CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3334393

Available online at: http://www.iajps.com *Research Article*

A RESEARCH STUDY TO INVESTIGATE THE ROLE OF OVARIAN FUNCTION AND ANDROGENS IN THE REPRODUCTIVE FUNCTION OF FEMALES

[1]Dr. Umair Ashfaq, [2]Dr. Amjad Ali Raza, [3]Dr. Sarwat Saif

[1]Consultant Physician and Endocrine Fellow, Services Hospital, Lahore.

Article Received: May 2019 **Accepted:** June 2019 **Published:** July 2019

Abstract:

Last decade investigations report that a direct and important role of androgens is crucial for the regulation of the reproductive system among females. Androgen receptor mediates the action of androgens which has been confirmed through mouse models. These AR-mediated androgens are important for the regulation of female fertility, ovulation, development and follicle health. This research proves the beneficial effects of the androgens through clinical data among poor respondents' females which has improved the global concept of in vitro fertilization (IVF). An excessive androgen which acts as AR also plays an important role in PCOS origins (Polycystic Ovary Syndrome). The target sites identification for AR actions and related molecular mechanisms are also involved in the PCOS development which is mandatory to achieve the required level for the new future developments, PCOS treatments and mechanisms-based disease management. Our research summarizes related scientific discoveries which will increase the awareness about the importance of androgens among the reproductive function of the females. More effective future strategies may also be developed for the role of androgens in the physiology of the females with improved IVF outcomes with improved symptoms among PCOS patients.

Keywords: *Androgens, Reproductive, Receptors, Cell, Fertility, Follicle, Ovulation, Polycystic and Ovary.*

Corresponding author:

Dr. Umair Ashfaq,

Consultant Physician and Endocrine Fellow, Services Hospital, Lahore.

QR code

Please cite this article in press Umair Ashfaq et al., ***A Research Study to Investigate the Role of Ovarian Function and Androgens in the Reproductive Function of Females.,*** *Indo Am. J. P. Sci, 2019; 06(07).*

INTRODUCTION:

Androgens are actually sexual steroid hormones which are crucial for the reproductive system of males. Androgens develop ovarian follicular among females which is important obligatory estradiol (E2). Serum concentrations in descending orders are such as dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), testosterone, androstenedione (A4) and dihydrotestosterone (DHT) which androgens circulating in females. Bioactive androgens, DHT and testosterone bind directly with AR; whereas, DHEA, pro-androgens and A4 need conversion to DHT or testosterone in order to exert androgenic effects. However, present studies also present a direct DHEA effect in vascular endothelial cells and brain.

Protein and AR mRNA are present at all levels of HPG (Hypothalamic-Pituitary-Gonadal) among females along with corpora lutea, ovarian follicles, ovarian stroma and brain. The expression of AR is also found in fetal and adults ovaries follicular stages; whereas, the expression patterns are special and differential temporal. Generally, The expression of AR is found with the entrance of follicles in growing pool, Preantral follicles theca cells, granulosa cells and oocyte show the presence of AR immunostaining; whereas, there is a progressive decline in the AR expression with the growth in follicular growth in outer mural granulosa cells which is intense in the cumulus cells. Various authors also support the AR-mediated androgen role in the ovarian function.

POOR OVARIAN RESPONSE (POR):

Poor Ovarian Response Features: Ovaries oocytes decrease with an increase in the age of women which correlates with reduces fecundity related to age which is even increased after 30 years and 40 years of age with natural sterility of reproductivity and menopause on 51 years taken as an average age [1]. The competence and quality of oocytes also reduce with age factor. Conception rate is 50% less among women in the age group of 35 – 39 years in comparison to 19 – 25 years. Infertility treatment is also increasing because of marriages conducted after thirty years of age. The poor ovarian response also correlates with age factor which is also because of follicular pool diminishing in the aged women ovaries [2].

POR refers to a condition which shows the presence of an advanced maternal age above forty years, abnormal ovarian and previous POR under three oocytes. Luteinizing hormone and FSH are secreted from the act of pituitary on the simulation of the ovary in the production of the androgen in granulosa cells estrogen synthesis and theca cells. There is a decrease in the circulating levels of A4, DHEA and DHEAS along with bioactive androgen testosterone with increasing age which is steepest in the early age of reproductivity having no effect on the level of circulating androgens and menopause which is different to the sharp decline of E2 [3]. This decline in androgen levels with age has been proposed to potentially contribute or reflect the diminishing ability of the ageing ovary to respond to FSH-based stimulation in IVF. As such, it has been suggested that the bioavailability of androgens within the ovary may increase follicular response. Several studies have reported on whether serum androgen levels can predict ovarian response or IVF outcomes. There is a positive association between ovarian response and levels of testosterone serum along with the outcomes of pregnancy in INF. Poor ovarian response has a relation with reduced testosterone levels which also reduces the chances of pregnancy [4].

Outcomes of Animal and Clinical Studies:

In the presence of excessive androgens among females like congenital adrenal hyperplasia testosterone-treated male to female PCOS and transsexuals reveal that androgens stimulation increases with the early development of follicle. Patients also exhibit ovaries like polycystic. Animal studies also confirm the early development of follicle with the influence of the androgen where DHT and bioactive androgens testosterone in primates and mice stimulate the initiation of the primordial follicle. According to Walters, the expression of the AR gene is abundant among several species in healthy growing follicles granulosa cells. Different androgens such as DHT, DHEA, A4 and testosterone significantly promote mice follicle growth from preantral to antral along with primates and sheep. Direct AR-mediated actions confirm such effects with the observation of mice stimulatory effects as blocked by AR antagonist (bicalutamide).

Importance of Androgens for the Development of Follicle:

Pharmacological research studies prove that ovarian function relies on an important role of androgens; however, the confusion about the mediating actions still remains outstanding. The possibility of this confusion remains because of the conversion of androgens into estrogens which exert an indirect action through ER (estrogen receptor). AR antagonists are important instruments but they can also make

difficult the deciphering of the specific mechanism, which his same for all of the steroid blockers, AR antagonists are mixed partial antagonist or agonists instead of pure blockers. However, the advanced Cre/LoxP models, global generation and mouse models of cell-specific AR-knockout play a vital role in the actions of androgens. Precise AR-mediated mechanisms also pose an important role in the regulation of the reproductivity of females[5].

Role of androgens/androgen-modulating agents among patients showing poor ovarian response to IVF:

For all those women who show a reduced and poor response towards stimulation; the challenge is in the enhancement of the ovarian response in upcoming cycles in the absence of any standard evidenced-based treatment. Most of the outcomes support the stimulation role of the androgens in the early growth of the follicle. It is also important to maintain the priming and health of follicle in the last development stages. On the basis of these outcomes, it is strongly supported to employ androgen before treatment of poor ovarian response among all the patients who are about to experience IVF with an objective of enhancement of response of follicle to IVF hyperstimulation. Pre-treatment use of androgen has been undertaken in the global IVF centres along with the use of DHEA supplementation. Three treatment modes have been under clinical trial to improve the poor ovarian response among IVF patients including systematic administration of testosterone and DHEA, endogenous androgen stimulation and production in theca cells by hCG or LH and letrozole administration. It increases the levels of androgens with the prevention of androgens conversion into estrogens [4, 5, 6].

ANDROGEN ADMINISTRATION:

Dehydroepiandrosterone (DHEA) and Testosterone:

After androgen pre-treatment approach the DHEA treatment study reported an increase in the oocyte yield (1 – 17) oocytes in subsequent cycles and in large-scale self-controlled research, fertilization and ovarian response also improved significantly. These outcomes support the supplementation of androgens as a new approach which can potently increase the ovarian response. Barad and Gleicher observed pre-treatment DHEA efficacy on large-scale study back in 2005 and 2006 and reported outcomes on 190 patients with a dose of 75 mg per day for a period of four months. The outcomes show that DHEA treatment poses beneficial effects on the response of ovarian with an enhanced oocytes number. The pregnancy rate was also significantly high among patients treated with DHEA. Studies have also evaluated the testosterone in the poor ovarian response women and IVF outcomes. Transdermal testosterone application from 5 – 20 days in poor ovarian response patients the response was not significant as reported in various Randomized Control Trials and Placebo-controlled trials. The beneficial outcomes include improved oocyte retrieval numbers, antral follicle numbers, embryo implantation rates, fertilization rates, clinical pregnancy rates, embryo quality and live birth rates in the same patient [5].

Combined Androgen or Androgen-modulating Agent Therapies:

Few patients with POR were treated with the combined modified approach of androgens or androgen-modulating agents. Combined therapy reported improved outcomes of oocytes number and pregnancy rates with the implementation of 12 weeks DHEA management, 4 weeks transdermal testosterone treatment and luteal phase hormone growth rate among patients. Moreover, another management therapy is known as ANDRO-IVF which combined hCG, letrozole and transdermal testosterone also increased fertilization rates and a number of oocytes among POR patients.

PCOS (Diagnosis and Characteristics):

Global prevalence of PCOS is significant as it affects 20% of women who are in the age of reproductivity. It causes a serious economic burden on the healthcare system. Women affected with PCOS also face endocrine issues, metabolic issues, reproductive issues and psychological issues. Polycystic ovaries present abnormal follicle maturation that results in reduced fertility rate and ovulatory dysfunction. In the case of pregnancy, such patients face severe pregnancy-related complications like premature delivery, hypertensive disorders and gestational diabetes. Substantial metabolic impacts of PCOS include metabolic syndrome, obesity, insulin resistance, hyperinsulinemia, hepatic steatosis, dyslipidemia and an increased T2DM development risk along with CVD. Moreover, PCOS also poses anxiety, depression, psychological and social issues among PCOS patients [6].

Present Implications & Future Directions for Development of Novel Treatment Approach for PCOS that Targets Androgen-driven Mechanisms:

Substantial evidence is available to support the androgen role for the excessive mediation in its actions

through AR in PCOS origin; whereas, the treatment through available antiandrogen generations is not suggested because of intolerable liver toxicity which prevents non-lethal chronic disorders utilization. Therefore, current research recent research has been aimed at trying to identify more targeted ways by which pharmacological strategies may be able to suppress excess androgenic effects in women with PCOS.

A specific signalling loss of AR in brain safeguards hyper androgenized mics PCOS against PCOS features development; it presents the brain a key site which is involved in the pathogenesis of experimental PCOS. The increase in the ration of LH-to-FSH and frequency of LH pulse are evident among PCOS patients along with PCOS models, primate, sheep, mouse and rate. GnRH neurons activity that regulates the secretion of gonadotrophin depends on the signalling of gonadal steroid hormone in the brain and homeostatic feedback. However, AR is not expressed by GnRH neurons rather it is presented intermediary neuronal networks which in the GnRH neurons and allows an indirect pathway which mediates the actions of AR. AR-mediated signalling is important in the regulation role of KNDy system and sheep hyper androgenized PCOS animal models exhibit KNDy circuitry and expression.

Moreover, the outcomes about specific AR signalling loss in brain safeguards hyper androgenized PCOS mice which is against the progression of key traits of metabolic PCOS include increased visceral fat and body weight, pronounced adipocyte hypertrophy, dyslipidemia and hepatic steatosis. It indicates about the various metabolic dysfunction aspects reported among patients of PCOS that can be mediated through AR-regulated mechanisms. Evidence is available to suggest the role of androgen–brain–adipocyte axis in PCOS-associated aetiology relating to metabolic dysfunction [7]. Adipokine leptin plays a vital role in the regulation of homeostasis of energy which reduces the energy expenditure impact in androgen excess mouse models. It also correlates with reduced sympathetic outflow to BAT (Brown Adipose Tissue). Neuropeptide Y/agouti associated peptide and Proopiomelanocortin (POMC) neurons are the targets of leptin and they are also influenced with the excess of androgens. Fibre projections and POMC mRNA are reduced in androgenized female mice; whereas, excess of ewe prenatal androgen leads to an enhanced number of NPY/AgRP cell and fibre projections. Moreover, management with AR antagonist flutamide inhibits the variations in NPY/AgRP neurons in androgenized sheep and it also improves PCOS women lipid profile which is independent of glucose metabolism, weight change and insulin sensitivity. Mutually, these outcomes support the important role of androgens in the mediation of PCOS-related metabolic dysregulation and more research work will determine the precise involvement of different mechanisms.

AR-mediated androgens are important for the regulation of female fertility, ovulation, development and follicle health. This research proves the beneficial effects of the androgens through clinical data among poor respondents' females which has improved the global concept of in vitro fertilization (IVF). An excessive androgen which acts as AR also plays an important role in PCOS origins (Polycystic Ovary Syndrome). The target sites identification for AR actions and related molecular mechanisms are also involved in the PCOS development which is mandatory to achieve the required level for the new future developments, PCOS treatments and mechanisms-based disease management. Our research summarizes related scientific discoveries which will increase the awareness about the importance of androgens among the reproductive function of the females. More effective future strategies may also be developed for the role of androgens in the physiology of the females with improved IVF outcomes with improved symptoms among PCOS patients [8].

CONCLUSION:

Animal studies and clinical outcomes provide valuable insight into the role of androgen in the regulation of reproductivity among females with related mechanisms which underpin PCOS development. An accurate and balanced androgenic action increase the development of ovarian follicle and fertility rates among females. Whereas, clinical series highlights that androgen pre-treatment before IVF cycle has a beneficial and promising impact on the outcomes of IVF. Recent studies support the outcomes derived from PCOS animal model studies. With the combination of combined outcomes of basic discovery and clinical outcomes; a precise regulating ovarian function of androgenic mechanisms and PCOS development highlights PCOS. It will surely increase the futuristic evidence-based research to increase the ovarian response among those patients who present poor ovarian response and upgrades symptoms among PCOS affected women.

REFERENCES:

1. Sen, Aritro, and Stephen R. Hammes. "Granulosa cell-specific androgen receptors are critical

regulators of ovarian development and function." *Molecular Endocrinology* 24.7 (2010): 1393-1403.
2. Hu, Yueh-Chiang, et al. "Subfertility and defective folliculogenesis in female mice lacking androgen receptor." *Proceedings of the National Academy of Sciences* 101.31 (2004): 11209-11214.
3. Eisner, Joel R., et al. "Ovarian hyperandrogenism in adult female rhesus monkeys exposed to prenatal androgen excess." *Fertility and sterility* 77.1 (2002): 167-172.
4. Walters, Kirsty, et al. "Androgens and ovarian function: translation from basic discovery research to clinical impact." *Journal of Endocrinology* 1.aop (2019).
5. Hammes, Stephen R., and Ellis R. Levin. "Impact of estrogens in males and androgens in females." *The Journal of clinical investigation* 129.5 (2019): 1818-1826.
6. Findlay, J. K., et al. "Follicle selection in mammalian ovaries." *The Ovary*. Academic Press, 2019. 3-21.
7. Astapova, Olga, Briaunna MN Minor, and Stephen R. Hammes. "Physiological and Pathological Androgen Actions in the Ovary." *Endocrinology* 160.5 (2019): 1166-1174.
8. Cardozo, Licy L. Yanes, et al. "Androgens and Cardiovascular Diseases in Women." *Sex Differences in Cardiovascular Physiology and Pathophysiology*. Academic Press, 2019. 3-12.