notably, another study revealed that DHEA treatment had a positive effect on women with POR undergoing ART, particularly in women <30 years old (5).

In conclusion, present studies indicate that DHEA treatment may enhance clinical pregnancy and live birth rates by increasing the number of oocytes retrieved according to limited data. However, the lack of large scale RCT avoids its utilization in clinical practice by physicians.

Transdermal Testosterone Supplementation

Testosterone is an androgen that directly binds to the specific receptor and has a key role in steroidogenesis, follicular activation, and follicular growth (7). It has been shown to have a role in both earlier and later stages of follicular growth by increasing the ovarian response to FSH. Several studies have been conducted to show the beneficial effect of transdermal testosterone pretreatment in poor responders undergoing IVF, yet there is no consensus in the literature over the best pretreatment scheme of testosterone.

According to a systematic review including three trials (3 RCTs, 113 women in the testosterone group, 112 in the control group), testosterone-treated women achieved significantly higher live birth rate as compared with women undergoing

standard ovarian stimulation (RR 1.91, 95% CI 1.13 - 3.78) (8). These three RCTs also showed an increased rate of clinical pregnancies in the transdermal testosterone group compared with the control group (RR 2.07, 95% CI 1.13 - 3.78). In the same review, a similar mean number of oocytes were retrieved among women receiving transdermal testosterone treatment and the control group (RR 1.28, 95% CI 0.77 to 1.78) (8).

Another meta-analysis published three years later including 4 RCTs (n=345) showed that pretreatment with testosterone was associated with higher live birth rates (OR 2.60, 95% CI 1.30 - 5.20) and higher clinical pregnancy rates (OR 2.52, 95% CI 1.36 - 4.68) (9). The authors underlined that in women with an 8% chance of live birth with placebo or no treatment, the live birth rate in women using testosterone will be between 10% and 32%.

Recently, one of the largest investigator-initiated studies regarding the use of transdermal testosterone gel in women with poor ovarian response has been carried on since 2015, April (NCT02418572). This trial, Testosterone Transdermal Gel for Poor Ovarian Responders Trial (T-TRANSPORT), includes more than 5 IVF centers in at least 4 European countries. The results from this ongoing trial might guide clinical practice in favor of or against the use of androgens for poor ovarian responders.

In conclusion, although recent literature favors the administration of transdermal testosterone in poor ovarian responders undergoing IVF, there is still no conclusive evidence on whether it improves the reproductive outcome in poor ovarian responders. The optimal dose and the time to commence and cease are not clear and present heterogeneity across the available studies. Therefore, further RCTs are needed in order for firm conclusions to be drawn.

Growth Hormone (GH) Supplementation

Growth hormone plays an essential role in follicular development and steroidogenesis in granulosa cells by stimulating follicular and hepatic production of insulin-like growth factor-1 (IGF-1). There are IGF-1 receptors within oocytes, granulosa, and theca cells. In women undergoing IVF, IGF-1 concentrations are directly related to the number of developing follicles due to the suppressive effect of IGF-1 on follicular apoptosis. GH itself is also required for follicular development and inhibition of follicular apoptosis.

Several studies have been conducted to evaluate the effect of GH supplementation in women with POR undergoing ART. The main success parameters considered in those studies are clinical pregnancy rate, live birth rate and the number of oocytes retrieved. In 1996, Busacca et al., (10) reported that GH might decrease the duration of ovarian stimulation by reducing follicle stimulating hormone (FSH) dose required and increase the number of developing follicles. Others such as Levy et al. and Suikkari et al., failed to present any significant

difference between variables (10-12). Tesarik et al., reported that GH may increase the live birth rate in patients >40 years old, but it had little effect on pregnancy rates or the number of oocytes retrieved. In a prospective cohort study that aimed to reduce the cost of GH therapy in IVF (14), it was reported that even a low dose of GH (0.5 IU per day) may still increase clinical pregnancy rate in poor responders(13-14)

One of the largest studies done on the supplementation of GH, namely LIGHT (Live birth rate In vitro fertilization and Growth Hormone Treatment) trial was performed in Australia and New Zealand in 2016 (15). When patients were prospectively randomized to study arm (12IU/day GH beginning on the day of stimulation) or controls, although there were some improvements in response to ovarian stimulation, the authors did not notice any improvement with regard to live birth rate in the study arm. However, one should be cautious that this study has not been published as a full paper.

In a recent retrospective study including 400 women in which 161 had been treated with GH (average of 1.5 IU per day), Keane et al (16), reported that GH supplementation significantly increased clinical pregnancy rate by 3.42-fold (95% CI 1.82 to 6.44, $p<0.0005$) and live birth rate by 6.16-fold (95% CI 2.83 to 13.39 $p<0.0005$) (16). When the data were analyzed based on female age, the authors noticed that the effect of GH was mainly related to patient's age. Whereas between 35 and 49 years, it was 4.50 more likely to get pregnant in GH cycles, it didn't have a significant effect on the chance of clinical pregnancy in those aged <35 years or ≥ 40 years. Contrarily, GH supplementation increased the live birth rates for all patients up to age 44 years.

In a recent systematic review (17) that has been conducted in 2017 including 11 articles and 663 women, it was reported that GH addition significantly increased clinical pregnancy rate (RR 1.65, 95% CI 1.23 - 2.22; $p<0.001$), live birth rate (RR 1.73, 95% CI 1.25 - 2.40; $p<0.001$) and number of oocytes retrieved (SMD 1.09, 95% CI 0.54 - 1.64; $p<0.001$) . (17)The subgroup analysis indicated that clinical pregnancy and live birth rates were significantly increased when GH was co-treated with gonadotropin, however, there were no significant differences found as for the clinical pregnancy rate and live birth rate when it was supplemented during the preceding luteal phase of the cycle (17).

To sum up, considering all the studies performed to date, there is some evidence that declares an improvement with regard to clinical pregnancy rate, live birth rate and the number of oocytes retrieved when GH supplementation was preferred. However, for more definite results, further studies are needed to confirm the effects of GH supplementation and to define the optimal dose and schema in women with POR undergoing ART.

Conclusion

Recent studies appear to support the use of DHEA, transdermal testosterone and growth hormone in women who are considered poor responders, and these treatments have shown to significantly improve the clinical outcomes in parameters such as live birth rate, pregnancy rate and the number of oocytes retrieved. Although the results of these studies are promising, additional high-quality clinical trials, particularly RCTs evaluating the role of hormonal supplementations in poor ovarian response and using different protocols are required to reinforce these findings.

Acknowledgments: None

Financial support: None

Conflict of interest: None

References

1. Tsui KH, Lin LT, Chang R, Huang BS, Cheng JT, Wang PH. Effects of dehydroepiandrosterone supplementation on women with poor ovarian response: A preliminary report and review. *Taiwan J Obstet Gynecol.* 2015;54(2): 131-6.
2. Zhang M, Niu W, Wang Y, Xu J, Bao X, Wang L, et al. Dehydroepiandrosterone treatment in women with poor ovarian response undergoing IVF or ICSI: a systematic review and meta-analysis. *J Assist Reprod Genet.* 2016; 33(8):981-91.
3. Bozdag G, Polat M, Yarali I, Yarali H. Live birth rates in various subgroups of poor ovarian responders fulfilling the Bologna criteria. *Reprod Biomed Online.* 2017;34 (6):639-44.
4. Li J, Yuan H, Chen Y, Wu H, Wu H, Li L. A meta-analysis of dehydroepiandrosterone supplementation among women with diminished ovarian reserve undergoing in vitro fertilization or intracytoplasmic sperm injection. *Int J Gynaecol Obstet.* 2015;131(3):240-5.
5. Al-Turki HA. Dehydroepiandrosterone supplementation in women undergoing assisted reproductive technology with poor ovarian response. A prospective case-control study. *J Int Med Res.* 2018;46(1):143-9.
6. Artini PG, Simi G, Ruggiero M, Pinelli S, Di Berardino OM, Papini F, et al. DHEA supplementation improves follicular microenvironment in poor responder patients. *Gynecol Endocrinol.* 2012;28(9):669-73.
7. Kahyaoğlu I, Yilmaz N, Kahyaoğlu S, Türkkani A, Çiçek MN, Mollamahmutoğlu L. Effect of Basal Testosterone and Dehydroepiandrosterone Sulphate Levels on in Vitro Fertilization Outcome in Normoresponders. *Gynecol Obstet Reprod Med.* 2013;3:171-5.
8. Gonzalez-Comadran M, Duran M, Sola I, Fabregues F, Carreras R, Checa MA. Effects of transdermal testosterone in poor responders undergoing IVF: systematic review and meta-analysis. *Reprod Biomed Online.*

2012;25(5):450-9.

9. Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. *Cochrane Database Syst Rev.* 2015(11):CD009749.
10. Busacca M, Fusi FM, Brigante C, Bonzi V, Gonfiantini C, Vignali M, et al. Use of growth hormone-releasing factor in ovulation induction in poor responders. *J Reprod Med.* 1996;41(9):699-703.
11. Levy T, Limor R, Villa Y, Eshel A, Eckstein N, Vagman I, et al. Another look at co-treatment with growth hormone and human menopausal gonadotrophins in poor ovarian responders. *Hum Reprod.* 1993;8(6):834-9.
12. Suikkari A, MacLachlan V, Koistinen R, Seppala M, Healy D. Double-blind placebo controlled study: human biosynthetic growth hormone for assisted reproductive technology. *Fertil Steril.* 1996;65(4):800-5.
13. Tesarik J, Hazout A, Mendoza C. Improvement of delivery and live birth rates after ICSI in women aged >40 years by ovarian co-stimulation with growth hormone. *Hum Reprod.* 2005;20(9):2536-41.
14. Lattes K, Brassesco M, Gomez M, Checa MA. Low-dose growth hormone supplementation increases clinical pregnancy rate in poor responders undergoing in vitro fertilisation. *Gynecol Endocrinol.* 2015;31(7):565-8.
15. Norman R, Alvino H, Hart R, Rumbauts L, investigator Ls. A randomised double blind placebo controlled study of recombinant human growth hormone (h-GH) on live birth rates in women who are poor responders. *Hum Reprod.* 2016;31(Suppl):i37.
16. Keane KN, Yovich JL, Hamidi A, Hinchliffe PM, Dhaliwal SS. Single-centre retrospective analysis of growth hormone supplementation in IVF patients classified as poor-prognosis. *BMJ Open.* 2017;7(10):e018107.
17. Li XL, Wang L, Lv F, Huang XM, Wang LP, Pan Y, et al. The influence of different growth hormone addition protocols to poor ovarian responders on clinical outcomes in controlled ovary stimulation cycles: A systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96(12):e6443.