WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 20, 222-250. Review Article ISSN 2277–7105

PROPHYLACTIC STRATEGIES IN THE MANAGEMENT OF PCOS AND OHSS: CURRENT EVIDENCE AND FUTURE DIRECTIONS

Komal Dagar*[1], Ujjwal Maan[2] and Ashwani Kumar[3]

[1]M. Pharm. (Pharmacology), [2]Doctor of Pharmacy (PB) and [3]Project Guide (Assistant Professor)

School of Pharmaceutical Sciences, Jaipur National University, Jaipur (302017), Rajasthan, India.

Article Received on
27 August 2024,

Revised on 17 Sept. 2024,
Accepted on 07 October 2024

DOI: 10.20959/wjpr202420-34208

***Corresponding Author**
Komal Dagar
M. Pharm. (Pharmacology), School of Pharmaceutical Sciences, Jaipur National University, Jaipur (302017), Rajasthan, India.

ABSTRACT

Polycystic ovary syndrome (PCOS) is a common symptom in reproductive-aged women. It is characterized by persistent mild inflammation. The symptom cluster known as PCOS is becoming increasingly common among reproductive-age women. The disorder known as ovarian hyperstimulation syndrome (OHSS) occurs when there is an accumulation of fluid in the abdomen and chest (ascites and pleural effusion) as a result of problems in inducing ovulation. The pathogenesis of this condition is not completely understood, but it may be related to genetics, environmental variables, and other aspects of lifestyle. This review provides a current picture of PCOS offers prophylactic methods and makes some pathologic connection hypotheses.

KEYWORDS: Hyperstimulation, cluster, inflammation.

INTRODUCTION

Some diseases strike men and women differently. Problems with female reproductive or estrogen-controlled organs are known as gynecological difficulties. Some of these issues affecting women may be treated, but others can be lifelong or even deadly. Fertility is affected by several of these conditions. Hormonal disruptions are more common than ever before due to the growth of chemical invasion and exposure, which are largely endocrine disruptors. Menstruation irregularities, endometriosis, fibroids, polycystic ovarian syndrome, infertility, ovarian cancer, miscarriage, ectopic pregnancy, premature birth, etc. are among the most

prevalent hormonal and reproductive abnormalities.[1-6] The symptom cluster known as polycystic ovarian syndrome (PCOS) is becoming increasingly common among reproductive-aged women. This condition causes cysts to form in the antral follicles of the ovaries and is caused by an imbalance in the female sex hormones. Typically, the egg would have been released from its water-filled sac, known as a cyst, in preparation for fertilization. When an egg develops into a cyst, this process stops the egg from ovulating. "Amenorrhea" occurs when the menstrual cycle is disrupted due to the blocking of ovulation. Periodontal disease (PCOS) is defined as the development of many cysts in the ovarian follicles as a result of an imbalance in hormones. Ovaries can swell to a width of 10 centimeters due to water-retained cysts, some of which are 10 millimeters across. Fertilization and conception are hindered when ovulation and the menstrual cycle do not occur, making pregnancy challenging.[5,7] Ovarian theca cells normally act as a scaffold for the developing follicle, which in turn helps to generate mature oocytes.[9] Ovarian hyperthecosis occurs when these cells in PCOS individuals respond excessively to insulin's stimulatory actions. Insulin resistance worsens polycystic ovary syndrome by increasing the theca cells' androgenic potential.[8] The theca cells of the ovaries normally act as a scaffold for the developing follicle, which in turn helps to generate mature oocytes.[9] Ovarian hyperthecosis occurs when these cells in PCOS individuals respond excessively to insulin's stimulatory actions. Insulin resistance worsens polycystic ovary syndrome by increasing the theca cells' androgenic potential.[10] Additionally, PCOS is associated with androgenism because of theca cells' heightened sensitivity to gonadal steroid gonadotropin activation. The hypothalamus's failure to secrete the pulsatile gonadotropin-releasing hormone (GnRH) is one cause of polycystic ovary syndrome (PCOS).[11] Gonadotropin-releasing hormone (GnRH) triggers the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The two separate stages of a woman's menstrual cycle cannot occur without these two hormones. Because these hormones are insufficient in PCOS, the egg is unable to develop or to be released from the follicle. Thus, either primary or secondary amenorrhea develops as a result of the cycle being interrupted. Hypothalamic amenorrhea, a kind of secondary amenorrhea, occurs when a woman does not have a monthly cycle for three months in a row, as opposed to primary amenorrhea, which occurs when a woman is unable to achieve menarche for reasons related to her genes or anatomy.[12] An excess of the peptide hormone prolactin inhibits the GnRH.[13] A disruption to one metabolite can have knock-on effects on the others due to the interconnected nature of the human body's systems. Symptoms of polycystic ovary syndrome (PCOS) include abnormalities in the levels of proteins, sugars, peptides, lipids, and hormones such as prolactin,

Müllerian hormone (AMH), cortisol, androgen. Amenorrhea, galactorrhea (inappropriate milk production from the breasts), and osteoporosis are symptoms of hypogonadotropichypogonadism, which is caused by hyperprolactinemia.[14] Prolactin often promotes milk production by the alveolar cells in the breasts following parturition. One reason for elevated prolactin levels is pituitary prolactinoma. Later sections have covered the functions of these components in PCOS.

SYMPTOMS OF PCOS

One typical sign of polycystic ovary syndrome is anovulatory dysfunction. When some cysts release androgens, it causes females to exhibit traits more commonly associated with males, a process known as virilization. Thus, a wide range of manly symptoms, sometimes known as "hyperandrogenism," manifest in PCOS patients. Weight increase, belly and subcutaneous fat, hirsutism, male-pattern baldness, clitoromegaly, deep voice, seborrhea, acne, and enlarged clitoris are all outward manifestations of hyperandrogenism.[15] Changes to metabolic profile also occur alongside these physical changes. Diabetes mellitus type 2 (PCOS) is characterized by insulin resistance. Hyperinsulinemia and diabetes mellitus are possible outcomes.[5,16] The accumulation of fat in the abdominal region, also known as central adiposity, is caused by elevated insulin levels. The majority of PCOS-affected women have a BMI of 30 or above. Additionally, PCOS is associated with several co-morbidities, such as hypertension, cardiovascular disorders, dyslipidemia, etc.[5.16] For women, a blood pressure reading of 120 over 80 is considered healthy. People with polycystic ovary syndrome are more likely to get cardiovascular disease at a younger age. Sugar cravings, nocturnal urination, sluggish healing, extreme tiredness, impaired eyesight, tingling feeling, erratic moods, anxiety, and sadness are common symptoms of polycystic ovary syndrome (PCOS). This makes sense, given the close relationship between diabetes and several other health issues. Symptoms such as constipation, urinary tract infections, nausea, vomiting, fever, and pelvic discomfort are common. Anomalies in bowel and urine movement are caused by the pressing of the big cysts against the rectum or bladder. Another symptom of polycystic ovary syndrome (PCOS) is sleep apnea, a condition in which breathing regularly stops and begins while asleep. This problem is caused by abnormal levels of sex steroids.[17] Endometrial hyperplasia, caused by a lack of progesterone and a persistently high estradiol level, increases a woman's risk of uterine cancer in polycystic ovary syndrome(PCOS).[18] One symptom of polycystic ovary syndrome (PCOS) that can be seen during a pelvic exam is a lack of mucus in the endocervix and a smooth vagina. The hormonal imbalance in polycystic ovary syndrome causes a skin disorder called "acanthosisnigricans,"

which manifests as light brown or black spots. This kind of pigmentation is more common on the breasts, thighs, armpits, and neck. In some areas, you could also see skin tags. A skin indicator of insulin resistance, the dark pigmentation.[19] Polycystic ovary syndrome (PCOS) occurs in a large number of people. Bilateral diseases, such as metabolic syndrome, and chronic inflammations can cause polycystic ovary syndrome (PCOS). Evidence suggests a new hepatoovarian axis in the connection between polycystic ovary syndrome (PCOS) and non-alcoholic fatty liver disease (NAFLD), a chronic liver disease that causes hepatic damage due to fatty liver infiltration and ultimately leads to end-stage liver disease.[20] Because PCOS symptoms develop differently in different racial and ethnic groups, it is more accurate to think of them as a spectrum. Due to differences in androgen sensitivity, hirsutism is moderate or nonexistent in PCOS women of South Asian and Scandinavian descent[21], nonetheless, hirsutism is more common among PCOS individuals of Middle Eastern and Mediterranean backgrounds.[22] A disorder known as ovarian hyperstimulation syndrome (OHSS) occurs when there is an accumulation of fluid in the abdomen and chest (ascites and pleural effusion) as a result of problems in inducing ovulation. The third space, which includes the abdominal and pleural cavities, is filled with fluids because of vascular hyperpermeability.[23] The symptoms are used to grade OHSS. Ovarian distension (ranging from 5 to 12 cm), nausea, vomiting, bloating (abdominal distension), insufficient salt excretion in the urine, oliguria, and modest weight gain are all possible symptoms. On the other hand, when the condition gets bad enough, symptoms like breathing problems, ionic imbalance, deep vein thrombosis, hypovolemia, ovarian cyst rupture causing heavy bleeding, ovarian torsion, pregnancy loss due to complications or miscarriage, pulmonary embolism, kidney failure, etc., can appear. Severe pain and bleeding can result from ovarian torsion, a medical emergency that can cause a blockage of blood flow to the ovaries. Hypovolemia, hypercoagulation, respiratory failure, and circulatory collapse are all potential causes of mortality in extreme circumstances.[23] This indicates that the functions of the sodium and potassium pumps are impacted. Ovarian luteinization, triggered by the hormone human chorionic gonadotrophin (HCG), results in the secretion of an excess of estrogens, progesterone, and local cytokines. The molecule known as vascular endothelial growth factor (VEGF) causes the blood vessels to become more permeable. Increased capillary permeability in OHSS is brought about by VEFG-induced HCG. The female becomes more prone to OHSS due to PCOS.[24] A patient's mental health may also be impacted by polycystic ovary syndrome (PCOS), in addition to the physical health concerns. One or more of the following conditions may accompany polycystic ovary syndrome: anxiety, depression, bipolar disorder, or binge eating disorder.[25,26] Brain white matter lesions

occur in postmenopausal individuals who have polycystic ovary syndrome. Nervous system injury is probably to blame for the neurological symptoms.

CAUSES OF PCOS

Multiple causes can contribute to polycystic ovary syndrome. Pattern baldness in women (PCOS) can be caused by a combination of hereditary factors and unhealthy lifestyle choices. Congenital adrenal hyperplasia, Cushing's syndrome (a condition linked with elevated cortisol levels), androgen-secreting tumors, hyperprolactinemia, and thyroid dysfunction can all play a role in the development of polycystic ovary syndrome (PCOS). Many people believe that PCOS develops as a result of chemical exposure. These days, it's not uncommon for people to be exposed to several chemicals, either accidentally (from things like pesticides, car exhausts, industrial pollution, etc.) or intentionally (from things like cosmetics, home cleaning products, chemotherapeutics, etc.). The increasingly common occurrence of polycystic ovary syndrome (PCOS) is mostly attributable to personal care products, which have evolved into fundamental grooming elements including perfume, sunscreen, deodorant, hair color, etc. These seemingly harmless personal care products are endocrine disruptors, but most buyers have no idea this. Some of the chemicals included in these chemical goods include phthalates, parabens, isopropanol, glutaraldehyde, benzophenones, turpentine oil, and metals like nickel sulfate and cobalt chloride.[27-29] Bisphenol A (BPA) and other chemicals found in certain packaged and canned foods have the potential to cause PCOS and other reproductive problems if exposed to them for an extended length of time.[30-32] Many common consumer goods contain these and other compounds in various forms, such as flavor enhancers, emulsifiers, preservatives, colors, fixatives, and so on. Perfume chemicals have a significant impact on hormonal balance, which can lead to disorders like polycystic ovary syndrome (PCOS).[33]

GENETICS OF PCOS

There is a genetic component to polycystic ovary syndrome. Multiple genes and mechanisms that mediate polycystic ovary syndrome have been identified. Possible causes of polycystic ovary syndrome (PCOS) include changes to these genes, such as SNPs, deletions, additions, inversions, translocations, etc. A number of these causal genes have been genotyped using next-generation sequencing and polymerase chain reaction (PCR).

One of the genes that has received a lot of attention is SIRT1 (sirtuin-1, a NAD-dependent deacetylase). A gene product known as SIRT1 controls DNA damage response.[34] Research on the calpain-10 gene is focusing on SNP-63 and indel-19 variations. Its pathogenic

involvement has been suggested by the prior detection of the calpain III protein domain in the Ebola virus.[35] Patients with polycystic ovary syndrome have cytokine gene polymorphisms. Evidence linking polymorphisms in the tumor-specific ligand 2 (TLR2) and the insulin receptor beta 1 (ICAM1) gene to polycystic ovary syndrome (PCOS) and obesity has emerged. A correlation between PCOS development and the TGFβ1 gene was found in a study of Korean women.[36]

Folate metabolism, DNA methylation, and RNA synthesis are all significantly impacted by methylenetetrahydrofolate reductase (MTHFR). Researchers have linked some variants of the MTHFR gene to an increased risk of polycystic ovary syndrome (PCOS).[37] Insulin resistance has been associated with polymorphisms in the INS-VNTR insulin gene, which is located on chromosome 11. In polycystic ovary syndrome (PCOS), LH has an amplified effect, and these individuals have been shown to have LH β-subunit genetic variations.[38]

According to research, there is a strong correlation between PCOS and the development of the condition in a woman's daughters. A high AMH level, which is present in PCOS moms, is the determinant of this propensity.[39] This suggests that the AMH-coding gene may also play a role. Personality disorder with estrogen receptor gamma (PCOS) is associated with the HSD3B2 gene. PCOS and endometrial cancer are characterized by elevated gene expression of SREBP1. Both the PCOS phenotype and the susceptibility to PCOS are influenced by the single-nucleotide polymorphism (SNP) at rs10830963 in the MTNR1B (melatonin receptor 1B) gene.[40] Metabolic characteristics in polycystic ovary syndrome (PCOS) were investigated about copy-number variants (CNVs). The research focused on the GCKR gene's rs780094 and the NEGR1 gene's intragenic rs1244979 and rs2815752. Researchers discovered that SNPs impact metabolic characteristics but are unrelated to PCOS pathophysiology. Genetic variations and copy number variations (CNVs) in genes that are involved in metabolism have an impact on metabolic characteristics in polycystic ovary syndrome (PCOS) patients.[41] Glucocorticoid receptor polymorphisms have recently been linked to metabolic and clinical characteristics in polycystic ovary syndrome (PCOS). There is evidence linking a polymorphism in the LH/HCG receptor gene to polycystic ovary syndrome. Genetic variations in the fokI, bsmI, apaI, and taqI regions of the vitamin D receptor gene have been associated with polycystic ovary syndrome (PCOS). Estrogen imbalance is mediated by critical enzymes including aromatase and serine protease[42,43], as well as polycystic ovary syndrome (PCOS). Polycystic ovary syndrome is likely to include genes that code for these enzymes as well as

additional enzymes in their pathway. Serine proteases mediate estrogen'simmunomodulatory actions. Granzyme A, a serine protease, was discovered to be more highly expressed and activated by IL-12 in a mouse model when estrogen was administered.[44] The tumor progression marker PRSS23 and the marker of human breast cancer, estrogen receptor α (ERα), are co-expressed. The association between ERα and PRSS23 was demonstrated by a study of a breast cancer microarray dataset.[45] Few papers have been published about the relationship between estrogen and serine proteases, even though it is clear and widely believed. A paper from a few decades ago said that the human uterine estrogenreceptor's ligand binding site and the serine protease chymotrypsin's substrate binding site are structurally similar and have some functional overlap.[46]

Regulatory elements at the epigenetic level Investigations about the genesis of PCOS are ongoing. Protein functions, which are like an on/off switch, rely on post-translational changes. Modifications to proteins, such as methylation, acetylation, glycosylation, and so on, can alter their functions. Prenatal androgenization altered DNA methylation patterns in adult visceral adipose tissue and babies, according to a study that used the Rhesus monkey model. A potential risk factor for polycystic ovary syndrome (PCOS) might be such an epigenome change.[47] Researchers observed several transcriptional and epigenetic alterations in the adipose tissues of PCOS patients in a research included sixty-four PCOS females and thirty healthy controls.[48] Multiple follicles have been linked to a "fertility storage condition," according to studies on the evolutionary relevance of polycystic ovary syndrome (PCOS). When a woman's reproductive system is under stress due to inflammation, she may decide to store her eggs in a protective sac called a cyst rather than let them hatch. This way, the eggs will be ready to be released when the weather is more suitable. Multiple pregnancies are commonly seen in PCOS individuals, and this is one reason why.

DIAGNOSIS OF PCOS

You can prevent PCOS from getting worse by getting diagnosed early. The gynecologist can diagnose polycystic ovary syndrome (PCOS) based on the patient's history of symptoms (such as oligomenorrhea) and physical characteristics (hirsutism). Nevertheless, there are established criteria that are used to diagnose polycystic ovary syndrome. The initial diagnostic criteria for polycystic ovary syndrome (PCOS) were established in 1990 at a meeting called by the National Institutes of Health (NIH).[49] Key symptoms of polycystic ovary syndrome (PCOS) were identified in the 2003 Rotterdam Consensus workshop as hyperandrogenism, monthly

abnormalities, and insulin resistance.[50] Indicators of polycystic ovary syndrome (PCOS) can be found in a variety of anthropomorphometric and ultrasound characteristics, as well as in endocrine tests (SHBG, testosterone, free androgen index, FSH, AMH, thyroid function tests, etc.), and lipid profiles. There are several tests that can reveal PCOS, including the glucose tolerance test (GTT) and the prolactin test. For women, a prolactin level below 500 mIU/L is considered normal. One imaging method that can diagnose polycystic ovary syndrome is ultrasound. Cysts can be revealed using transabdominal and vaginal ultrasonography.

PATHOLOGIC MECHANISMS AND BIOMARKERS OF PCOS

Patients with polycystic ovary syndrome can be detected using a plethora of biomarkers. In patients with polycystic ovary syndrome (PCOS), these indicators are either abnormally low or abnormally high relative to healthy women.

A greater quantity of the intercellular adhesion molecule (ICAM)-1, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein (MCP)-1 has been seen in PCOS patients. The presence of these markers suggests that the body is experiencing inflammation. Patients with polycystic ovary syndrome (PCOS) have greater neutrophil-to-lymphocyte ratios and mean platelet volumes (MPVs) compared to healthy women. It is common for PCOS blood profiles to reveal leukocytosis, neutrophilia, and platelet aggregation.[51] One of the leading causes of morbidity is high platelet reactivity. Patients with polycystic ovary syndrome (PCOS) and abnormally high prolactin levels had an elevated MPV level, according to a clinical trial.[52] There was an increase in blood IL-6 levels compared to controls in women with polycystic ovarian syndrome.[53]

Patients with polycystic ovary syndrome have low progesterone levels and excessive levels of estrogen and androgens.[54] The AMH gene codes for AMH, a glycoprotein hormone that belongs to the TGF-β superfamily.[55] In ovarian follicles, granulosa cells secrete this hormone. High levels of AMH (> 10 ng/mL) in PCOS-stricken women prevent folliculogenesis and, hence, anovulation.[55,56] A high AMH level may suggest polycystic ovary syndrome. An increase in pain in the PCOS group is associated with a higher plasma β-endorphin level, and some investigations have found a connection between PCOS and the endogenous opioid system.[57]

Known to cause polycystic ovary syndrome (PCOS), adipocytokines disrupt typical metabolic patterns. Here, researchers have looked at the roles played by adipocytokines like chemerin,

omentin-1, leptin, and adiponectin. Among PCOS patients, there is an upregulation of blood chemerin levels, which are chemoattractant proteins that bind to the G protein-coupled receptor CMKLR1 (chemokine-like receptor-1).[58] Adiposity and insulin resistance are associated with chemerin.[59] Proteases that cleave serine bonds activate chemerin. There is now strong evidence linking the rs17173608 polymorphism in the chemerin gene to polycystic ovary syndrome (PCOS).[60] The control of energy balance relies on leptin, a 16-kDa peptide that is produced by white adipocytes and functions as both an adipokine and a satiety hormone.[61] Ghrelin, a peptide of 28 amino acids that is octanoylated, is the hunger hormone that opposes leptin, which suppresses hunger. To control hunger, both hormones bind to specific receptors in the hypothalamus. Compared to women without polycystic ovary syndrome (PCOS), those with PCOS had higher leptin levels. Insulin resistance, metabolic disorders, infertility, and even the risk of cardiovascular disease are all associated with elevated leptin levels, which may play a role in the development and pathogenesis of polycystic ovary syndrome (PCOS). In obese PCOS patients, ghrelin levels are related to AMH levels independently. Ghrelin is a neuropeptide that functions in the brain and spinal cord. By binding to the growth hormone secretagogue receptor (GHSR), it regulates inflammation, cell proliferation, apoptosis, and angiogenesis, which in turn reduces benign prostatic hyperplasia or an enlarged prostate.[62] In obesity and other insulin-resistant conditions, the plasma level of Omentin-1, which is generated by visceral adipose tissue, is lowered.

A gene called PBEF1 encodes an enzyme called nicotinamidephosphoribosyltransferase (NAMPT), which is also called visfatin or pre-B-cell colony-enhancing factor 1. For mammals to be able to synthesize nicotinamide adenine dinucleotide (NAD+), this protein plays a crucial role as the rate-limiting enzyme in the NAD+ salvage pathway. NAMPT is a cytokine that enhances B cell maturation and prevents neutrophil apoptosis; it is also known as pre-B cell colony enhancing factor (PBEF). Regardless of insulin resistance, cardiovascular disease is associated with increased visfatin. One possible function of this enzyme in polycystic ovary syndrome is not yet known. Metabolic and hormonal pathways in polycystic ovary syndrome include phosphatidylinositide-3 kinase as a molecular target.

The research found that women with polycystic ovary syndrome had a higher level of the monocyte/macrophage-specific marker, serum soluble CD163 (Cluster of Differentiation 163).[63] When intestinal inflammation is present, neutrophil migration to the mucosa of the intestines is indicated by fecalcalprotectin levels that are higher than usual.[64] The levels of

CRP (C-reactive protein), a metric of inflammation, are elevated in PCOS patients. The link between high CRP and other inflammatory diseases such as diabetes, atherosclerosis, cardiovascular illnesses[65], cystic fibrosis[66], and Crohn's disease[67] is well-substantiated. Clotting, enhanced production of adhesion molecules, and oxygen radical formation are all facilitated by CRP.

One dietary medium-chain fatty acid (MCFA) that suppresses the recruitment of Nur[77], NGFIB, and NR4A1, is decanoic. In humans, the NR4A1 gene encodes the protein known as Nur.[77] Nur[77] controls the signaling of androgens through their receptors. Decanoic acid has been shown to effectively reverse the endocrine and metabolic problems associated with polycystic ovary syndrome (PCOS) in rat models.[68]

The diagnosis of polycystic ovary syndrome (PCOS) may be made by analyzing the levels of insulin, plasma glucose, glycatedhemoglobinA1c (HbA1c), and c-peptide during fasting. Plasma glucose concentration can be indicated by the HbA1c level. Insulin resistance, a feature of polycystic ovary syndrome, is indicated by a high glucose level.[69-71] When a woman has polycystic ovary syndrome (PCOS), her LDL cholesterol levels rise while her HDL cholesterol levels fall. The danger of coronary artery plaque development and, by extension, of heart attacks, is posed by this dyslipidemia condition.

A new understanding of the function of microRNAs (miRNAs) in androgen metabolism and polycystic ovary syndrome (PCOS) has emerged. Researchers have looked at miRNA 23a and miRNA 23b in the blood of PCOS patients. In metaphase II oocytes from PCOS-afflicted women, the miR-483-5p and miR-486-5p are down-regulated in the cumulus cells.[72] It is reasonable to assume that epigenetics plays a role in PCOS development, given that miRNAs may regulate patterns of gene expression.

Metabolites serve purposes beyond their recognized responsibilities. To get strong insights into polycystic ovary syndrome (PCOS), it is necessary to profile the serum and plasma components and determine their function in the immune-neural-endocrine axis. Researchers should look into the roles of AMH and inhibin B, a glycoprotein that inhibits FSH levels and is generated by ovarian granulosa cells, in the development of polycystic ovary syndrome. To eliminate creatinine, the kidneys filter out this waste product of the muscles. As with cystatin C, a high blood creatinine level suggests a suboptimal glomerular filtration rate (GFR), which is associated with polycystic ovary syndrome (PCOS).[73] Acute kidney damage can be detected

by measuring serum cystatin C, a biomarker of renal function. Plasma C-reactive protein and uric acid levels are also increased in polycystic ovary syndrome individuals with an enhanced GFR.[74] Patients with polycystic ovary syndrome (PCOS) and obesity tend to have higher serum ferritin levels. Insulin resistance and hyperglyceridemia are indicated by a high blood ferritin level.[75] Research using serum metabolomics has the potential to identify new prognostic indicators and characterize their levels.

THERAPY

Drugs and surgeries are two of the many treatment options for polycystic ovary syndrome (PCOS). The cysts associated with polycystic ovary syndrome (PCOS) are self-resolving cysts. However, acute, unexpected discomfort in the lower abdomen might occur if a cyst bursts and bleeds.

By reducing the frequency and severity of menstrual cycles ovulation suppression and cyst development, oral contraceptives (OCPs) that are used for six months help with hyperandrogenism. Nevertheless, venous thrombosis is a potential concern.[76] The blood 25-hydroxy vitamin D levels are also lowered, which has implications for bone health. Among PCOS patients, this treatment raises levels of plasma ICAM-1, MCP-1, and TNF-α. Despite their inflammatory nature, these cytokines regulate insulin, lipids, and plasma glucose levels.[77] By reducing elevated parameters like insulin, androgens, and circulating free T levels while increasing SHBG and IGFBP levels, the insulin sensitizer metformin improves the quality of life for females with polycystic ovary syndrome (PCOS).[78] The levels of SHBG and androgens are inversely related. Preventing OHSS was the goal of metformin medication before and during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) in women diagnosed with polycystic ovary syndrome (PCOS).[79] Metformin regulates metabolism by acting on adipocytokines such as IL6, IL-8, angiogenic proteins (VEFG), adiponectin, and leptin. Additionally, by enhancing mitochondrial integrity, this medication decreases platelet hyperreactivity in PCOS patients. Patients with polycystic ovary syndrome (PCOS) can lose weight with the use of the glucagon-like peptide-1 (GLP-1) receptor agonistsexenatide and liraglutide, either on its own or in conjunction with metformin.[80] Period cyclicity, hormonal markers, and overall health were all enhanced by a combination of exenatide and metformin.

Overweight, insulin-resistant, oligoovulatory women with polycystic ovary syndrome: metabolic profiles and inflammatory markers. Metformin does have several negative effects,

though. These include lactic acidosis, extreme lethargy, fainting, cold skin, muscular discomfort, difficulty breathing, irregular heartbeat, nausea, vomiting, and diarrhea.[81]

One other approach to treating polycystic ovary syndrome is using steroid hormone supplements. Research on aromatase inhibitors, such as letrozole, to induce ovulation is ongoing.[82] Spironolactone, flutamide, cyproterone acetate, and finasteride are some of the antiandrogens that can be used to treat androgenism. To combat insulin resistance, medications like N-acetyl-cysteine are used. In cases of anovulatory infertility, the anti-estrogen drug clomiphene citrate is prescribed.[83] For PCOS cases where clomiphene was unsuccessful, a combination of metformin and clomiphene citrate proved successful. To address clomiphene resistance, gonadotrophin stimulation is also utilized.

Therefore, while each of the aforementioned treatments has its place, they are all only partially successful. Plus, there are potential adverse effects associated with various treatment methods. Host variables determine the therapy's relevance and danger. Among many other side effects, long-term use of these hormone manipulators can lead to obesity, cancer, and mental health problems.

Surgical removal of the cysts is necessary if they do not disappear after a few months and cause ovarian torsion. Both laparoscopy and laparotomy are capable of accomplishing this. Successful treatment of polycystic ovary syndrome has been demonstrated using laparoscopic ovarian cautery (drilling).[84] By making incisions near the pubic hairline, the cyst can be removed with the use of a laparoscope. Laparotomy is utilized for large cysts. The omentum, a fold of fatty tissue, the uterus, both ovaries, and a few lymph nodes are removed in extreme instances.

Female infertility can be caused by either hyperprolactinemia or polycystic ovary syndrome (PCOS). Since both conditions have many clinical symptoms, they are thought to be related. Having both disorders at the same time does not always indicate that they are pathologically dependent, according to research.[85] The difficult and sometimes dangerous treatment for hyperprolactinemia is a dopamine agonist, also known as a dopamine receptor activator. This medication decreases prolactin release and frequently results in the shrinking of prolactinoma.[86] When it comes to treating hyperprolactinemia, one dopamine agonist that has been authorized is L-DOPA. One of the treatment choices to postpone neurological diseases triggered by estrogen deprivation is this dopamine precursor, L-DOPA. Other possibilities

include monoamine oxidase-B (MAO-B) and ergot alkaloid derivatives. Modifications in gene transcription are caused by the activation of signaling pathways by these agonists, which involve trimeric G-proteins and β-arrestins. A powerful agonist on D2 dopamine receptors, cabergoline is an ergot derivative. Nevertheless, there is some evidence that people taking medication for Parkinson's disease may be more likely to develop heart valve abnormalities. When treating hyperprolactinemia, the medication dose must be significantly reduced to half a milligram twice weekly. Because schizophrenia is caused by an excess of dopamine, the psychiatric disorder is treated using dopamine antagonists.[87] However, hyperprolactinemia is a side effect of these antagonists. Another research found that prolactin inhibits dopamine release while increasing its synthesis.[88] Consequently, PCOS is greatly endangered by the side effects of dopamine modification. In rat models of polycystic ovary syndrome, melatonin is protected against metabolic and reproductive abnormalities. Menstrual cyclicity might be restored in PCOS patients with 6-month melatonin medication, according to cohort research.[89] Many women who suffer from polycystic ovary syndrome have difficulties sleeping. Since melatonin aids in sleep, its positive impact on polycystic ovary syndrome (PCOS) is comprehensible. The skin is also protected from oxidative stress by this hormone and neurotransmitter that is released by the pineal gland.[90] This association suggests that oxidative stress and inflammations are the root causes of abnormalities in several organs, including the brain, skin, and ovaries.

The use of Acupuncture to treat polycystic ovary syndrome has gained some support.

Acupuncture stimulates the circulating GnRH and adiponectin systems. Compared to a control group that did not get electroacupuncture, those who did saw an increase in menstruation frequency in a randomized controlled experiment.[91] The usefulness of acupuncture in treating ovulation problems in PCOS patients requires further randomized controlled trials (RCTs).[91] In PCOS, researchers looked at the effects of transcutaneous acupointelectrostimulation on sex hormone levels in the blood. By regulating sympathetic nerve activity or sex steroid production, the application reduced endocrine and reproductive abnormalities in PCOS women.[92]

Indices of insulin disruption and metabolic syndrome include body mass index (BMI), glycemic index (GI), lipid accumulation product (LAP), and visceral adiposity index (VAI). Therefore, these parameters should be checked at regular intervals. Optimal treatment choices for polycystic ovary syndrome require research with long-term follow-up.

Obesity, which is defined as a high body mass index (BMI) (>25), a large waist circumference, and excess fat around the abdomen, is a major contributor to polycystic ovary syndrome (PCOS).[71] Reducing testosterone levels, stimulating ovulation, and reestablishing metabolic processes are all outcomes of a reduction in belly fat, which in turn reduces inflammation. Although glucagon-like peptide-1 receptor agonists (GLP-1RA) cause adverse effects such as nausea, they are effective in causing weight reduction.[80] To reduce body mass index (BMI), it is recommended that overweight people with polycystic ovary syndrome exercise regularly and eat healthily.[93] Losing weight has been found to alleviate most of the negative symptoms associated with polycystic ovary syndrome. Cardiometabolic profile in polycystic ovary syndrome women can be improved with exercise training. On the other hand, cardiovascular problems might arise from abrupt, intense activity due to platelet activation. Also, because our bodies are so reactive to changes in energy levels, things like extreme diets and exercise can throw off our hormone levels. On the contrary, PCOS can be managed via moderate exercise daily. The following is an incomplete list of the phytochemicals that have demonstrated ameliorative effects in animal models of polycystic ovary syndrome (PCOS). In rat models of polycystic ovary syndrome (PCOS), the flavonoid rutin restores metabolic, biochemical, and hormonal abnormalities.[94] Rutin reduced the amount of cystic follicles and had an effect similar to metformin. A better antioxidant and lipid profile in polycystic ovary syndrome (PCOS) patients was the treatment method. Research has demonstrated that rutin can reduce CRP levels. Quercetin reduces insulin resistance in polycystic ovary syndrome (PCOS) via relieving inflammatory milieu, according to rat model research.[95] By acting as an anti-androgenic agent, soy isoflavones improve the rat PCOS model caused by letrozole.[96] Due to its antioxidant characteristics, resveratrol is beneficial in treating polycystic ovary syndrome (PCOS) in rats when administered at a dosage of 10 mg/kg/d.[97] Resveratrol reduced levels of AMH hormone and elevated glutathione levels.[97] The histopathological characteristics in animal models of polycystic ovary syndrome were improved by colchicine, a secondary metabolite derived from plants of the genus Colchicum. A benzylisoquinoline alkaloid derived from poppy plants, noscapine, may help reduce PCOS symptoms.[98] A decoction of Chinese xiangqi, which is made from the root of Polygonummultiflorum, has a strong therapeutic impact on rat models of polycystic ovary syndrome (PCOS). This action was thought to be caused by the modulation of the insulin signal transduction system.[99] Herbal products are often sought after by PCOS sufferers due to claims of their usefulness in intervention. Citrus aurantium, TribulusTerrestris, Glycyrrhiza spp., Paeonialactiflora, Cinnamomum cassia, and Vitexagnuscastus are some of the plants that have been found to

have an impact on polycystic ovary syndrome.[100] Herbal medications, on the other hand, are often not standardized. By causing additional disruptions in hormone control, they can make the situation worse. They still have the same negative side effects, even though they are plant-based. Ion channels, neuronal receptors, and thrombocytes are all susceptible to their manipulation, which can have devastating effects.

DISCUSSION

The symptoms of polycystic ovary syndrome (PCOS) are more nuanced than just a hormonal imbalance. The pathophysiology of polycystic ovary syndrome involves all three essential parts of the neuro-immune endocrine axis. In addition to polycystic ovary syndrome (PCOS), autoimmune thyroiditis, anti-thyroid antibodies, and goiter are more common in this population.[101] Age and co-morbidities affect PCOS severity differently in different persons. Dyslipidemia, hypothyroidism, and insulin resistance are all symptoms of polycystic ovary syndrome (PCOS), which increases the risk of cardiovascular disease in individuals. Nevertheless, it is not possible to map the real occurrences of cardiovascular illnesses and strokes. There are a lot of complicated interconnections and the linkages aren't easy. Despite PCOS's reputation as an illness affecting only reproductive-age women, the disease's harmful consequences can manifest even after menopause has passed. Some of the consequences of polycystic ovary syndrome include hyperandrogenism, an increased risk of cardiovascular disease, and a vulnerability to type 2 diabetes.[102] Because of their shared inflammatory parameters—including oxidative stress, C-reactive protein (CRP), interleukin-18 (IL-18), and matrix metalloproteinase-1—it is very probable that multiple sclerosis (MS) and polycystic ovary syndrome (PCOS) are co-morbidities. However, the nature of this relationship is still largely unexplored.

The pathophysiology of polycystic ovary syndrome (PCOS) includes hypothalamic-pituitary, ovarian, and adrenal components. Research is shedding light on the condition's hepatic aspects; for example, PCOS patients often have NAFLD, or non-alcoholic fatty liver disease.[20] Given the interconnected nature of all bodily systems, this finding should come as no surprise. There is strong evidence from several research between diabetes with polycystic ovary syndrome (PCOS). The hallmark of diabetes, impaired glucose metabolism and utilization, is also a risk factor for Alzheimer's disease.[103] It further suggests a connection between polycystic ovary syndrome and neuropathology. A correlation between depression, a PCOS co-morbidity, and decreased glucocorticoid receptor activity has recently emerged.[104] While it is outside the

scope of this article to explore PCOS metabolic circuitry, the activated renin-angiotensin-aldosterone system (RAAS), a significant inflammatory mechanism, is involved at some point.[105]

Since polycystic ovary syndrome (PCOS) is becoming more common, women should be educated on what causes it and how to manage it naturally, without medication, since all of these treatments have adverse effects. The hormonal medications administered for polycystic ovary syndrome (PCOS) have unpleasant side effects since the condition is a result of hormonal imbalance. Medications provide only a temporary fix and come with their own set of risks. It is important for patients and susceptible women to closely examine their lifestyle choices and steer clear of substances that cause inflammation. Tobacco, processed meals, and alcoholic beverages should all be avoided. The use of chemically-based personal care products should be minimized above everything else. These products' potential to damage the endocrine system is grossly understated. Instead of focusing on treating the symptoms, they should educate themselves and work to eliminate the root causes. A lady may seek out mechanical and chemical methods to remove lip hair (hirsutism) if she notices it. Waxing, threading, plucking, epilation creams, and laser hair removal are her methods of choice. These medications exacerbate polycystic ovary syndrome by further evading the hormones. An evaluation of FAERS, the Adverse Event Reporting System of the Food and Drug Administration[107] revealed that personal care product use was the root cause of most unwanted systemic or topical responses, with ovarian problems ranking highest.

Salon beauticians often come into contact with caustic solutions, metals, perfumes, hair colors, bleaches, and bleaching agents. Many allergic reactions, including urticaria, photodermatoses, conjunctivitis, conjunctivitis, conjunctivitis, and respiratory tract disorders (asthma included), are caused by these substances.[106] Chronic exposure worsens these inflammations, which can lead to uterine and ovarian illnesses, such as polycystic ovary syndrome (PCOS). They stay in the profession despite the high risk of serious illness or death since it provides a means of subsistence. Nobody, not even chimpanzees, has evolved to withstand the relentless barrage of harm that chemicals may dish out. When exposed to them over an extended period, they will eventually cause harm. So, it's important to see a doctor to figure out what's wrong with your health, and then you should work on losing weight, changing your lifestyle, and staying away from inflammation. These three fundamental choices aren't simple, but they are doable with self-control.

Eating rice is not advised for PCOS patients since insulin resistance is common in this condition. However, wheat, another common grain, can lead to inflammatory bowel syndrome and gluten intolerance. Under these competing demands, there is no simple solution. Because of the interconnected nature of human bodily systems, there is a strong correlation between inflammation in the intestines and inflammation in the ovaries. The focus is on the increased activity of inflammatory enzymes and the body's acidity levels.[108]

Pregnant women should be aware that seemingly unrelated causes might promote polycystic ovary syndrome (PCOS). Even if they are working out regularly and are cognizant of the need to maintain a healthy weight, many are unaware that some personal care products might cause them to put on weight due to changes in their metabolism. An estimated 12–21% of teenage girls are found to have polycystic ovary syndrome (PCOS), with an additional 70% not even knowing they have it.[109]

Although polycystic ovary syndrome (PCOS) is not a new condition, the increased prevalence of its negative consequences and co-morbidities is cause for worry. Although it is an obstacle to living a healthy life, it may be overcome or managed with lifestyle changes, such as losing weight and avoiding inflammatory chemicals. It is reasonable to assume, however, that PCOS symptoms will worsen as a result of the aggressive marketing of chemicals and the rising levels of pollution.

The condition of polycystic ovary syndrome (PCOS) is characterized by persistent mild inflammation. Inflammasome activation occurs when the immune system detects danger.[110] Almost every illness revolves around inflammation. Inflammation can be triggered by any kind of stressor event or inflammatory substance. It forms an acidic environment and the inverse is also true. The process by which acidosis creates a hypoxic, tumor-inducing microenvironment and abnormal enzyme cascades has been extensively studied.[108] So, it's important to be cautious around inflammatory substances in regular life and avoid them if possible. Fragrances and other common, everyday compounds can disrupt hormone levels, which can cause polycystic ovary syndrome (PCOS).[111] Even seemingly harmless cosmetics, such as those that whiten the skin, reduce the appearance of wrinkles, prevent sweating, lighten hair color, etc., can throw off hormonal balance and lead to polycystic ovary syndrome (PCOS). Developed nations have a greater PCOS prevalence due to the increased use of medicines and cosmetics. Occupation may put a woman at increased risk for polycystic ovary syndrome, however this has received little research.

Medications are not a sustainable solution to the PCOS condition, but meticulous lifestyle revision is, which can be achieved by a balanced diet, exercise, and chemical-free lifestyle. With the rising access to digital information, garnering information on PCOS should not be a problem for the general public. The patients should not self-medicate, but they should self-educate themselves. Awareness can help females recognize the signs of PCOS and seek medical help before things cross the point beyond repair.

Some ethnic groupings have a greater frequency of polycystic ovary syndrome. The Han Chinese and the Aborigines of Australia are among the groups that have had polycystic ovary syndrome (PCOS) examined. Metabolic syndrome linked to polycystic ovary syndrome is more common in some racial and ethnic groups than in others. It suggests that environmental variables, including food and climate, as well as other aspects of lifestyle, have a significant role in the development of polycystic ovary syndrome (2F). Insulin resistance and obesity are more common in certain racial groups, and PCOS is more common in those groups as a whole. Consequently, it is important to continue investigating PCOS genetic and metabolic indicators. Further understanding of polycystic ovary syndrome can be derived from large-scale investigations involving the general public. To further understand PCOS and its causes, potential dangers, and the effectiveness of treatments, bigger trials with longer durations are required.

CONCLUSION

Endocrine disorders such as polycystic ovary syndrome (PCOS) provide cause for concern. There has been a dramatic increase in the number of cases of this cluster of diseases, which is not just one condition. It affects women's general health continues after menopause and reduces their fertility. The exact effect of polycystic ovary syndrome on longevity is unclear, but there's no doubt that it lowers quality of life. Additionally, adverse effects are probably caused by the chemical habit it causes. Therefore, polycystic ovary syndrome (PCOS) diagnostics, epidemiology, genetics, and molecular causes require more investigation. Therapy alone will not be enough to alleviate inflammation, the underlying cause of polycystic ovary syndrome (PCOS), hence making changes to one's way of life is also recommended. Reducing oxidative stress, acidosis, and immunological activation can help those suffering from polycystic ovary syndrome. Not only does this review provide a current picture of polycystic ovary syndrome (PCOS), but it also offers prophylactic methods and makes some pathologic connection hypotheses.

CONFLICT OF INTEREST

There is no conflict of interest in the submission of this manuscript.

REFERENCES

1. E.K. Chung, L. Nurmohamed, L. Mathew, I.T. Elo, J.C. Coyne, J.F. Culhane, Risky health behaviors among mothers-to-be: the impact of adverse childhood experiences, Acad. Pediatr, 2010; 10: 245–251, http://dx.doi.org/10.1016/j.acap.2010. 04.003.
2. A.L. Beavis, A.J.B. Smith, A.N. Fader, Lifestyle changes and the risk of developing endometrial and ovarian cancers: opportunities for prevention and management, Int. J. Womens Health, 2016; 8: 151–167, http://dx.doi.org/10.2147/IJWH. S88367.
3. J.-B. Dai, Z.-X. Wang, Z.-D. Qiao, The hazardous effects of tobacco smoking on male fertility, Asian J. Androl, 2015; 17: 954–960, http://dx.doi.org/10.4103/1008-682X.150847.
4. S.M. Seifert, J.L. Schaechter, E.R. Hershorin, S.E. Lipshultz, Health effects of energy drinks on children, adolescents, and young adults, Pediatrics, 2011; 127: 511–528, http://dx.doi.org/10.1542/peds.2009-3592.
5. S.M. Sirmans, K.A. Pate, Epidemiology, diagnosis, and management of polycystic ovary syndrome, Clin. Epidemiol, 2013; 6: 1–13, http://dx.doi.org/10.2147/ CLEP.S37559.
6. N. Cuhaci, S.B. Polat, B. Evranos, R. Ersoy, B. Cakir, Gynecomastia: clinical evaluation and management, Ind. J. Endocrinol. Metab, 2014; 18: 150–158, http:// dx.doi.org/10.4103/2230-8210.129104.
7. G.W. Bates, R.S. Legro, Longterm management of polycystic ovarian syndrome (PCOS), Mol. Cell. Endocrinol, 2013; 373: 91–97, http://dx.doi.org/10.1016/j. mce.2012.10.029.
8. R. Homburg, Pregnancy complications in PCOS, in diagnosis manage, Polycyst. Ovary Syndr., 2009; 135–142, http://dx.doi.org/10.1007/978-0-387-09718-3_11.
9. J.M. Young, A.S. McNeilly, Theca: the forgotten cell of the ovarian follicle, Reproduction, 2010; 140: 489–504, http://dx.doi.org/10.1530/REP-10-0094.
10. J. Qu, Y. Wang, X. Wu, L. Gao, L. Hou, R. Erkkola, Insulin resistance directly contributes to the androgenic potential within ovarian theca cells, Fertil. Steril, 2009; 91: 1990–1997, http://dx.doi.org/10.1016/j.fertnstert.2008.02.167.
11. R. Tsutsumi, N.J.G. Webster, Gn R.H. Pulsatility, The pituitary response and reproductive dysfunction, Endocr. J., 2009; 56: 729–737, http://dx.doi.org/10. 1507/endocrj.K09E-185.
12. D.A. Klein, M.A. Poth, Amenorrhea: an approach to diagnosis and management, Am. Fam. Phys., 2013; 87: 781–788.

13. N. Martin, Prolactin disorders, Med. (United Kingdom), 2017; 45: 484–487, http://dx.doi.org/10.1016/j.mpmed.2017.05.003.
14. A. Capozzi, G. Scambia, A. Pontecorvi, S. Lello, Hyperprolactinemia: pathophysiology and therapeutic approach, Gynecol. Endocrinol, 2015; 31: 506–510, http://dx.doi.org/10.3109/09513590.2015.1017810.
15. N. Madnani, K. Khan, P. Chauhan, G. Parmar, Polycystic ovarian syndrome, Indian J. Dermatol. Venereol. Leprol, 2013; 79: 310–321, http://dx.doi.org/10.4103/0378-6323.110759.
16. H. Teede, A. Deeks, L. Moran, E. Diamanti-Kandarakis, C. Kouli, A. Bergiele, et al., Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan, BMC Med., 2010; 8: 41, http://dx.doi.org/10.1186/1741-7015-8-41.
17. E. Tasali, E. Van Cauter, D.A. Ehrmann, Polycystic ovary syndrome and obstructive sleep apnea, Sleep Med. Clin., 2008; 3: 37–46, http://dx.doi.org/10. 1016/j.jsmc.2007.11.001.
18. X. Li, Y. Feng, J.F. Lin, H. Billig, R. Shao, Endometrial progesterone resistance and PCOS, J. Biomed. Sci., 2014; 21(2), http://dx.doi.org/10.1186/1423-0127-21-2.
19. S. Venkatswami, S. Anandan, Acanthosisnigricans: a flag for insulin resistance, J. Endocrinol. Metab. Diabetes South Afr., 2014; 19: 68–74, http://dx.doi.org/10. 1080/16089677.2014.11073603.
20. R. Karoli, J. Fatima, A. Chandra, U. Gupta, F. Islam, G. Singh, Prevalence of hepatic steatosis in women with polycystic ovary syndrome, J. Hum. Reprod. Sci., 6: 9, http://dx.doi.org/10.4103/0974-1208.112370.
21. E. Vanky, S. Kjotrod, K.A. Salvesen, P. Romundstad, M.H. Moen, S.M. Carlsen, Clinical, biochemical and ultrasonographic characteristics of Scandinavian women with PCOS, Acta Obstet. Gynecol. Scand, 2004; 83: 482–486, http://dx.doi.org/ 10.1111/j.0001-6349.2004.00373.x.
22. Y. Zhao, J. Qiao, Ethnic differences in the phenotypic expression of polycystic ovary syndrome, Steroids, 2013; 78: 755–760, http://dx.doi.org/10.1016/j. steroids.2013.04.006.
23. P. Kumar, S.F. Sait, A. Sharma, M. Kumar, Ovarian hyperstimulation syndrome, J. Hum. Reprod. Sci., 2011; 4: 70–75, http://dx.doi.org/10.4103/0974-1208.86080.
24. S. Kol, R. Homburg, B. Alsbjerg, P. Humaidan, The gonadotropin-releasing hormone antagonist protocol–the protocol of choice for the polycystic ovary syndrome patient undergoing controlled ovarian stimulation, Acta Obstet. Gynecol. Scand, 2012; 91: 643–647, http://dx.doi.org/10.1111/j.1600-0412.2012. 01399.x.

25. S.L. Blay, J.V.A. Aguiar, I.C. Passos, Polycystic ovary syndrome and mental disorders: a systematic review and exploratory meta-analysis, Neuropsychiatr. Dis. Treat., 2016; 12: 2895–2903, http://dx.doi.org/10.2147/NDT.S91700.
26. S.M. Sirmans, K.A. Pate, Epidemiology, diagnosis, and management of polycystic ovary syndrome, Clin. Epidemiol, 2013; 6: 1–13, http://dx.doi.org/10.2147/ CLEP.S37559.
27. O. Yang, H.L. Kim, J.-I. Weon, Y.R. Seo, Endocrine-disrupting chemicals: a review of toxicological mechanisms using molecular pathway analysis, J. Cancer Prev., 2015; 20: 12–24, http://dx.doi.org/10.15430/JCP.2015.20.1.12.
28. J. Boberg, C. Taxvig, S. Christiansen, U. Hass, Possible endocrine disrupting effects of parabens and their metabolites, Reprod. Toxicol, 2010; 30: 301–312, http://dx. doi.org/10.1016/j.reprotox.2010.03.011.
29. S. Özen, Ş. Darian, Effects of environmental endocrine disruptors on pubertal development, J. Clin. Res. Pediatr. Endocrinol, 2011; 3: 1–6, http://dx.doi.org/ 10.4274/jcrpe.v3i1.01.
30. A. Konieczna, A. Rutkowska, D. Rachoń, Health risk of exposure to bisphenol a (BPA), Rocz. PaństwowegoZakładuHig, 2015; 66: 5–11. (Accessed 05, August 2015), http://www.ncbi.nlm.nih.gov/pubmed/25813067.
31. G.O. Noonan, L.K. Ackerman, T.H. Begley, Concentration of bisphenol in highly consumed canned foods on the U.S. Market, J. Agric. Food Chem., 2011; 59: 7178–7185, http://dx.doi.org/10.1021/jf201076f.
32. S. De Coster, N. van Larebeke, Endocrine-disrupting chemicals: associated disorders and mechanisms of action, J. Environ. Public Health, 2012; 2012: 713696, http://dx.doi.org/10.1155/2012/713696.
33. S. Patel, Fragrance compounds: the wolves in sheep's clothing, Med. Hypotheses, 2017; 102: 106–111, http://dx.doi.org/10.1016/j.mehy.2017.03.025.
34. Y.A. Lee, E.J. Cho, T. Yokozawa, Protective effect of persimmon (Diospyros kaki) peel proanthocyanidin against oxidative damage under H2O2-induced cellular senescence, Biol. Pharm. Bull., 2008; 31: 1265–1269 (Accessed 07, October 2016), http://www.ncbi.nlm.nih.gov/pubmed/18520066.
35. S. Patel, S. Patel, Analysis of Ebola virus polymerase domains to find strain-specific differences and to gain insight on their pathogenicity, VirusDisease, 2016; 27: 242–250, http://dx.doi.org/10.1007/s13337-016-0334-8.
36. E.Y. Roh, J.H. Yoon, E.Y. Song, J.J. Kim, K.R. Hwang, S.H. Seo, S. Shin, Single nucleotide polymorphisms in the TGF-β1 gene are associated with polycystic ovary

syndrome susceptibility and characteristics: a study in Korean women, J. Assist. Reprod. Genet, 2017; 34: 139–147, http://dx.doi.org/10.1007/s10815- 016-0824-z.

37. J.B. Wu, J.F. Zhai, J. Yang, Role of methylenetetrahydrofolate reductase C677T and A1298C polymorphisms in polycystic ovary syndrome risk, Genet. Mol. Res., 2016; 15, http://dx.doi.org/10.4238/gmr15048570.
38. S. Dasgupta, P.V.S. Sirisha, K. Neelaveni, K. Anuradha, G. Sudhakar, B.M. Reddy, Role of luteinizing hormone β-subunit gene variants among South Indian women with polycystic ovary syndrome, Gene, 2012; 494: 51–56, http://dx.doi.org/10. 1016/j.gene.2011.11.054.
39. M. Olszanecka-Glinianowicz, A. Zachurzok, A. Drosdzol-Cop, M. BożętowiczWikarek, A. Owczarek, A. Gawlik, J. Chudek, V. Skrzypulec-Plinta, E. MałeckaTendera, Circulating anti-müllerian hormone levels in daughters of women with and without polycystic ovary syndrome, Horm. Mol. Biol. Clin. Invest, 2016; 85: 372–378, http://dx.doi.org/10.1159/000444637.
40. C. Li, Y. Shi, L. You, L. Wang, Z.-J. Chen, Association of rs10830963 and rs10830962 SNPs in the melatonin receptor (MTNR1B) gene among Han Chinese women with polycystic ovary syndrome, Mol. Hum. Reprod, 2011; 17: 193–198, http://dx.doi.org/10.1093/molehr/gaq087.
41. B. Knebel, S. Lehr, O.E. Janssen, S. Hahn, S. Jacob, U. Nitzgen, D. Müller-Wieland, J. Kotzka, Association between copy-number variation on metabolic phenotypes and HDL-C levels in patients with polycystic ovary syndrome, Mol. Biol. Rep., 2017; 44: 51–61, http://dx.doi.org/10.1007/s11033-016-4080-1.
42. S. Patel, A critical review on serine protease: key immune manipulator and pathology mediator, Allergol. Immunopathol. (Madr.), 2017; 45: 579–591, http://dx. doi.org/10.1016/j.aller.2016.10.011.
43. S. Patel, Disruption of aromatase homeostasis as the cause of a multiplicity of ailments: a comprehensive review, J. Steroid Biochem. Mol. Biol., 2017; 168: 19–25, http://dx.doi.org/10.1016/j.jsbmb.2017.01.009.
44. E. Karpuzoglu, C.W. Schmiedt, J. Pardo, M. Hansen, T.L. Guo, S.D. Holladay, R.M. Gogal, Serine protease inhibition attenuates rIL-12-Induced GZMA activity and proinflammatory events by modulating the Th2 profile from estrogen-treated mice, Endocrinology, 2014; 155: 2909–2923, http://dx.doi.org/10.1210/en.2014- 1045.
45. H.-S. Chan, S.-J. Chang, T.-Y. Wang, H.-J. Ko, Y.-C. Lin, K.-T. Lin, K.-M. Chang, Y.-J. Chuang, Serine protease PRSS23 is upregulated by estrogen receptor α and associated

with proliferation of breast cancer cells, PLoS One, 2012; 7: e30397, http://dx.doi.org/10.1371/journal.pone.0030397.

46. A. Lukola, R. Punnonen, Interaction of serine protease inhibitors and substrates with human uterine estrogen receptor, Biochem. Biophys. Res. Commun, 1982; 108: 822–827, http://dx.doi.org/10.1016/0006-291X(82)90903-2.
47. N. Xu, S. Kwon, D.H. Abbott, D.H. Geller, D.A. Dumesic, R. Azziz, X. Guo, M.O. Goodarzi, Epigenetic mechanism underlying the development of polycystic ovary syndrome (PCOS)-like phenotypes in prenatally androgenized rhesus monkeys, PLoS One, 2011; 6, http://dx.doi.org/10.1371/journal.pone.0027286.
48. M. KoKosar, A. Benrick, A. Perfilyev, R. Fornes, E. Nilsson, M. Maliqueo, C.J. Behre, A. Sazonova, C. Ohlsson, C. Ling, E. Stener-Victorin, Epigenetic and transcriptional alterations in human adipose tissue of polycystic ovary syndrome, Sci. Rep., 2016; 6, http://dx.doi.org/10.1038/srep22883.
49. A. Zawadzki, J.K. Dunaif, Diagnostic criteria for polycystic ovary syndrome: towards a rational approach, Polycyst. Ovary Syndr, 1992; 337–384.
50. T.R.E.-S.P.C.W.G. PCOS Consensus Workshop Group, Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, Fertil. Steril, 2004; 81: 19–25, http://dx.doi.org/10.1016/j.fertnstert. 2003.10.004.
51. C.A. Dasanu, B.A. Clark, T.E. Ichim, D.T. Alexandrescu, Polycystic ovary syndrome: focus on platelets and prothrombotic risk, South Med. J., 2011; 104: 174–178, http://dx.doi.org/10.1097/SMJ.0b013e31820c0172.
52. Ö. Yilmaz, M. Calan, T. Kume, M. Temur, P. Yesil, M.Y. Senses, The effect of prolactin levels on MPV in women with PCOS, Clin. Endocrinol. (Oxf.), 2015; 82: 747–752, http://dx.doi.org/10.1111/cen.12647.
53. Z. Peng, Y. Sun, X. Lv, H. Zhang, C. Liu, S. Dai, Interleukin-6 levels in women with polycystic ovary syndrome: a systematic review and meta-analysis, PLoS One, 2016; 11: e0148531, http://dx.doi.org/10.1371/journal.pone.0148531.
54. L. Bartolone, G. Smedile, V. Arcoraci, F. Trimarchi, S. Benvenga, Extremely high levels of estradiol and testosterone in a case of polycystic ovarian syndrome. Hormone and clinical similarities with the phenotype of the αestrogen receptor null mice, J. Endocrinol. Invest, 2000; 23: 467–472, http://dx.doi.org/10.1007/ BF03343757.
55. P. Bhide, R. Homburg, Anti-Müllerian hormone and polycystic ovary syndrome, Best Pract. Res. Clin. Obstet. Gynaecol, 2016; 37: 38–45, http://dx.doi.org/10. 1016/j.bpobgyn.2016.03.004.

56. R. Tal, D.B. Seifer, M. Khanimov, H.E. Malter, R.V. Grazi, B. Leader, Characterization of women with elevated antimüllerian hormone levels (AMH): correlation of AMH with polycystic ovarian syndrome phenotypes and assisted reproductive technology outcomes, Am.
57. J. Obstet. Gynecol, 2014; 211(59): e1–59, http://dx.doi.org/10.1016/j.ajog.2014.02.026 e8.
58. M. Kiałka, T. Milewicz, S. Mrozińska, I. Rogatko, K. Sztefko, R. Majewska, Pressure pain threshold and beta-endorphins plasma level are higher in lean polycystic ovary syndrome women, Minerva Endocrinol, 2016; 42: 297–305. (Accessed 15, May, 2017), http://www.ncbi.nlm.nih.gov/pubmed/27603705.
59. R. Huang, J. Yue, Y. Sun, J. Zheng, T. Tao, S. Li, W. Liu, Increased serum chemerin concentrations in patients with polycystic ovary syndrome: the relationship between insulin resistance and ovarian volume, Clin. Chim. Acta, 2015; 450: 366–369, http://dx.doi.org/10.1016/j.cca.2015.09.015.
60. D.H. Kort, A. Kostolias, C. Sullivan, R.A. Lobo, Chemerin as a marker of body fat and insulin resistance in women with polycystic ovary syndrome, Gynecol. Endocrinol, 2015; 31: 152–155, http://dx.doi.org/10.3109/09513590.2014. 968547.
61. Z. Movahed, L. Kohan, S. Fallahi, O. Tabiee, Influence of chemerin rs17173608 polymorphism on polycystic ovary syndrome susceptibility, Taiwan, J. Obstet. Gynecol, 2015; 54: 280–283, http://dx.doi.org/10.1016/j.tjog.2014.05.007.
62. R.S. Ahima, Revisiting leptin's role in obesity and weight loss, J. Clin. Invest, 2008; 118: 2380–2383, http://dx.doi.org/10.1172/JCI36284.
63. M. Clyne, Prostate cancer: ghrelin imaging probe specific for prostate cancer, Nat. Rev. Urol., 2012; 9: 293, http://dx.doi.org/10.1038/nrurol.2012.93.
64. K. Kowal, R. Silver, E. Sławińska, M. Bielecki, L. Chyczewski, O. Kowal-Bielecka, CD163 and its role in inflammation, Folia Histochem. Cytobiol, 2011; 49: 365–374. (Accessed 27, September 2017), http://www.ncbi.nlm.nih.gov/pubmed/ 22038213.
65. R. Sherwood, N. Walsham, Fecalcalprotectin in inflammatory bowel disease, Clin. Exp. Gastroenterol, 2016; 9: 21, http://dx.doi.org/10.2147/CEG.S51902.
66. N. Boulman, Y. Levy, R. Leiba, S. Shachar, R. Linn, O. Zinder, Z. Blumenfeld, Increased c-reactive protein levels in the polycystic ovary syndrome: a marker of cardiovascular disease, J. Clin. Endocrinol. Metab, 2004; 89: 2160–2165, http:// dx.doi.org/10.1210/jc.2003-031096.
67. E.T. Zemanick, J.K. Harris, B.D. Wagner, C.E. Robertson, S.D. Sagel, M.J. Stevens, F.J.

Accurso, T.A. Laguna, Inflammation and airway microbiota during cystic fibrosis pulmonary exacerbations, PLoS One, 2013; 8, http://dx.doi.org/10.1371/ journal.pone.0062917.

68. S. Vermeire, C-reactive protein as a marker for inflammatory bowel disease, Inflamm. Bowel Dis., 2004; 10: 661–665, http://dx.doi.org/10.1097/00054725- 200409000-00026.
69. B.H. Lee, I.R. Indran, H.M. Tan, Y. Li, Z. Zhang, J. Li, E.L. Yong, A dietary mediumchain fatty acid, decanoic acid, inhibits recruitment of Nur77 to the HSD3B2 promoter in vitro and reverses endocrine and metabolic abnormalities in a rat model of polycystic ovary syndrome, Endocrinology, 2016; 157: 382–394, http:// dx.doi.org/10.1210/en.2015-1733.
70. J.C. Marshall, A. Dunaif, Should all women with PCOS be treated for insulin resistance? Fertil. Steril, 2012; 97: 18–22, http://dx.doi.org/10.1016/j.fertnstert. 2011.11.036.
71. D.W. Stovall, A.P. Bailey, L.M. Pastore, Assessment of insulin resistance and impaired glucose tolerance in lean women with polycystic ovary syndrome, J. Womens Health (Larchmt.), 2011; 20: 37–43, http://dx.doi.org/10.1089/jwh. 2010.2053.
72. J. Rojas, M. Chávez, L. Olivar, M. Rojas, J. Morillo, J. Mejías, M. Calvo, V. Bermúdez, Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth, Int. J. Reprod. Med., 2014; 2014: 719050, http://dx.doi.org/10.1155/2014/719050.
73. L. Shi, S. Liu, W. Zhao, J. Shi, miR-483–5p and miR-486–5p are down-regulated in cumulus cells of metaphase II oocytes from women with polycystic ovary syndrome, Reprod. Biomed. Online, 2015; 31: 565–572, http://dx.doi.org/10.1016/j. rbmo.2015.06.023.
74. M.H. Gozashti, A. Gholamhosseinian, F. Musavi, M. Mashrouteh, Relationship between serum cystatin C and polycystic ovary syndrome, Iran. J. Reprod. Med., 2013; 11: 71–76. (Accessed 27, September 2017), http://www.ncbi.nlm.nih.gov/ pubmed/24639696.
75. I.O. Gozukara, K.H. Gozukara, S.K. Kucur, E.U. Karakılıc, H. Keskin, D. Akdeniz, A.N. Aksoy, A. Carlıoglu, Association of glomerular filtration rate with inflammation in polycystic ovary syndrome, Int. J. Fertil. Steril, 2015; 9: 176–182, http://dx.doi.org/10.22074/IJFS.2015.4238.
76. P.-C. Ko, S.-Y. Huang, C.-H. Hsieh, M.-I. Hsu, C.-S. Hsu, Serum ferritin levels and polycystic ovary syndrome in obese and nonobese women, Taiwan J. Obstet. Gynecol, 2015; 54: 403–407, http://dx.doi.org/10.1016/j.tjog.2014.06.005.
77. K.G. Piparva, J.G. Buch, Deep vein thrombosis in a woman taking oral combined

contraceptive pills, J. Pharmacol. Pharmacother, 2011; 2: 185–186, http://dx.doi.org/10.4103/0976-500X.83284.

78. S.D. Yousuf, F. Rashid, T. Mattoo, C. Shekhar, S. Mudassar, M.A. Zargar, M.A. Ganie, Does the Oral contraceptive pill increase plasma intercellular adhesion molecule-1, monocyte chemoattractant protein-1, and tumor necrosis factor-α levels in women with polycystic ovary syndrome: a pilot study, J. Pediatr. Adolesc. Gynecol, 2017; 30: 58–62, http://dx.doi.org/10.1016/j.jpag.2016.06.010.
79. N. Naderpoor, S. Shorakae, B. de Courten, M.L. Misso, L.J. Moran, H.J. Teede, Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis, Hum. Reprod. Update, 2015; 21: 560–574, http://dx.doi.org/10.1093/humupd/dmv025.
80. L.O. Tso, M.F. Costello, L.E.T. Albuquerque, R.B. Andriolo, J. Marjoribanks, C.R. Macedo, Metformin treatment before and during in vitro fertilization or intracytoplasmic sperm injection in women with polycystic ovary syndrome: summary of a Cochrane review, Fertil. Steril, 2015; 104: 542–544, http://dx.doi.org/10.1016/j.fertnstert.2015.05.038.
81. E.M. Lamos, R. Malek, S.N. Davis, GLP-1 receptor agonists in the treatment of polycystic ovary syndrome, Expert Rev. Clin. Pharmacol, 2017; 10: 401–408, http://dx.doi.org/10.1080/17512433.2017.1292125.
82. H. Nasri, M. Rafieian-Kopaei, Metformin: current knowledge, J. Res. Med. Sci., 2014; 19: 658–664 (Accessed 17, February 2015), http://www.ncbi.nlm.nih.gov/pubmed/25364368.
83. S. Franik, J.A.M. Kremer, W.L.D.M. Nelen, C. Farquhar, Aromatase inhibitors for subfertile women with polycystic ovary syndrome, Cochrane Database Syst. Rev., 2014; CD010287, http://dx.doi.org/10.1002/14651858.CD010287.pub2.
84. R. Davidson, T. Motan, C. Korownyk, Clomiphene for anovulatory infertility, Can. Fam. Phys., 2016; 62(492). (Accessed 27, September 2017), http://www.ncbi.nlm.nih.gov/pubmed/27303007.
85. S. Mitra, P.K. Nayak, S. Agrawal, Laparoscopic ovarian drilling: an alternative but not the ultimate in the management of polycystic ovary syndrome, J. Nat. Sci. Biol. Med., 2015; 6: 40–48, http://dx.doi.org/10.4103/0976-9668.149076.
86. K. Szosland, P. Pawlowicz, A. Lewiński, Prolactin secretion in polycystic ovary syndrome (PCOS), NeuroEndocrinol. Lett., 2015; 36: 53–58. http://www.ncbi.nlm.nih.gov/pubmed/25789595.

87. J. Webster, Dopamine agonist therapy in hyperprolactinemia, J. Reprod. Med., 1999; 44: 1105–1110 (Accessed 27, September 2017), http://www.ncbi.nlm.nih.gov/pubmed/10649819.
88. S. Gupta, P. Kulhara, What is schizophrenia: a neurodevelopmental or neurodegenerative disorder or a combination of both? A critical analysis, Indian J. Psychiatry, 2010; 52: 21–27, http://dx.doi.org/10.4103/0019-5545.58891.
89. D.R. Grattan, The hypothalamo-prolactin axis, J. Endocrinol, 2015; 226: T101–T122, http://dx.doi.org/10.1530/JOE-15-0213.
90. V. Tagliaferri, D. Romualdi, E. Scarinci, S. De Cicco, C. Di Florio, V. Immediata, A. Tropea, C.M. Santarsiero, A. Lanzone, R. Apa, Melatonin treatment may be able to restore menstrual cyclicity in women with PCOS: a pilot study, Reprod. Sci., 2017; 25: 269–275, http://dx.doi.org/10.1177/1933719117711262 193371911771126.
91. O. Kose, T. Arabaci, A. Kara, H. Yemenoglu, E. Kermen, A. Kizildag, S. Gedikli, S. Ozkanlar, Effects of melatonin on oxidative stress index and alveolar bone loss in diabetic rats with periodontitis, J. Periodontol, 2016; 87: e82–e90, http://dx.doi.org/10.1902/jop.2016.150541.
92. C.E.D. Lim, R.W. Ng, K. Xu, N.C.L. Cheng, C.C. Xue, J.P. Liu, N. Chen, Acupuncture for polycystic ovarian syndrome, in: C.E.D. Lim (Ed.), Cochrane Database Syst. Rev. John Wiley & Sons, Ltd., Chichester, UK, 2016, http://dx.doi.org/10.1002/14651858.CD007689.pub3 p. CD007689.
93. J. Zhou, X. Zhang, M. Yu, S. Lu, X. Chen, Effect of transcutaneuosacupointelectrostimulation on serum sex hormone levels and expression of ovarian steroid hormone metabolic enzymes in polycystic ovary syndrome rats, Zhen Ci Yan Jiu = Acupunct. Res., 2016; 41: 11–17. (Accessed 27, September 2017), http://www.ncbi.nlm.nih.gov/pubmed/27141614.
94. A.P. Delitala, G. Capobianco, G. Delitala, P.L. Cherchi, S. Dessole, Polycystic ovary syndrome, adipose tissue and metabolic syndrome, Arch. Gynecol. Obstet, 2017; 296: 405– 419, http://dx.doi.org/10.1007/s00404-017-4429-2.
95. S. Jahan, F. Munir, S. Razak, A. Mehboob, Q.U. Ain, H. Ullah, T. Afsar, G. Shaheen, A. Almajwal, Ameliorative effects of rutin against metabolic, biochemical and hormonal disturbances in polycystic ovary syndrome in rats, J. Ovarian Res., 2016; 9: 86, http://dx.doi.org/10.1186/s13048-016-0295-y.
96. Z. Wang, D. Zhai, D. Zhang, L. Bai, R. Yao, J. Yu, W. Cheng, C. Yu, Quercetin decreases insulin resistance in a polycystic ovary syndrome rat model by improving

inflammatory microenvironment, Reprod. Sci., 2017; 24: 682–690, http:// dx.doi.org/10.1177/1933719116667218.

97. R.K. Rajan, M. SSK, B. Balaji, Soy isoflavones exert beneficial effects on letrozoleinduced rat polycystic ovary syndrome (PCOS) model through anti-androgenic mechanism, Pharm. Biol., 2017; 55: 242–251, http://dx.doi.org/10.1080/13880209.2016.1258425.
98. M. Ergenoglu, N. Yildirim, A.G.S. Yildirim, O. Yeniel, O. Erbas, A. Yavasoglu, D. Taskiran, N. Karadadas, Effects of resveratrol on ovarian morphology, plasma anti-mullerian hormone, IJF-1 levels, and oxidative stress parameters in a rat model of polycystic ovary syndrome, Reprod. Sci., 2015; 22: 942–947, http://dx. doi.org/10.1177/1933719115570900.
99. A. Priyadarshani, Relevance of an opioid, noscapine in reducing cystogeneses in rat experimental model of polycystic ovary syndrome, J. Endocrinol. Invest, 2009; 32: 837–843, http://dx.doi.org/10.1007/BF03345755.
100. L. Wang, X. Wang, X. Yu, W. Xu, Potent therapeutic effects of ShouwuJiangqi Decoction (首乌僵芪汤) on polycystic ovary syndrome with insulin resistance in rats, Chin. J. Integr. Med., 2016; 22: 116–123, http://dx.doi.org/10.1007/s11655- 015-2147-9.
101. S. Arentz, J.A. Abbott, C.A. Smith, A. Bensoussan, Herbal medicine for the management of polycystic ovary syndrome (PCOS) and associated oligo/amenorrhoea and hyperandrogenism; A review of the laboratory evidence for effects with corroborative clinical findings, BMC Complement. Altern. Med., 2014; 14: 511, http://dx.doi.org/10.1186/1472-6882-14-511.
102. M. Kachuei, F. Jafari, A. Kachuei, A.H. Keshteli, Prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome, Arch. Gynecol. Obstet., 2012; 285: 853–856, http://dx.doi.org/10.1007/s00404-011-2040-5.
103. D. Shah, S. Bansal, Polycystic ovaries - beyond menopause, Clim. J. Int. Menopause Soc., 2013; 109–115, http://dx.doi.org/10.3109/13697137.2013. 828687.
104. V. Calsolaro, P. Edison, Alterations in glucose metabolism in Alzheimer's disease, Recent. Pat. Endocr. Metab. Immune Drug. Discov, 2016; 10: 31–39. (Accessed 27, September 2017), http://www.ncbi.nlm.nih.gov/pubmed/27306508.
105. C. Anacker, P.A. Zunszain, L.A. Carvalho, C.M. Pariante, The glucocorticoid receptor: pivot of depression and of antidepressant treatment? Psychoneuroendocrinology, 2011; 36: 415–425, http://dx.doi.org/10.1016/j. psyneuen.2010.03.007

106. S. Patel, A. Rauf, H. Khan, T. Abu-Izneid, Renin-angiotensin-aldosterone (RAAS): the ubiquitous system for homeostasis and pathologies, Biomed. Pharmacother, 2017; 94: 317– 325, http://dx.doi.org/10.1016/j.biopha.2017.07.091.
107. M. Kieć-Swierczyńska, D. Chomiczewska-Skóra, D. Swierczyńska-Machura, B. Krecisz, Manicurists and pedicurists - occupation group at high risk of workrelateddermatoses, Med. Pr., 2013; 64: 579–591 (Accessed 25, July 2016), http:// www.ncbi.nlm.nih.gov/pubmed/24502122.
108. H. Fang, Z. Su, Y. Wang, A. Miller, Z. Liu, P.C. Howard, W. Tong, S.M. Lin, Exploring the FDA adverse event reporting system to generate hypotheses for monitoring of disease characteristics, Clin. Pharmacol. Ther., 2014; 95: 496–498, http://dx.doi.org/10.1038/clpt.2014.17.
109. S. Patel, Stressor-driven extracellular acidosis as tumor inducer via aberrant enzyme activation: a review on the mechanisms and possible prophylaxis, Gene, 2017; 626: 209–214, http://dx.doi.org/10.1016/j.gene.2017.05.043.
110. V. De Leo, M.C. Musacchio, V. Cappelli, M.G. Massaro, G. Morgante, F. Petraglia, Genetic, hormonal and metabolic aspects of PCOS: an update, Reprod. Biol. Endocrinol, 2016; 14, http://dx.doi.org/10.1186/s12958-016-0173-x.
111. S. Patel, Inflammasomes, the cardinal pathology mediators are activated by pathogens, allergens and mutagens: a critical review with focus on NLRP3, Biomed. Pharmacother, 2017; 92: 819–825, http://dx.doi.org/10.1016/j.biopha.2017.05. 126.
112. S. Patel, Fragrance compounds: the wolves in sheep's clothings, Med. Hypotheses, 2017; 102: 106–111, http://dx.doi.org/10.1016/j.mehy.2017.03.025