Journal of Steroid Biochemistry and Molecular Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy

Seema Patel

Bioinformatics and Medical Informatics Research Center, San Diego State University, Campanile Dr, San Diego, CA, 92182, USA

ARTICLE INFO

Keywords:
Polycystic ovary syndrome (PCOS)
Endocrine disorder
Amenorrhea
Anovulation
Hyperandrogenism
Hyperprolactinemia

ABSTRACT

Polycystic ovary syndrome (PCOS) is an endocrine disorder, afflicting females of reproductive age. This syndrome leads to infertility, insulin resistance, obesity, and cardiovascular problems, including a litany of other health issues. PCOS is a polygenic, polyfactorial, systemic, inflammatory, dysregulated steroid state, autoimmune disease, manifesting largely due to lifestyle errors. The advent of biochemical tests and ultrasound scanning has enabled the detection of PCOS in the affected females. Subsequently, a huge amount of insight on PCOS has been garnered in recent times. Interventions like oral contraceptive pills, metformin, and hormone therapy have been developed to bypass or reverse the ill effects of PCOS. However, lifestyle correction to prevent aberrant immune activation and to minimize the exposure to inflammatory agents, appears to be the sustainable therapy of PCOS. This holistic review with multiple hypotheses might facilitate to devise better PCOS management approaches.

1. Introduction

A number of ailments are gender-specific. Gynecological issues involve the impairment in reproductive or the estrogen-controlled organs in the females. While some of these feminine problems are curable, some are chronic, or fatal. Several of these disorders interfere with fertility. With the upsurge in the invasion of, and exposure to chemicals, which are to a large extent endocrine disruptors, the instances of hormonal disturbances are on the sharp rise.

Some of these commonly-encountered reproductive and hormonal anomalies include amenorrhea, endometriosis, polycystic ovary syndrome, fibroids, infertility, ovarian cancer, miscarriage, ectopic pregnancy, preterm delivery etc. [1–6]. Polycystic ovary syndrome (PCOS), a constellation of symptoms, affecting women of child-bearing age is assuming epidemic proportions. This disease, a resultant of imbalance in female sex hormones, leads to cysts in the ovarian antral follicles. A cyst is a water-filled sac containing the egg, that should have been normally discharged for possible fertilization. The conversion of the egg into a cyst, termed as 'functional cyst', prevents ovulation. As ovulation is blocked, it results in the disruption of the menstrual cycle, causing 'amenorrhea'. When multiple cysts are formed in the ovarian follicles due to the hormonal imbalance, it is characterized as PCOS. Because of the water-retained cysts, some of which can be as big as 10 mm wide, the size of ovary increases, up to 10 cm wide. Absence of ovulation and menstrual cycle prevents fertilization, and conception, thus pregnancy becomes difficult [5,7]. Even if implantation occurs, abortion and still birth risks increases. Eclampsia and the small-for-gestational-age babies can occur. PCOS can cause pregnancy-related complications such as gestational diabetes, pregnancy-induced hypertension [8].

Normally, ovarian theca cells provide support to the growing follicle, assisting in mature oocyte generation [9]. But, these cells in PCOS patients are hyper-responsive to the stimulatory effects of insulin, so they proliferate, causing ovarian hyperthecosis. Insulin resistance amplifies the androgenic potential in the theca cells, aggravating PCOS [10]. Also, the high sensitivity of theca cells to gonadal steroid gonadotropin stimulation aid to androgenism in PCOS.

Disrupted secretion of the pulsatile gonadotropin-releasing hormone (GnRH) from hypothalamus is a factor responsible for PCOS [11]. GnRH induces the pituitary gland to secrete follicle stimulating hormone (FSH) and luteinizing hormone (LH). These two hormones are essential for the two distinct phases of menstrual cycle. In PCOS, as these hormones are scanty, the egg is either not formed, or cannot be liberated from the follicle. So, the cycle is disrupted and amenorrhea occurs, which can be of two types, the primary or secondary amenorrhea. While primary amenorrhea is the inability to reach menarche due to chromosomal or anatomic issues, secondary amenorrhea, also called hypothalamic amenorrhea, is characterized by the absence of menstrual cycles for 3 or more consecutive months [12]. High level of prolactin, a peptide hormone, blocks the GnRH [13].

As the human body is a complex system and the metabolites are functionally-interlinked, disturbance in one can affect the others as well. Upset in the level of a number of hormones (prolactin, anti-

E-mail addresses: seemabiotech83@gmail.com, Patel3@rohan.sdsu.edu.

https://doi.org/10.1016/j.jsbmb.2018.04.008
Received 23 January 2018; Received in revised form 3 February 2018; Accepted 16 April 2018

Müllerian hormone (AMH), cortisol, androgen), neurotransmitters (dopamine), peptides, lipid, protein, and glucose are associated with PCOS manifestation. Hyperprolactinemia causes hypogonadotropic hypogonadism, characterized with amenorrhea, galactorrhea (abnormal milk production from the breasts), and osteoporosis [14]. Normally, after parturition, prolactin stimulates the production of milk by the alveolar cells in the breasts. Prolactinoma of the pituitary gland is one cause of high prolactin level. Roles of these components in PCOS have been discussed in later sections.

1.1. Symptoms of PCOS

Anovulation or oligovulation is a common symptom of PCOS. Some of the cysts produce androgens, which result in the virilization or the expression of male-like characters in the females. So, PCOS leads to the appearance of a gamut of masculine symptoms or 'hyperandrogenism'. Visible signs of hyperandrogenism include weight gain, abdominal and subcutaneous fat, hirsutism (facial and body hair), male-pattern alopecia (hair loss), clitoromegaly (enlargement of the clitoris), deep voice, seborrhea (oily skin), acne etc. [15]. Apart from these morphological features, alteration in metabolic profile occurs. Insulin resistance is a major symptom of PCOS. It results in hyperinsulinemia, and can lead to diabetes mellitus [5,16]. High insulin level is responsible for the deposition of fat around the abdomen or central adiposity. In a majority of females with PCOS, the body mass index (BMI) is 30 or higher. Other than that, hypertension, cardiovascular issues, dyslipidemia, etc. are co-morbidities of PCOS [5,16]. A healthy blood pressure for women is 120 over 80 or less. PCOS patients are at a high risk for the development of early-onset cardiovascular disease. The PCOS patients often display sugar cravings, frequent urination, delayed healing, fatigue, blurred vision, tingling sensation, mood swing, anxiety, and depression episodes. It is understandable, as these conditions are tied to diabetes as well. The patients often feel pelvic pain, fever, nausea, vomiting, urinary conditions, constipation etc. Pressing of the large cysts against the bladder or rectum is responsible for the anomalous urinary and bowl movement. Sleep apnea (sleep disorder in which breathing repeatedly stops and starts) is another symptom of PCOS, arising due to altered sex steroid level [17]. PCOS can put a female at the risk for uterine cancer, as the prevailing high estradiol level and the lack of progesterone due to ovarian malfunction increases the risk of endometrial hyperplasia [18]. Mucus-deficient endocervix, and smooth vagina is a feature of PCOS, which can be observed during a pelvic exam. Due to the hormonal imbalance in PCOS, skin develops light brown or black patches, a condition known as 'acanthosis nigricans'. Skin of neck, armpits, thighs, and breasts are more prone to this skin pigmentation. Also, skin tags appear in those regions. In fact, the dark pigmentation is a cutaneous marker for insulin resistance [19]. The metabolic syndrome resultant of PCOS is vast. In fact, the pathologies are bilateral, as metabolic syndrome, and the constant inflammations, can lead to PCOS. Based on evidences, the link between non-alcoholic fatty liver disease (NAFLD), a chronic liver disease characterized by hepatic damage from fatty liver infiltration leading to end-stage liver disease, and PCOS has been traced, which has indicated a novel hepato-ovarian axis [20].

However, PCOS symptoms can be considered as a spectrum, as the manifestations vary among races, and individuals. Hirsutism is mild or absent in PCOS females of South Asian and Scandinavian origin, for the androgen sensitivity of pilo-sebaceous glands differ [21], but Middle Eastern and Mediterranean origin PCOS patients are more affected by hirsutism [22].

Ovarian hyperstimulation syndrome (OHSS) is a condition of fluid collection in the abdomen and chest (ascites and pleural effusion), resulting due to complications in ovulation induction. This shift of fluids into the third space *i.e.* abdominal and pleural cavity is due to vascular hyperpermeability [23]. OHSS is graded based on the symptoms. It can be mild, leading to weight gain, abdominal pain, nausea and vomiting, bloated abdomen due to ovarian distension (from 5 to 12 cm), low urinary sodium excretion, oliguria etc. But sometimes, the condition is severe, manifesting in difficulty with breathing; ionic imbalance; deep vein thrombosis; hypovolemia, rupture of a cyst in an ovary leading to serious bleeding; ovarian torsion; pregnancy loss from miscarriage, or termination because of complications; pulmonary embolism, kidney failure etc. Ovarian torsion is a medical emergency, and it can cut off blood to the ovaries, causing intense pain and bleeding. In serious cases, death can occur due to hypovolemia, hypercoagulation, respiratory, and circulatory collapse [23]. It means the sodium, and potassium pump functionality is affected. The hormone HCG (human chorionic gonadotrophin) causes the ovary to undergo extensive luteinization, causing the release of excess estrogens, progesterone, and local cytokines. Vascular endothelial growth factor (VEGF) is a substance that induces vascular hyperpermeability. VEGF induces HCG to increase capillary permeability in OHSS. PCOS makes the female susceptible to OHSS [24].

Apart from the physical effects, PCOS can affect the psychiatric aspects of a patient's life. Anxiety, depression, binge eating disorder, and bipolar disorder have been observed as PCOS co-morbidities [25,26]. In postmenopausal women with PCOS, cerebral white matter develops lesions. The neural pathology is likely to be due to neural damages.

1.2. Causes of PCOS

The factors causing PCOS are multiple. Genetic, or lifestyle mistakes, and their combinations can cause PCOS. Thyroid dysfunction, hyperprolactinemia, androgen-secreting tumors, Cushing's syndrome (a syndrome associated with excess cortisol levels), and congenital adrenal hyperplasia can drive PCOS pathogenesis. Chemical exposure has been held responsible for the development of PCOS. The exposure to a number of chemicals, by accidental (pesticide, vehicle exhausts, industrial pollutants etc.) or deliberate (cosmetics, household cleaning agents, chemotherapeutics etc.), means are common in current times. Personal care products such as perfume, sunscreen, deodorant, hair dye etc., which have become the quintessential grooming ingredients, are major culprits behind the rising instances of PCOS. A majority of consumers are unaware of the fact that these innocuous-seeming hygiene substances are endocrine disruptors. These chemical products contain phthalates, parabens, isopropanol, glutaraldehyde, benzophenones, oil of turpentine, metals (nickel sulfate, cobalt chloride), benzophenones etc. [27–29]. Chemicals such as bisphenol A (BPA), present in packaged and canned foods, which when exposed to for a long period, can lead to reproductive issues, including PCOS [30–32]. These and other chemicals are included in consumer products in the form of fragrance, emulsifier, preservative, color, fixatives etc. The strong role of fragrance compounds in perturbing hormonal homeostasis and paving the path for conditions like PCOS has been reviewed [33].

1.3. Genetics of PCOS

Genetic predisposition is one risk factor of PCOS. A number of genes and pathways, mediating PCOS, have been recognized. Variations in these genes such as single nucleotide polymorphisms (SNPs), deletions, additions, inversions, translocations etc. are likely reasons for PCOS development. Several of such causative genes have been genotyped by polymerase chain reaction (PCR) and next generation sequencing (NGS).

Some of the well-studied genes include *SIRT1* (NAD-dependent deacetylase sirtuin-1). The *SIRT1* gene product regulates DNA damage [34]. SNP-63 and indel-19 variant in the *calpain-10* gene is being studied. The protein domain calpain_III has been previously detected in Ebola virus, which indicates its pathologic role [35]. Cytokine gene polymorphisms has been observed in PCOS patients. Association of TLR2 S450S and ICAM1 K469E polymorphisms with PCOS and obesity