وزارة التعليم العالي والبحث العلمي

جامعة بابل / كلية العلوم للبنات

association of androgens in ovarian health and disease

بحث مقدم من قبل

بنين علي حاتم

كجزء من متطلبات نيل شهادة البكلوريوس في علوم الحياه

إشراف

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

(قَالُواْ سُبْحَٰنَكَ لَا عِلْمَ لَنَآ إِلَّا مَا عَلَّمْتَنَآ ۖ إِنَّكَ أَنتَ ٱلْعَلِيمُ ٱلْحَكِيمُ)

صدق الله العظيم

[البقرة: 32]

الاهداء

مَّرت قاطرة البحث بكثير من العوائق، ومع ذلك حاولت أن أتخطها بثبات بفضل من الله ومنِّه.

إلى أبي وأمي واختي وأخوتي وأصدقائي، فلقد كانوا بمثابة العضد والسند في سبيل استكمال البحث.

ولا ينبغي أن أنسى أساتذتي ممن كان لهم الدور الكبير في مُساندتي ومَدّي بالمعلومات القيمه وهم لا يبخلون بمعرفتهم و وقتهم اهدي لكم بحث تخرُّجي كهديه خاصه لكم لأعبر لكم عن أعمق احترامي وامتناني .....

داعيًا المولى - عَّز وجّل – أن يُطيل في أعماركم، ويرزقكم بالخيرات .....

شكر وتقدير

الحمد لله رب العالمين و الصلاه والسلام على أشرف الخلق و المرسلين الرسول الكريم محمد و على آله الطيبين الطاهرين.

أول مشكور هو الله عز وجل له الشكر والحمد فأليه ينسب الفضل في إكمال هذا العمل ، ثم والداي على كل مجهوداتهم ومساندتهم لي منذ ولادتي إلى هذه اللحظات، أنتم كل شيء أحبكم في الله أشد الحب.

أتوجه بالشكر الجزيل إلى جميع أساتذتي الافاضل في قسم علوم الحياه كليه العلوم للبنات جامعه بابل الذين بذلوا جهداً في توجيهي و أمدادي بما احتجت اليه من النصيحه.

لكل والتقدير بالشكر اتقدم واشكر كل من ساعدني و اعانني من الأصدقاء. كما الدراسية مسيرتي ولو بكلمه طيبه في ساهم في مد العون لي من.

Association of androgens in ovarian health and disease

Abstract

In women, ovary and adrenal gland produce androgens. Androgens are essential drivers of the primordial to antral follicle development, prior to serving as substrate for estrogen production in the later stages of folliculogenesis. Androgens play a crucial role in the follicular–stromal intertalk by fine tuning the extracellular matrix and vessel content of the ovarian stroma. Local auto-and paracrine factors regulate androgen synthesis in the pre-antral follicle. Androgen excess is a hallmark of polycystic ovary syndrome and is a key contributor in the exaggerated antral follicle formation, stromal hyperplasia and hypervascularity. Hyperandrogenaemia resulting in follicular arrest and disturbed ovulation. On the other hand, androgen deficiency is likely to have a negative impact on fertility as well, and further research is needed to examine the benefits of androgen-replacement therapy in subfertility.

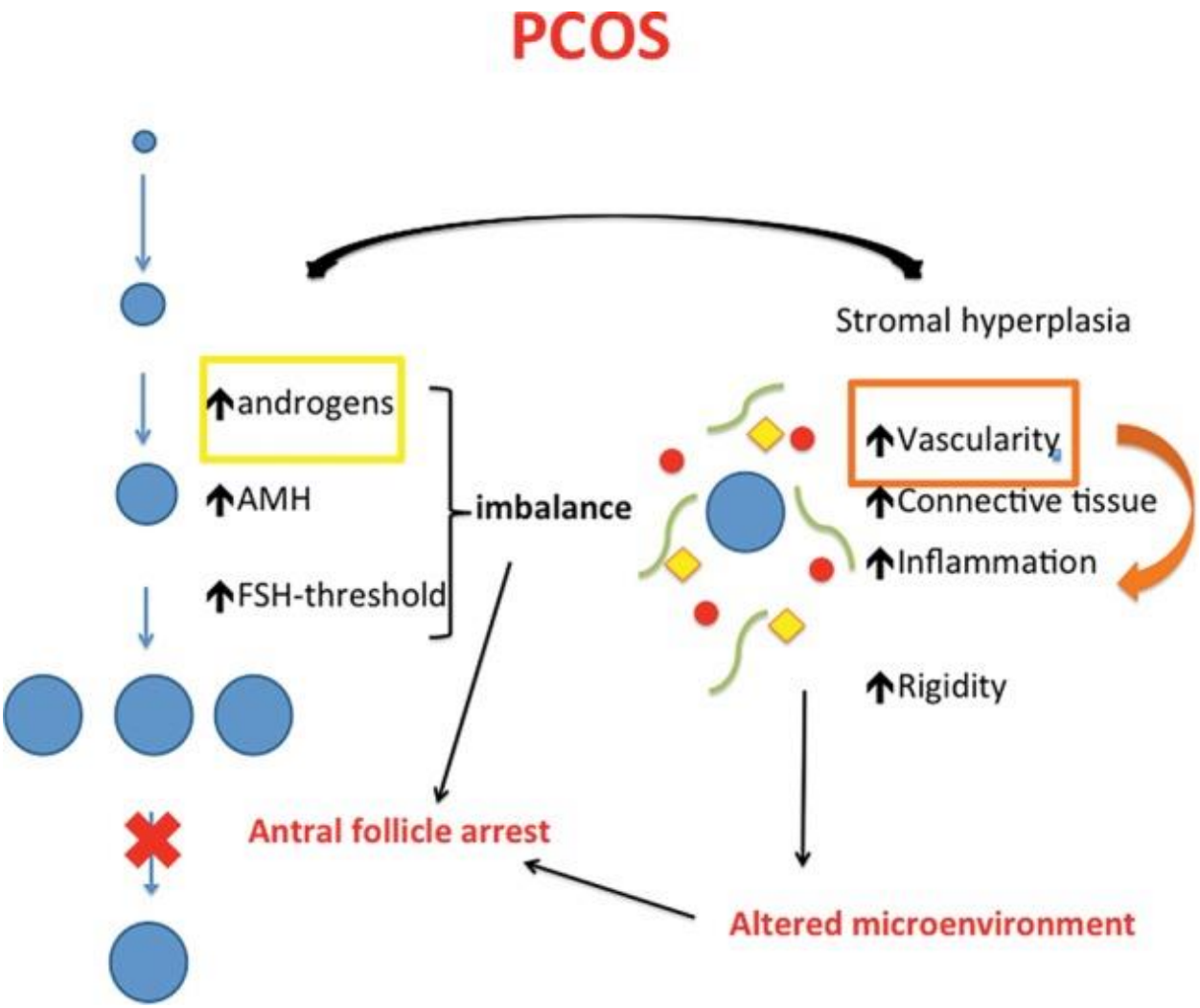
Introduction

The effect of androgens on female fertility is an emerging field in reproductive science at the interface of endocrinology and gynecology. In the following section, the authors aim to describe androgen action on the early growing follicle and its environment, and highlight new implications and developments in the fiel[1].

The single follicle is the fundamental unit of the ovary and is composed of an oocyte surrounded by specialized endocrine cells. It produces peptide hormones and sex steroids that modulate the maturation of the oocyte and regulate follicle cell growth and differentiation through local auto-

and paracrine-signaling pathways [2]. Secreted into the bloodstream, these hormones also exert endocrine effects and prepare the reproductive organs for fertilization and implantation. Primordial follicles are continuously recruited for growth, and this phenomenon, as well as the subsequent stages of follicular development, is considered to be locally regulated and independent of gonadotrophin action. While the majority of growing follicles are lost in atresia, a small cohort of antral follicles is recruited for further growth, dominance and ovulation under the cyclic stimulation of gonadotrophins[3].

The outer cortex of the ovary contains immature follicles and is a rigid, avascular environment. It is made up of tightly packed spindle-shaped fibroblasts, vasculature-related cells (smooth muscle cells and endothelial cells), inflammatory cells and precursor theca cells [54]. The inner medulla is more elastic and composed of loose connective tissue and ovarian vasculature[5]. The ovarian stroma consists of connective tissue and its extracellular matrix sustains the ovarian architecture and provides structural support to the growing follicles. The stroma also produces a variety of cytokines, chemokines and growth factors that tightly co-regulate—in an autocrine and paracrine fashion—the early growth phase of its enclosed follicles[6].



Working model for excess androgen action on follicle and stroma in PCOS. In PCOS, the disturbed balance between androgens, AMH and FSH leads to antral follicular arrest. Circulating FSH-levels are insufficient to reach the increased FSH-threshold of the follicles and selection for dominance does not occur. The hypervascular, rigid and inflammatory cortex negatively impacts the follicular dynamics. Exaggerated blood supply, partly mediated by local androgen overproduction, fuels the whole process. The blue ovals indicate follicles, red circles blood vessels, yellow squares inflammatory cells and green bowed lines stand for connective tissue.

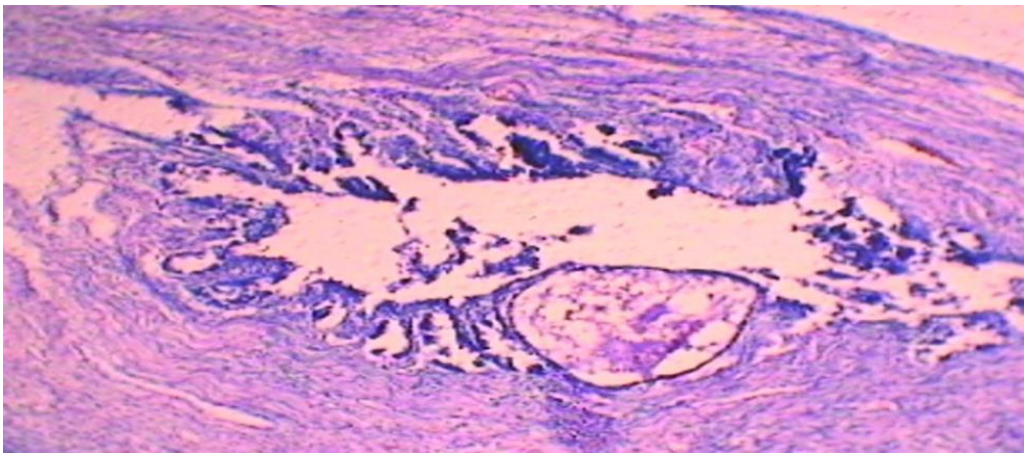
Materials and Methods

All procedures performed in studies involving human participants. Informed consents were obtained from all patients after full explanation of the purpose and nature of all procedures used. All the enrolled patients participated in the research voluntarily and freely. All the procedures were performed in accordance with the relevant guidelines and

regulations.All study participants—PCOS women and controls—followed the same study protocol. Clinical examination was performed in all women. Clinical hyperandrogenism was evaluated using the modified Ferriman–Gallwey score for hirsutism (more than eight points was considered as clinical hyperandrogenism) and/or presence of acne. Oligo/amenorrhea and anovulation were considered when women had fewer than six menses during the previous year. After separating the lesion were preserved in 10% formalin. The tissue was dehydrated and followed by embedding in paraffin and 5 micron serial sections were generated with the help of rotator microtome. The sections were stained with hematoxylin and eosin, xylene, cover slid and microscopic examination display the lesion .

Results and Discussion

Clinical examination was performed in all women. Clinical hyperandrogenism was evaluated Histopathology Figure exhibit changes within the follicles displays significant fibrosis and absence of cilia cells tissue and accumulation of fluid in follicles. Overall, the histologic changes in follicles are pronounced[7]. .



In women, the main sources of circulating androgens are the adrenal glands and ovaries (8). Dehydroepiandrosterone (DHEA), mainly from the adrenal glands, acts as a crucial precursor of sex steroids in the ovary and other target tissues (9). Depending on the intracellular availability of steroidogenic enzymes in target tissues, DHEA is converted to androstenedione and testosterone, both of which can be aromatized to

estrogens. Testosterone can also be converted to the much more potent 5α-dihydrotestosterone (DHT). Testosterone and DHT are the only two hormones that bind and activate the androgen receptor (AR). Serum levels of DHEA and androgens peak in the early reproductive years, followed by a steep decline with age (10).

Androgens exert their action mainly through the AR. The AR functions as a ligand-activated nuclear transcription factor (11). It has recently become clear that many effects of androgens in non-ovarian target tissues depend on other complex-signaling pathways, including rapid non-genomic pathways. The reported non-genomic effects of androgens at physiological concentrations appear to be mediated through the cytosolic AR, involved in the activation of mitogen-activated protein kinase-extracellular signal-related kinase (ERK) pathways (12). There is evidence that this non-genomic stimulation results in an enhancement of AR transcriptional activation, thereby creating an autocrine loop between AR and its ligand (13). It is currently unclear whether androgens exert non-genomic actions in the ovary. Interestingly, the activation of the PI3-K/Akt pathway in the minutes following testosterone supplementation has been reported in neonatal mouse ovaries, an effect reverted by the AR-antagonist flutamide and suggestive of non-genomic androgen signaling (14).

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