Inositol and lipoic acid treatment in patients with polycystic ovary syndrome

Boro, Tea

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Tea Boro

Inositol and lipoic acid treatment in patients with polycystic ovary syndrome

GRADUATION PAPER

Zagreb, 2023

UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Tea Boro

Inositol and lipoic acid treatment in patients with polycystic ovary syndrome

GRADUATION PAPER

Zagreb, 2023

This graduation paper was made at the Department of Obstetrics and Gynecology at University Hospital Center Zagreb under the supervision of prof. dr. sc. Dinka Pavičić Baldani, dr. med and it was submitted for evaluation in the academic year 2022/2023.

Abbreviations

α-LA	Alpha-lactalbumin
ALA	Alpha-lipoic acid
AES	Androgen Excess Society
AMH	Anti Mullerian hormone
ANSD	Androstenedione
BMI	Body mass index
CVD	Cardiovascular disease
DCI	D-Chiro-inositol
DHEA-S	Dehydroepiandrosterone sulfate
ESHRE	European Society of Human Reproduction and Embryology
FAI	Free androgen index
FPHL	Female pattern hair loss
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin releasing hormone
HA	Hyperandrogenism
HDL-C	High-Density lipoprotein cholesterol
IPG	Inositol phosphoglycan
IP3	Inositol triphosphate
IR	Insulin resistance
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
MI	Myo-Inositol
mFG	modified Ferriman-Galway
NIH	National Institute of Health
OA	Oligo-anovulation
OD	Ovarian dysfunction
PCOM	Polycystic ovarian morphology
PCOS	Polycystic ovary syndrome
SHBG	Sex hormone binding globulin
T2DM	Type 2 Diabetes mellitus

Table of Contents

SUMMARY

Inositol and lipoic acid treatment in patients with polycystic ovary syndrome

Tea Boro

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age. It is characterized by metabolic and hormonal abnormalities, menstrual irregularity, and female anovulatory infertility. According to Rotterdam criteria from 2003, the diagnosis of PCOS can be made in the presence of two out of three of the following: clinical or biochemical hyperandrogenism, oligo or anovulation, and polycystic ovarian morphology, after excluding all other possible diagnoses. PCOS is a heterogenous condition which may present at any stage in life and poses a major public health challenge due to its long-term health implications such as obesity, metabolic syndrome, diabetes mellitus type 2, cardiovascular risk, and an increase in the risk of endometrial cancer. Furthermore, women with PCOS are at a higher risk of pregnancy complications such as spontaneous abortion, hypertensive disorders of pregnancy, gestational diabetes, and preterm birth. The risk of complications varies according to PCOS phenotype. The etiology of PCOS is still unclear, and it is thought to be caused by a combination of hereditary and environmental susceptibility, hypothalamic and ovarian dysfunction, excess androgen exposure, insulin resistance, and obesity. Insulin resistance and subsequent hyperinsulinemia play a crucial role in PCOS pathogenesis. They stimulate the overproduction of androgens which disrupt the ovarian function and lead to the characteristic symptoms of PCOS, including hirsutism, acne, and alopecia. Treatment for PCOS is currently focused on managing symptoms and includes lifestyle modifications and medical interventions. Lifestyle changes such as adopting a balanced diet and engaging in regular exercise are recommended to prevent weight gain and address metabolic issues. Medical management options include metformin, which improves insulin resistance and metabolic features, combined oral contraceptive pills for menstrual regulation and hyperandrogenism, and anti-androgen medications for refractory hyperandrogenism. Inositols, specifically myo-inositol (MI) and D-chiro-inositol (DCI) have gained attention as potential therapeutic agents for PCOS. These naturally occurring sugar alcohols are involved in insulin, follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH) signaling. MI aids in glucose uptake and use, while DCI controls glycogen synthesis. In PCOS, insulin resistance disrupts the

balance between MI and DCI, leading to decreased MI levels and in ovaries, leading to pathological synthesis of androgens. Supplementation with MI and DCI, either individually or in a physiological ratio of 40:1, has shown promising results in improving metabolic and reproductive outcomes in women with PCOS, particularly those with insulin resistance. However, further research is needed to establish their effectiveness and understand their mechanisms of action. Inositols should be considered as an experimental therapy, and individuals using them are advised to consult their healthcare providers.

Key words: polycystic ovary syndrome, insulin resistance, hyperandrogenism, inositols

SAŽETAK

Liječenje inozitolima i lipoičnom kiselinom pacijentica sa policističnim sindromom jajnika

Tea Boro

Sindrom policističnih jajnika (PCOS) najčešći je endokrini poremećaj kod žena reproduktivne dobi. Karakteriziraju ga metabolički i hormonalni poremećaji, neredovite menstruacije i ženska anovulatorna neplodnost. Prema Rotterdamskim kriterijima iz 2003. godine, dijagnoza PCOS-a može se postaviti u prisutnosti dva od tri kriterija: klinički ili biokemijski hiperandrogenizam, oligo ili anovulacija te morfologija policističnih jajnika, nakon isključenja drugih mogućih dijagnoza. PCOS je heterogeno stanje koje se može javiti u različitim životnim razdobljima i predstavlja veliki izazov za javno zdravstvo zbog dugoročnih zdravstvenih posljedica poput pretilosti, metaboličkog sindroma, dijabetesa tipa 2, kardiovaskularnog rizika i povećanog rizika od endometrijskog karcinoma. Uz navedeno, žene s PCOS-om također imaju veći rizik od komplikacija tijekom trudnoće poput spontanog pobačaja, hipertenzivnih poremećaja trudnoće, gestacijskog dijabetesa i prijevremenog poroda. Rizik od razvoja komplikacija ovisi o fenotipu PCOS-a. Etiologija ovog sindroma još uvijek nije potpuno razjašnjena, a smatra se da je uzrokovan kombinacijom nasljedne predispozicije i okolišnih čimbenika, disfunkcijom hipotalamusa i jajnika, prekomjernom izloženošću androgenima, inzulinskom rezistencijom i pretilošću. Inzulinska rezistencija i posljedična hiperinzulinemija imaju ključnu ulogu u patogenezi PCOS-a jer potiču prekomjernu proizvodnju androgena, što poremećuje funkciju jajnika i dovodi do karakterističnih simptoma PCOS-a, uključujući hirzutizam, akne i alopeciju. Trenutačno je liječenje PCOS-a simptomatsko i uključuje promjene u načinu života i farmakološko liječenje. Promjena životnog stila uključuje zdravu uravnoteženu prehranu i redovitu tjelesnu aktivnost kako bi se spriječio višak tjelesne težine i ograničile komplikacije PCOS-a. Opcije farmakološkog liječenja uključuju metformin, koji poboljšava inzulinsku rezistenciju i metaboličke karakteristike, kombinirane oralne kontracepcijske pilule za regulaciju menstruacije i hiperandrogenizma, te antiandrogene lijekove za hiperandrogenizam. Inozitoli, posebno Mio-inozitol (MI) i D-kiro-inozitol (DCI), privukli su pažnju kao potencijalni terapijski agensi za PCOS. Ovi šećerni alkoholi su prisutni u prirodi i u organizmu sudjeluju u signalizaciji inzulina, folikul-stimulirajućeg hormona (FSH) i tireo-stimulirajućeg hormona (TSH). MI pomaže u prihvatu i upotrebi glukoze, dok DCI regulira sintezu glikogena.

Međutim, kod PCOS-a, inzulinska rezistencija narušava ravnotežu između MI i DCI, dovodeći do smanjenih razina MI i povećanih razina DCI u jajnicima, što vodi patološkoj sintezi androgena.
Liječenje PCOS-a koristeći MI i DCI, pojedinačno ili u fiziološkom omjeru 40:1, pokazalo je obećavajuće rezultate u poboljšanju metaboličkih i reproduktivnih ishoda kod žena s PCOS-om, posebno onih s inzulinskom rezistencijom. Međutim, potrebna su daljnja istraživanja kako bi se utvrdila njihova učinkovitost i razumjeli mehanizmi djelovanja. Inozitoli se smatraju eksperimentalnom terapijom, a osobe koje ih koriste trebaju se posavjetovati sa svojim liječnikom.

Ključne riječi: **sindrom policističnih jajnika, inzulinska rezistencija, hiperandrogenizam, inozitoli**

1. INTRODUCTION

PCOS is a clinical condition characterized by several signs and symptoms, including clinical and/or biological hyperandrogenism, oligo- or anovulation, and PCOM (1). It affects from 4 to 20% of women globally, depending on the diagnostic criteria employed (2), and is the leading cause of female anovulatory infertility (3). The etiology of PCOS is complex and unclear and includes genetic and epigenetic susceptibility, hypothalamic and ovarian dysfunction, excess androgen exposure, insulin resistance, and obesity (4). There are multiple diagnostic criteria used, and the most widely accepted one is the 2003 Rotterdam criteria, according to which the diagnosis of PCOS in adults can be made in the presence of two out of three criteria: hyperandrogenism (clinical or biochemical), irregular or absent menstrual cycles, and polycystic ovary morphology, and the exclusion of other conditions (5). The adult criteria, however, do not apply to adolescents (10 to 19 years), due to the overlap of PCOS symptoms with normal physiological changes that occur during puberty. Therefore, in diagnosing adolescents one should look at the specific criteria (6,7). Although the pathogenesis of PCOS is not fully understood, an increasing amount of evidence suggests that insulin resistance plays an important role and is associated with increased risk of various metabolic disorders, including type 2 diabetes mellitus (T2DM), dyslipidemia, nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD) (8). In addition, PCOS is a significant risk factor for infertility and adverse pregnancy outcomes (9,10). Treatment of PCOS should be tailored to the specific symptoms and goals of the individual. Many drugs commonly used for the symptomatic treatment of PCOS such as oral contraceptive pills, anti-androgens, insulin sensitizers, or aromatase inhibitors are used off-label and are not specifically approved by regulatory authorities such as the FDA (U.S. Food and Drug Administration) or the European Medicines Agency (EMA) for this particular condition. The main reason for the lack of treatment options seems to be the poor understanding of the pathophysiology of PCOS, the inadequacy of the naming and diagnostic criteria, and the heterogeneity of the condition (1).

2. POLYCYSTIC OVARY SYNDROME (PCOS)

2.1. Definition and diagnostic criteria

In 1935. Stein and Leventhal first described PCOS in a review published in the American Journal of Obstetrics and Gynecology, titled “Amenorrhea associated with polycystic ovaries“ (11). It was this groundbreaking report that helped establish the connection between the triad of polycystic ovaries, hirsutism (excessive hair growth), and oligo/amenorrhea (irregular or absent menstrual periods (1,11). The inclusion of PCOS as a distinct disorder in the International Classification of Diseases (ICD) did not occur until 1990 with the release of the 10th revision (ICD-10). Before this inclusion, the terminology used to describe PCOS varied, with terms like sclerocystic ovary syndrome and Stein-Leventhal syndrome being used interchangeably. The term 'polycystic' might be misleading because the appearance of the ovaries in PCOS is not attributable to the existence of actual cysts, but rather many fluid-filled follicles containing a developing oocyte. The recognition of PCOS as a complex endocrine condition comprising hormonal, metabolic, and reproductive elements has evolved beyond ovarian morphology, emphasizing the need for a more complete term (1). In the lack of a broadly agreed consensus, three alternative definitions of PCOS remain valid up to date.

Under the **1990 NIH criteria** (12), the diagnosis of PCOS is primarily based on the presence of clinical and biochemical signs of hyperandrogenism, as well as the exclusion of other disorders that could cause similar symptoms. Ultrasonographic evidence of polycystic ovaries is considered suggestive but not necessarily diagnostic.

In 2003, European Society of Human Reproduction (ESHRE) and the American Society of Reproductive Medicine (ASRM) jointly proposed the use new guidelines for the diagnosis of PCOS, named **Rotterdam criteria** (5). According to these guidelines, it is possible to reach a diagnosis of PCOS when at least 2 of these 3 elements are present: hyperandrogenism, chronic anovulation and polycystic ovarian morphology. Up to date, Rotterdam criteria are still the most widely used and accepted in scientific societies. (1).

The application of the Rotterdam criteria for diagnosing PCOS has led to an increase in prevalence as much as three times compared to the previously used 1990 National Institutes of Health (NIH) criteria (13). These criteria are a source of continuous debate in the medical world and one of the issues is that PCOS can be identified even when there is no androgen excess or menstrual irregularity, which was formerly regarded to be the major indications of the illness.

Due to the aforementioned reason, some researchers suggested there's a need for new criteria to capture the diverse phenotypes and manifestations of PCOS (14).

The Androgen Excess Society **(AES) guidelines** (15) published in 2006, emphasize the significance of both hyperandrogenism and ovarian morphology in the diagnosis of PCOS. According to the AES guidelines, the diagnosis of PCOS requires the presence of either hirsutism and/or biochemical evidence of hyperandrogenism. Additionally, there has to be evidence of either oligo-anovulation (irregular or absent menstrual cycles) or polycystic-appearing ovarian morphology (PCOM). The AES criteria, however, do not clearly distinguish a mild type of PCOS when little is known regarding metabolic state or long-term health implications (14).

All of the diagnostic criteria require excluding other possible causes of hyperandrogenism such as non-classical congenital adrenal hyperplasia (NC-CAH), Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, thyroid diseases, drug-induced androgen excess, as well as other causes of oligomenorrhea or anovulation (15,16).

The three different diagnostic criteria for diagnosing PCOS are named in Table 1.

Table 1. Criteria for diagnosing PCOS

NIH consensus criteria 1990 (All required)	Rotterdam criteria 2003 (two out of three required) + excl. of other disorders	AES definition 2008 (All required)
Menstrual irregularity due to oligo- or chronic anovulation	Oligo- or chronic anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction – oligo- or anovularion and/or polycystic ovaries on ultrasound
Exclusion of other disorders	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

The presence of various diagnostic criteria is the cause of confusion and is one of the causes of the lack of scientific progress in understanding of PCOS (13). Thus, in 2012, the NIH hosted an evidence-based methodology workshop on PCOS, at which experts on the condition once again advised using the broader 2003 Rotterdam criteria, while explicitly distinguishing phenotypes that are based on either two or all three of the Rotterdam criteria being present (17).

The features of each phenotype are grouped in Table 2.

Table 2. Classification of PCOS phenotypes (18)

Parameter	**Phenotype A**	**Phenotype B**	**Phenotype C**	**Phenotype D**
PCOS features	HA/OD/PCOM	HA/OD	HA/PCOM	OD/PCOM
Hyperandrogenism and hirsutism	PRESENT	PRESENT	PRESENT	ABSENT
Ovulatory dysfunction	PRESENT	PRESENT	ABSENT	PRESENT
PCOM	PRESENT	ABSENT	PRESENT	PRESENT
NIH 1990	X	X		
Rotterdam 2003	X	X	X	X
AE-PCOS 2006	X	X	X	

Abbreviations: **HA** – hyperandrogenism; **OA** – oligo-anovulation; **PCOM** – polycystic ovarian morphology

Phenotype A is also known as the “complete” PCOS phenotype, and both A and B are referred to as “classic” phenotypes (18,19). Phenotype C, referred to as "ovulatory" PCOS, is characterized by the presence of hyperandrogenism (HA) and polycystic ovarian morphology (PCOM), but without oligo-anovulation (OA). This phenotype acknowledges that not all women with PCOS experience menstrual irregularities and anovulation, yet they still exhibit hyperandrogenism and the characteristic ovarian morphology. Phenotype D, known as "non-hyperandrogenic" PCOS, is characterized by oligo-anovulation (OA) and polycystic ovarian morphology (PCOM), but without the presence of hyperandrogenism. This phenotype recognizes that some women with PCOS may have irregular menstrual cycles and polycystic ovaries but without the classical signs of excess androgens such as hirsutism or acne (18).

By identifying women with „classic“ PCOS phenotypes (phenotypes A and B), clinicians can identify those who are at higher risk of developing metabolic dysfunction, such as insulin resistance, poor glucose tolerance, and dyslipidemia. These women may benefit from more focused screening, lifestyle modifications, and targeted care in preventing or mitigating the metabolic problems associated with PCOS (18).

Applying the adult criteria for diagnosis of to adolescents (girls aged 10 to 19) might be challenging because puberty-related physiological changes can generate transient anomalies that do not always indicate the presence of PCOS (6). To address these issues, there are special guidelines developed for diagnosing PCOS in adolescents. According to the international evidence-based guidelines from 2020. (6,7), the criteria for diagnosis of PCOS in adolescents are irregular menstrual cycles for at least one year post-menarche; for girls who are more than one year post-menarche - menstrual cycles longer than 90 days for any one cycle; for girls who are between one and three years post-menarche - menstrual cycles shorter than 21 days or longer than 45 days; for girls who are more than three years post-menarche - menstrual cycles shorter than 21 days or longer than 35 days. In addition to irregular menstrual cycles, primary amenorrhea (the absence of menstruation) by age 15 or more than three years post-thelarche (the onset of breast development) is another criterion that can be used to assess PCOS in adolescents. Hyperandrogenism in adolescents is defined in the presence of hirsutism, severe acne, and/or biochemical hyperandrogenemia confirmed using high-quality assays. Pelvic ultrasound is not recommended for diagnosis of PCOS within 8 years post menarche. Those adolescents who do not meet the criteria are considered to be „at risk“ and require follow-up. Re-evaluation of the menstrual cycle can occur over a period of three years post-menarche. Additionally, ultrasound evaluation of the ovaries can be considered after eight years post menarche. (7).

Some authors suggest that Anti-Müllerian hormone (AMH) may be used as a substitute for PCOM in the Rotterdam classification, but that it should not be used as a single test for diagnosis of PCOS because it is not a suitable marker of oligo-anovulation nor hyperandrogenism. Differences in AMH levels between the different subgroups of PCOS may also be one of the reasons why AMH is not useful as a diagnostic indicator (19–21).

2.2. Epidemiology

PCOS prevalence worldwide varies from 4% to 6.6% by NIH 1990 criteria and approximately 4% to 21% when Rotterdam 2003 criteria are applied (18). Prevalence rates are also influenced by factors such as the study population, geographic region, and ethnicity. Around 50% of women with PCOS are not aware of their condition or experience a delayed diagnosis. Establishing the diagnosis often involves multiple healthcare professionals and can take a year or longer for many women in different regions of the world (22,23). According to data from 2020, the economic burden of PCOS in 2020. was US$8 billion annually (24).

Using NIH's 2012 phenotypic extension of the Rotterdam definition is the most convenient approach in epidemiological research and clinical practice. This approach allows researchers to create homogenous study groups for analysis and comparison in epidemiological studies and to identify high-risk individuals in clinical practice. Published data indicate that around two-thirds of patients studied in clinical settings have classic phenotypes A and B. Conversely, in medically unbiased (unselected) populations the most common phenotypes are B and C (18).

2.3. Clinical features

Polycystic ovarian syndrome (PCOS) is a clinical syndrome characterized by a group of signs and symptoms such as clinical and/or biological hyperandrogenism, oligo- or anovulation, and PCOM (2).

Clinical hyperandrogenism

Clinical features of hyperandrogenism frequently seen in PCOS patients include hirsutism, acne, and androgenic alopecia (15). Hirsutism is a common symptom, affecting approximately 60-70% of individuals with PCOS (15,25,26). Hirsutism is stimulated by the excess androgen levels which lead to increased terminal hair growth in most androgen-sensitive sites such as the upper lip, chin, chest, back, and upper abdominal area (27). Terminal hair is a mature type of hair that grows longer than 5 mm, has a central medulla, and exhibits shape and pigment (2). To assess the extent of terminal hair growth in male-like areas, the modified Ferriman-Gallwey (mFG) score is often used. This visual scale assigns a value from 0 to 4 for nine body areas (upper lip, chin and neck, chest, abdomen, back, arms, and thighs) based on the presence and

extent of terminal hair growth. The scores from these areas are added together to calculate the overall score (28). The definition of excessive terminal hair growth can vary among observers. Generally, scores above the 95th percentile in the population are considered excessive, with cutoff mFG scores ranging from 6 to 10 (2). However, Souter et al. (29) found that over 50% of women with hyperandrogenic disorder had only mild hirsutism (mFG scores from 1 to 5). Due to this reason, the threshold for abnormal hair growth in women remains a topic of debate (2). Amiri et al. (30) showed that there is a significant positive relationship between the level of hirsutism measured by mFG score and levels of androstenedione (ANSD) and dehydroepiandrosterone sulfate (DHEA-S). In addition, Guo et al. (31) demonstrated that among biochemical markers, the free androgen index (FAI), which reflects free testosterone, was the most powerful predictor of hirsutism in women aged 18-29 years. In women aged 30-40 years, clinical hyperandrogenism was mainly affected by levels of DHEA, DHEA-S, and dihydrotestosterone (DHT).

Other clinical signs of hyperandrogenism include comedogenic acne and female pattern hair loss (FPHL)/alopecia. The binding of androgens to androgen receptors on pilosebaceous units (hair follicles and sebaceous glands) stimulates sebaceous gland hyperplasia, increases sebum production, and leads to abnormal follicular epithelial cell keratinization, resulting in the development of acne (31). Androgens can convert terminal hair follicles into vellus hairs, which are fine and less pigmented. This process reduces the percentage of anagen (growth phase) hairs and contributes to the characteristic pattern of hair loss seen in FPHL.

However, it's important to note that acne and alopecia alone are not reliable indicators of androgen excess and precise methods to assess these parameters and determine the extent of androgen influence are lacking (2).

Hyperandrogenemia

In the diagnosis of PCOS biochemical hyperandrogenemia is assessed by measuring free serum testosterone, total testosterone and calculating the free androgen index (FAI (13). Testosterone levels, particularly in the free form unbound to sex-hormone-binding globulin (SHBG), are elevated in up to 89% of patients and are considered the most sensitive marker for diagnosis. Free testosterone represents only 1–3% of all testosterone and highly precise assays are required for measurement. DHEAS is elevated in 25 to 35% of PCOS women and may be the only abnormality in only 10% of cases and its measurement is not routinely performed.

Analysis of androgens in serum fails to demonstrate elevated levels of these hormones in 20-40% of women with hirsutism and polycystic ovaries. This is due to the lack of reliable methods for measuring androgens in serum, the variations in the level of androgens during the time of the day, and the lack of clear boundaries for normal values in women according to age. Therefore, according to Rotterdam criteria, the presence of other clinical signs does not exclude the diagnosis of PCOS, even if circulating androgen levels are within the normal range (13,17).

Ovulatory dysfunction (OD)

Ovulatory dysfunction in PCOS patients is often characterized by oligo-amenorrhea, which is defined as having cycles that are more than 35 days apart or having less than 8 cycles per year. Polymenorrhea is defined as cycles occurring less than 21 days apart and is unusual in PCOS patients. However, some diagnostic criteria contain this aspect as well. Regardless, if a patient has a high clinical suspicion of PCOS and has regular monthly cycles, polymenorrhea, or an unexplained menstrual pattern, ovulation should be confirmed by measuring serum progesterone. This is significant because ovulatory failure can develop in the absence of oligo-amenorrhea. Irregular menstrual cycles are considered normal within one year after menarche, and in one to three years post-menarche, irregular cycles should be defined as occurring less than 21 days apart or more than 45 days apart (13).

Polycystic ovarian morphology (PCOM)

In PCOS, the typical ovarian morphology is the result of impaired follicular development and premature cessation of follicular growth, as a result of hyperandrogenemia, LH hypersecretion, and hyperinsulinemia. The proposed thresholds by the 2003 Rotterdam criteria include the presence of 12 or more follicles measuring 2–9 mm in diameter or an ovarian volume > 10 cm3 for either ovary and under these criteria 30-50% of normal-androgenic women would be classified as having PCOM. Various researchers have presented different proposed thresholds for PCOM, which can be influenced by changes in ultrasound technology and differences in study methodologies. According to the 2018 International Evidence-Based Guidelines for the Assessment and Management of PCOS, PCOM should be defined as either ≥20 follicles per ovary and/or an ovarian volume of ≥10 cm3 on either ovary, using newer transvaginal ultrasound technology with a transducer frequency of 8 MHZ or more (13).

Anti-Müllerian Hormone (AMH) levels are correlated with follicle counts and its measurement has been useful for screening and prognosis of reproductive issues. The

determination of an AMH cutoff value is still lacking but may become an additional tool to define PCOM and PCOS phenotypes in the future (19–21).

2.4. Associated features and morbidities

Obesity

Obesity is a common feature of PCOS, with prevalence rates ranging from 12.5% to 100%, with a pooled estimated prevalence of 49% (32). It is believed that excess adipose tissue, particularly in the abdominal region, can lead to increased insulin resistance and promote the development and clinical manifestation of PCOS in women who are genetically predisposed (33). Compared with normal-weight PCOS women, obese PCOS women had lower SHBG and higher FT, free androgen index (FAI), insulin resistance homeostasis assessment (HOMA-IR), fasting insulin (FINS), and fasting blood glucose (FG) levels, showing that obesity may be an important cause of IR and HA in PCOS women (32).

Dyslipidemia and cardiovascular disease

The most common lipid abnormalities among women with PCOS are elevated levels of triglycerides, LDL-C, VLDL-C and low HDL-C levels (34). A meta-analysis by Wild et al. (35) suggested that beyond known alterations in TG and HDL-C, women with PCOS have higher LDL-C and nonHDL-C, regardless of BMI. In addition, women with PCOS have a 3-fold increased prevalence of type 2 diabetes (T2DM) (36).

It has been shown that PCOS poses a higher risk for non-fatal cerebrovascular disease events but not coronary disease events. Sensitivity meta-analyses only provided evidence of increased T2D and HT risks in women with PCOS in comparison to women without PCOS and is still unclear to which extent increased cardiometabolic risk is independent of obesity (37). According to recent guidelines, all women with PCOS should be screened for cardiovascular risk factors such as increased abdominal adiposity, smoking, hypertension, dyslipidemia, subclinical vascular disease, impaired glucose tolerance, family history of premature CVD, lack of physical activity, metabolic syndrome and T2DM, obstructive sleep apnea, high levels of CRP, and homocysteine (39). AE-PCOS Society recommends categorizing PCOS-related CVD risk patients in 2 categoris: patients at risk (PCOS patients with obesity, cigarette smoking, hypertension, dyslipidemia, subclinical vascular disease, IGT, family history of premature

CVD) or high risk (PCOS patients with metabolic syndrome, diabetes mellitus or overt vascular/renal disease (38).

Psychological implications

A 2021 study found that 40% of women with PCOS have depression and 16.6% have mood disorders, indicating that at least 56.6% of women with the condition have mental health problems (40). Body image and self-worth are predictors of anxiety and depression (regardless of PCOS status), and the time taken to diagnose PCOS is generally associated with poor psychological functioning (41).

2.5. Pathophysiology

Polycystic ovary syndrome (PCOS) is believed to result from a combination of genetic and environmental factors. The most common risk factors seem to be obesity and insulin resistance, which occur in about half of the cases and which themselves have heritable components (4).

The disorder tends to run in families, with an estimated prevalence of 20-40% among first-degree female relatives of women with PCOS (42). The research done on identical twins shows that about half of the sisters are hyperandrogenic, and half of these also have oligo-amenorrhea thus PCOS and polycystic ovaries appear to be inherited as an autosomal dominant trait (4,43). Furthermore, studies have shown a significant prevalence of PCOS among mothers and sisters of women with PCOS. Approximately 3-35% of mothers of women with PCOS have PCOS themselves, and about 25% of sisters are affected. Additionally, there is a higher prevalence of metabolic syndrome among parents and siblings of women with PCOS (4).

In the past decade, substantial evidence demonstrated that insulin resistance has a key role in the pathogenesis of PCOS. It refers to the reduced responsiveness of cells to the hormone insulin, leading to hyperinsulinemia as a compensatory response (8). In 1980, Burghen et al.(62) published a study that provided evidence of increased insulin responses during oral glucose tolerance testing (OGTT) in women with PCOS. More importantly, these increased insulin responses were independent of obesity, suggesting the role of insulin resistance in PCOS. Insulin resistance is now recognized as a key feature of PCOS and is believed to play a central role in the hormonal and metabolic abnormalities observed in the condition. The exact mechanisms underlying insulin resistance in PCOS are not fully understood but are thought to involve a combination of genetic and environmental factors. One of the proposed mechanisms

is related to abnormal insulin signaling pathways, including defects in insulin receptor signaling or downstream intracellular signaling molecules (63).

Insulin resistance is highly prevalent, occurring in up to 95% of women with PCOS who are obese and up to 75% of lean women with PCOS (44,45). However, not all women who are obese and IR develop PCOS. Therefore, it is hypothesized that there must be a concomitant defect that stimulates the hypersecretion of androgens, leading to characteristic signs of PCOS (46). There is a significant positive correlation between hyperinsulinemia and excess androgen secretion and due to the complex link between the two it is still unclear whether IR or hyperandrogenism develops first (46,47). Insulin plays a crucial role in stimulating androgen secretion in both healthy individuals and women with PCOS. This stimulation is particularly enhanced in PCOS women, suggesting possible intrinsic abnormalities in theca cells (48). High insulin levels can increase the sensitivity of the ovaries to GnRH, leading to an elevated production of androgens (49). Additionally, insulin directly activates specific pathways in ovarian cells, promoting the transcription of key enzymes involved in steroid hormone production, such as StAR, which contributes to increased androgen production. Hyperinsulinemia also affects the hypothalamic-pituitary-adrenal axis by increasing GnRH, LH pulse secretion, and altering LH/FSH ratio, leading to follicular dysfunction and anovulation. Moreover, hyperinsulinemia inhibits SHBG production by the liver, resulting in increased free testosterone bioavailability (4).

On the other hand, there is also evidence suggesting that insulin resistance may be a consequence rather than a cause of PCOS. Studies have shown that insulin resistance can develop rapidly after androgen administration in women (4). This indicates that hyperandrogenism can worsen insulin resistance, creating a vicious cycle of insulin resistance, hyperinsulinemia, and hyperandrogenism. Androgens can also induce lipolysis, leading to increased free fatty acid levels, which further reduces insulin sensitivity. The vicious cycle is further exacerbated by obesity, which enhances androgen synthesis in both ovaries and adrenals and promotes leptin-mediated inflammation. Increased testosterone levels and altered testosterone/androstenedione ratio in adipose tissue of PCOS women provide evidence of activated androgen synthesis in peripheral tissues, which can contribute to lipid accumulation and increased fat mass (4,50). The enhanced visceral adiposity plays a role in chronic inflammation partly by activating mononuclear cells, leading to increased production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1. These cytokines play a role in insulin resistance, negatively affecting insulin signaling (51).

Ultimately, the interplay between insulin resistance, hyperinsulinemia, hyperandrogenemia, dysregulated lipid metabolism, and chronic inflammation contributes to the various endocrine and metabolic disturbances observed in PCOS. These disturbances predispose individuals with PCOS to the development of comorbidities such as obesity, metabolic syndrome, CVD, and other health complications (4).

2.6. Treatment options

The selection of appropriate treatment option depends on the patient's phenotype, concerns, and goals. Therapeutic approaches may include oral contraceptive pills, anti-androgen medications, insulin-sensitizing agents, progestins, lifestyle modifications, and ovulation induction medications. Consulting with a healthcare professional is essential to determine the most appropriate treatment plan (2).

Non-pharmacological measures

Lifestyle interventions, such as exercise and diet are recommended as the first line of treatment for patients with PCOS, especially for overweight/obese patients (7). In women with excess weight, a weight loss of 5-10% is advised, aiming for an energy deficit of 30% or 500-750 kcal/day (1200-1500 kcal/day). A systematic review done by Lim SS (52) reported that lifestyle interventions compared with minimal intervention reduce weight and body mass index (BMI) and improve secondary reproductive outcomes such as free androgen index (FAI), testosterone, SHBG, and hirsutism (mFG score).

Pharmacological measures

Ovulation induction

The first-line treatment options for ovulation induction in the treatment of infertility are oral medications such as clomiphene citrate or letrozole (2,7). These medications work by blocking the negative feedback of estrogen on the hypothalamus, leading to increased production of follicle-stimulating hormone (FSH) and subsequent development and release of mature eggs.
Letrozole has shown comparable or even better ovulation and pregnancy rates compared to clomiphene citrate and is often preferred due to its lower risk of multiple pregnancies. Laparoscopic ovarian surgery could be second-line therapy for women with PCOS, who are

clomiphene citrate resistant, with anovulatory infertility and no other infertility factors. If oral medications are not effective, injectable gonadotropins may be used as a second-line option to stimulate ovulation (7). However, the use of injectable medications carries a higher risk of multiple pregnancies and requires careful monitoring to reduce the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (2,7). If all other therapies have failed, women with PCOS and anovulatory infertility could be offered IVF third line.

Combined Oral Contraceptive Pills (COCPs) are commonly prescribed as first-line pharmacological management for menstrual irregularity and hyperandrogenism in women with PCOS who do not wish to get pregnant (7). There is no specific formulation recommended, and low-dose preparations are generally preferred. COCPs can help regulate menstrual cycles, reduce androgen levels, and alleviate symptoms such as hirsutism (excessive hair growth) and acne. They may be prescribed together with metformin or antiandrogen medications in treatment for the management of metabolic features and adolescents with BMI ≥25 kg/m^2, where COC and lifestyle changes did not achieve results.

Metformin is an insulin-sensitizing medication and it is recommended as an additional treatment or as monotherapy for managing weight, hormonal, and metabolic features associated with PCOS. Metformin in addition to lifestyle, should be considered in adult women with PCOS with BMI ≥ 25 kg/m2 for the management of weight and metabolic outcomes (20).

Anti-androgenic medication

Where COCPs are contraindicated or poorly tolerated, in the presence of other effective forms of contraception, anti-androgens could be considered to treat hirsutism and androgen-related alopecia. Anti-androgen medication includes androgen receptor blockers such as spironolactone and flutamide, and 5a-reductase inhibitors such as finasteride.

All antiandrogen medications share common risks and effects, including potential modest decreases in libido and muscular strength. They also have significant teratogenic potential for the feminization of a male fetus (2). Spironolactone (50–200 mg per day) is the preferred first-line agent, although side effects occur in more than 50% of patients taking spironolactone, most notably polyuria, hypotension, and syncope; salt-craving; dyspepsia; sensitivity to sun; and rarely atopic reactions. However, few patients discontinue the medication. In patients who do not tolerate spironolactone, 125–500 mg daily of flutamide may be considered. Because

flutamide has been associated with rare acute hepatotoxic failure and death, liver function tests must be performed every 2-3 months.

Treatment of acne and alopecia

Several topical treatments for acne are available, including astringents, antibiotics, and retinoids (2). For androgenic alopecia, topical treatment with 2–5% topical minoxidil may be an option as well as topical finasteride. The hair transplant surgery may also be required. Long-term management of acne and alopecia would be best if carried out in consultation with a dermatologist.

3. INOSITOLS

3.1. Overview of Inositol Isomers: MI and DCI

Inositols are naturally occurring compounds that have been a focus of research studies for the past 20 years. German physicist and chemist, Johann Joseph Scherer first isolated this compound from muscle cells and named it Inositol (Greek s [ìς (is, in-, "sinew, fiber"), -ose (indicating a carbohydrate), -ite ("ester"), -ol ("an alcohol")] and because of its sweet taste (53). Maquenne described its chemical structure, cyclohexanol, by purifying it from leaves, and about a hundred years later, Pastere established the configuration of its main stereoisomer myoinositol (MI). The basic hexahydroxycyclohexane backbone allows for the establishment of nine isomers (*cis-, epi-, allo-, myo-, neo-, scyllo-, L-chiro-, D-chiro- and muco-inositol*).

Out of nine different stereoisomers that exist in nature, MI is the most ubiquitous form, especially in animals and mammals. The sources of MI in nature are phytate (inositol-6-phosphate) rich food such as fruits, grains, nuts, and the intake in the Western diet does not exceed 500-700mg (46,54). Other than obtaining inositols by dietary intake, a large proportion of daily requirements is actively synthesized endogenously (about 4 g/day), mainly by kidneys, liver, and brain. Within cells inositols can be present in free form and in the form of phosphatidylinositols (PI) as a component of the cell membrane phospholipids (46). Its phosphorylated derivatives participate in chromatin remodeling and gene expression, mediate protein phosphorylation and facilitate mRNA export from the nucleus (55). MI in the form of

phosphatidyl MI(PMII) and its derivative inositol phosphoglycan (InsP3) is a structural part of all eukaryotic membranes (46,53,56). Furthermore, Ins3P acts as a second messenger in many biochemical processes, including the transduction of endocrine signals of insulin, follicle-stimulating hormone (FSH), and thyrotropin (TSH) (46).

While MI can be synthesized in cells, the second most abundant stereoisomer, D-chiro-inositol (DCI) is primarily obtained through conversion from MI by tissue-specific epimerase enzymes, stimulated by insulin. MI and DCI modulate metabolic processes differently and each organ has a specific intracellular MI: DCI ratio depending on the activity of the epimerase enzyme e.g., in normal (healthy) women the plasma ratio of MI: DCI is 40:1, whereas in ovarian follicular fluid is close to 100:1. Both MI and DCI have been studied for their potential therapeutic benefits in conditions such as polycystic ovary syndrome (PCOS) and gestational diabetes mellitus (GDM), where abnormalities in inositol metabolism have been observed.

3.2. Biosynthesis of MI

MI is actively synthesized in living cells from glucose 6-phosphate (G6P). In the first step of the process, D-3-myo-inositol-1L-phosphate synthase (MIPS) converts Glucose-6-phosphate to Myo-inositol-1-phosphate (MIP), which is then dephosphorylated by myo-inositol-1-phosphatase (IMPase) to produce free MI. (55) Free MI can also be obtained by recycling inositol 1,4,5 triphosphate (InsP3) and inositol 1,4-bisphosphate (InsP2) (54,57). Different tissues have different rates of synthesis of MI, depending on their functional needs. For example, the brain produces MI in quantities up to 10- to 15-fold those seen in circulating blood.

The uptake of free inositol by tissues occurs by a membrane-dependant sodium inositol cotransporter, for which MI has 10 times greater affinity than DCI (46). DCI, glucose transporter inhibitors, and sugars like sorbitol and maltodextrin appear to limit MI absorption, resulting in lower MI plasma concentrations.

3.3. Absorption of inositols

The complex relationship between glucose and inositol uptake has been explained by several studies which suggest the possibility of competitive activity of glucose and inositol for the same transporter system (57). It has been observed that bean flour's glycemic index rises when

phytate is removed and that MI significantly inhibits duodenal glucose absorption and lowers blood glucose rise. In addition, inhibitors of sodium-glucose transporters (SGLT) 1,2 prevent both glucose and inositol uptake in hepatocytes. On the other hand, as seen in diabetic individuals, glucose may cause MI depletion by activating the glucose-sorbitol pathway, in which glucose is first transformed to sorbitol by aldose reductase and subsequently to fructose by sorbitol dehydrogenase. The absorption of other important osmolytes, such as inositol, is inhibited by downregulating the expression of their carriers, which prevents the detrimental increase in intracellular osmolarity caused by increased sorbitol synthesis. MI levels are restored in cultured cells when aldose reductase is inhibited, counteracting the depleting impact of sorbitol.

The research demonstrated that both hyperglycemia and insulin resistance alter the relative ratio of MI and DCI (about 100: 1), present in tissues and these variations in the ratio of plasma and urine MI/DCI levels may serve as an early indicator of hyperglycemia and insulin resistance.

3.4. Mechanism of action of inositols

When insulin binds to its receptor, it causes the liver plasma membrane to release Inositol phosphoglycans (IPGs), which are generated by the hydrolysis of glycosylphosphatidylinositol (GPI) lipids and/or specific proteins located on the outer part of the cell membrane. Two IPGs are formed: IPG-DCI (or IPG-P) and IPG-MI (or IPG-A). IPG-P will directly activate the glycogen synthase but will also indirectly activate it via the activation of phosphoprotein phosphatase 1 (PP1). IPG-A causes direct glucose uptake and inhibits cAMP protein kinase A and adenylate cyclase, thereby activating PP1. Regardless of the signal flowing through the insulin receptor, these effects allow for a drop in blood glucose levels (insulin-like effect) (46).

MI and DCI decrease postprandial blood glucose by mediating different actions of insulin in humans. MI levels are higher in tissues with high glucose utilization such as the brain, heart, and ovary. Intracellularly, MI is involved in the cellular uptake and use of glucose through stimulation of GLUT-4 translocation to the cell membrane (46,54,58). Its derivative MI-IPG inhibits adenylate cyclase, thus reducing the release of free fatty acids from adipose tissue, mimicking the lipolytic effect of insulin. Conversely, DCI levels are high in tissues that store glycogen such as liver, muscle, and fat, and in those where glucose is actively used. DCI

participates in glycogen synthesis and upregulates enzyme pyruvate dehydrogenase, leading to the production of ATP by the Krebs cycle (54).

Recent evidence suggests that DCI can reduce free fatty acid uptake by the liver via lipid trafficking inhibition, reduced diacylglycerol deposition, and hepatic Protein kinase C epsilon type (PKC) translocation, resulting in improved insulin sensitivity via suppressed hepatic gluconeogenesis (59).

3.5. Role of inositols in the reproductive system

Other than their effect as insulin-sensitizing and modulatory agents, inositols are abundant in the ovaries and follicular fluid and are important for follicular development. MI (as InsP3) acts as second messenger for FSH and is involved in pathways that control granulosa cell proliferation and maturation (46). In the FSH signaling pathway, there are two main pathways involved: the cAMP/PKA pathway and the inositol-dependent pathway. The cAMP/PKA pathway is activated by the Gs protein and leads to aromatase induction, leading to estrogen biosynthesis from androgens. The inositol-dependent pathway is activated by the Gq protein and stimulates phospholipase C, which cleaves phosphatidylinositol-4,5-bisphosphate (PIP2) into inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).
IP3 acts as a ligand for calcium channels, causing their opening and the release of calcium ions from intracellular compartments. High calcium ion concentrations have been associated with oocyte maturation in various species (59). This dual signaling system is important for ovulation.

In the follicular phase, FSH receptor stimulation leads to the activation of a cAMP pathway that at high concentration maintains oocytes in prophase 1 and stimulates the growth and proliferation of granulosa cells. Conversely, LH surge and modulation of FSH receptor concentration in dominant follicles activate the inositol pathway. The change in cAMP and increased Ca concentration allow for the continuation of meiosis and the release of mature oocytes (46). A study done on mice has shown that the mutation in the Gq protein had a direct impact on the ability of the follicles to rupture properly, leading to impaired follicle rupture and infertility as a result. MI appears to enhance the meiotic progression of oocytes into fertilization-competent eggs in animal models, and its depletion inside the ovary can affect the physiological process of oocyte maturation. Furthermore, MI is required to speed oocyte transport in the oviduct.

Studies indicate that MI signaling may also boost anti-Müllerian hormone (AMH) synthesis, driven by FSH, in the granulosa cells of non-PCOS patients with reduced ovarian reserve (DOR). AMH participates in the regulation of follicle maturation by decreasing oocyte sensitivity to FSH (46,59).

DCI's role in ovaries was first studied by Nestler et al. (60) and they demonstrated that by adding insulin to theca cells, the IPG-P second messenger (in conjunction with DCI), functioning as an insulin mediator, directly increases (in a dose-response manner) testosterone production in human theca cells from healthy and PCOS patients. An antibody directed against the inositol phosphoglycan containing DCI, however, negated this impact. Sacchi et al. (61) proposed a second mechanism which involved directly downregulating the production of estrogens by altering the expression of the aromatase enzyme by decreasing in dose–response way the expression of the aromatase gene (CYP19A1) and therefore reducing the conversion of testosterone to estrogen.

As a result, DCI causes a systemic increase in testosterone levels while decreasing estrogen levels. This effect is more than four times stronger in PCOS theca cells than in normal women's cells, and it helps to explain why PCOS patients make more testosterone than healthy subjects (59).

4. INOSITOLS AS A TREATMENT OPTION FOR PCOS

4.1. Role of inositols in insulin resistance and epimerase activity

The role of inositols as insulin sensitizers is supported by several studies that demonstrated reduced DCI levels in muscle tissue and urine in patients with type 2 diabetes and both PCOS and non-PCOS women (46,57). Some researchers suggest that insulin resistance is triggered by reduced availability and levels of DCI, with consequently decreased incorporation of DCI into IPG (64). Moreover, DCI-IPG release is decreased in the blood of diabetic subjects during OGTT and in women with PCOS during an insulin clamp (64).

It remains unclear if insulin resistance depends on deficiency in membrane-bound IPGs, a primary defect in IPG release, and/or reduced intracellular availability of DCI due to the impaired epimerase-dependent conversion of MI into DCI (57). Studies on rats with T2DM demonstrated that in insulin-sensitive tissues (muscle, liver, fat), MI conversion to DCI was

reduced from 20-30% in control rats to less than 5% in T2DM rats, and this was associated with decreased epimerase activity (65).

Heimark et al. (66) conducted a study comparing the characteristics of theca cells from normal cycling women with normal insulin sensitivity to theca cells from women with PCOS and hyperinsulinemic insulin resistance (IR) and demonstrated that the ratio of MI to DCI in the theca cells from women with PCOS was lower compared to the healthy women. This finding suggests an imbalance in inositol metabolism in the theca cells of PCOS patients. Additionally, the study found increased thecal epimerase activity in the cells obtained from women with PCOS compared to those from healthy women.

Unfer et al. (67) reported that the ratio of MI to DCI in follicular fluid was 100:1 in healthy women but only 0.2:1 in PCOS patients. This imbalance was attributed to a significant reduction in follicular MI levels and an increase in DCI levels in women with PCOS.

Larner et al. (68) suggested that increased activity of the epimerase enzyme leads to an elevated concentration of DCI, which is then incorporated into phospholipids. This, in turn, triggers signaling pathways that promote increased glucose deposition, enhancing insulin sensitivity. Increased insulin sensitivity has a positive effect on testosterone synthesis, which, in peripheral tissues, induces insulin resistance.

Ovaries, unlike other tissues, may retain adequate insulin sensitivity even in the presence of insulin resistance. This phenomenon was explained by Carlomagno et al. (69). In the presence of insulin resistance, compensatory hyperinsulinemia leads to increased epimerization of MI, resulting in excessive DCI synthesis at the expense of MI. The deficiency of MI and the increase in DCI in the ovaries of PCOS patients with hyperinsulinemia can impair FSH signaling. This can lead to reduced oocyte quality, deficient oocyte maturation, anovulation (lack of ovulation), and an increased risk of ovarian hyperstimulation syndrome.

4.2. Effects on metabolic abnormalities and obesity

Nestler et al. (60) first reported that inositol supplementation resulted in improvement of ovulatory function and decreased blood pressure, serum androgen, and triglyceride concentrations in obese patients with PCOS. Unfer et al. (58) reported a significant decrease in fasting serum insulin and HOMA index. Another research by Minozzi et al. (70) showed a significantly higher reduction in the HOMA index after 12-month treatment in combination with oral contraceptives and inositol compared to COC alone. Serum androgen levels were

lower in a combined therapy group, as well as LDL levels, while there was no significant change in BMI. The beneficial effect of inositols was also observed in adolescents aged 13-19, in which combination therapy with COC and inositols did not change weight or BMI, while insulin and HOMA index were reduced (71).

4.3. Effects on hyperandrogenism

In addition to its positive effects on insulin sensitivity, the meta-analysis conducted by Unfer et al. (58) revealed a slight trend towards decreased testosterone levels in individuals treated with MI compared to control groups. Circulating androstenedione levels were unaffected by treatment, while a trend towards the total decrease of total testosterone was observed. Furthermore, MI supplementation was found to significantly increase SHBG levels, but only after at least 24 weeks of administration.

Treatment duration was found to be crucial in the improvement of hyperandrogenism. In the study by Zacche et al. (72), an improvement in acne and hirsutism was seen after 6 months of supplementation. These findings suggest that MI may have a positive impact on hormonal profiles in individuals with PCOS, potentially contributing to the regulation of androgen levels and an increase in SHBG production, leading to lower bioavailability of testosterone. The results of a clinical trial by Minozzi et. al. (73) showed that administration of 2g of MI twice daily for 6 months significantly decreased hirsutism severity measured by using a modification of the mFG score and improved hormonal parameters, such as reducing levels of total androgens, FSH, LH, and LDL cholesterol, whereas estradiol and HDL cholesterol concentrations raised. In women with PCOS who do not desire to get pregnant, therapy with combined oral contraceptives (COC) is shown to be effective. These substances help to regulate menstrual cycles, preserve the endometrium, and alleviate symptoms associated with hyperandrogenism (hirsutism, acne) (59). Nevertheless, therapy with COC can cause serious adverse effects (such as hepatotoxicity).

Combining MI with combined oral contraceptives (COCs) in PCOS women has shown better control of hyperandrogenism and hyperinsulinemia compared to COCs alone. The addition of MI allowed for a lower dose of COCs, reducing the risk of side effects.

Overall, MI administration effectively controls hirsutism and hyperandrogenism in PCOS women and has positive effects on metabolic and hormonal parameters. Combining MI with COCs can improve symptom control and reduce the potential side effects of COCs.

4.4. Effect on ovulation induction

Because of ovulatory abnormalities, PCOS patients are generally infertile and require ovulation induction medicines such as clomiphene citrate or FSH, which can increase the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). According to research done by Papaleo et al. (74), MI is capable of restoring spontaneous ovarian activity and fertility in the majority of PCOS patients, and therapy with MI did not result in multiple pregnancies. In a study done by Raffone et al. (75), 65% of MI-treated women regained spontaneous ovulation activity, compared to 50% of metformin-treated patients.

Studies demonstrated that both MI and combination oral contraceptives (COC) had a significant impact on various parameters in PCOS patients. Progesterone and anti-Müllerian hormone (AMH) levels decreased, along with reductions in ovarian volume, ovarian antral follicles, and total antral follicle counts, indicating a positive effect on ovarian function and follicular development (76).

In an observational study done by Regidor et al. (77), treatment with MI and folic acid for an average duration of 10.2 weeks resulted in positive outcomes for infertile women with PCOS. Approximately 70% of the women resumed ovulation, and 15.1% of all patients who received MI treatment achieved pregnancy. These findings suggest that MI, in combination with folic acid, can effectively improve ovulation and fertility outcomes in women with PCOS.

Human studies in PCOS women showed that a 40:1 ratio of MI/DCI was most effective in restoring ovulation and normalizing important parameters (progesterone, LH, SHBG, estradiol, and testosterone) while other formulations (1:3.5; 2.5:1; 5:1; 20:1; 80:1) showed decreased activity, especially when the 40:1 ratio was modified in favor of DCI (78,79). The reduced effectiveness seen in certain trials when high dosages of DCI were used in PCOS therapy is hypothesized to be due to competing with myo-Ins for absorption at the gut level, thus decreasing the myo-Ins/D-Chiro-Ins ratio in plasma (79). DCI has also been shown to function as an aromatase inhibitor, which can lead to elevated testosterone levels. Elevated androgen levels can impair normal ovulatory activity, reducing the effectiveness of DCI in the treatment of PCOS. These observations point out that excess DCI in the ovary stimulates ovarian androgen production and can help to explain the worsening of oocyte and blastocyst quality observed with high DCI levels (78).

4.5. Role of inositols in assisted reproductive technology

Several studies have shown that MI is required for optimal oocyte maturation, and its higher content in human follicular fluid is regarded as a marker of good oocyte quality (79). MI supplementation three months before the initiation of ovarian stimulation at the dose of 4 g/day reduces the doses of FSH necessary for the follicular response, lowers the E2 peak level, and reduces the risk of ovarian hyperstimulation (OHSS) and the number of cycles (80). Conversely, when different DCI dosages were delivered to non-obese PCOS women with normal insulin sensitivity undergoing IVF, oocyte quality and ovarian response deteriorated as the DCI dose was gradually raised.

However, up to date, no sufficient data is showing clinical pregnancy rate ((i.e., without assisted reproductive technology, ART), spontaneous live birth rate, and miscarriage rate. Several systematic reviews and meta-analyses were published with largely contradictory results on the role of oral inositol supplementation in PCOS women receiving ART. The review study by Mendoza et al. (81) on the effect of MI supplementation on women with PCOS undergoing ICSI argued that there is a lack of evidence to support the role of inositol complex in improving oocyte and embryo quality.

Another systematic review by Lagana et al. (82) studied MI versus folic acid in PCOS and non-PCOS women undergoing IVF and concluded that MI reduces the amount of FSH usage in the IVF cycle, although it shows no improvement in the total number of oocytes or mature oocytes. Oral MI can reduce the length of controlled ovarian hyperstimulation only in PCOS patients. The improvement in the number of gonadotropins used can be explained by the theory of inositol's role in FSH signaling. However, there was heterogeneity among the studies included, and the quality of the embryo was not assessed in all the studies.

Zheng et al. (83) stated that MI has a role in improving clinical pregnancy rates and the number of good-quality embryos while reducing miscarriage rates and the number of germinal vesicles and degenerated oocytes. There was no significant difference in the MII stage, or the total number of oocytes retrieved. However, both PCOS and non-PCOS trials were included in their study.

Based on current evidence there is a promising role of inositols as a treatment for PCOS-related infertility. However, there is still a need for larger cohort studies with greater statistical significance which would assess fertility outcomes post-treatment and establish a therapeutic strategy.

4.6. Role of MI in gestational diabetes mellitus

PCOS is known to be a risk factor for adverse pregnancy outcomes, including gestational diabetes (GDM), pregnancy-induced hypertension, preeclampsia, preterm delivery, and SGA infants (84). GDM is more prevalent in obese women with PCOS and often requires insulin treatment during pregnancy (85). The results of the randomized controlled trial done by D'Anna et al. (2021) revealed that women who received the combination of MI and α-LA experienced a reduction in insulin resistance, a lower proportion of women requiring insulin therapy decreased fetal abdominal circumference, and reduced thickness of neonatal subcutaneous adipose tissue. The prevalence of GDM in the MI group was significantly lower at 17.4% compared to 54% in the control group. The odds of developing GDM were more than double in the control group compared to the MI group. Moreover, no cases of pre-term birth occurred in the treated group, compared with 15.2% in the control group.

Screening programs using early OGTT during pregnancy in PCOS women could help identify individuals at risk for GDM and focus on preventive measures.

4.7. Inositol resistance

Despite the efficacy of MI on metabolic, hormonal, and reproductive signs of PCOS, about 25 to 75% of patients treated with MI may be resistant to treatment (54). The etiology of this phenomenon is still not fully understood, but it could correlate to metabolic and hormonal dysregulations, including obesity, insulin resistance, hyperandrogenemia, or differences in the bioavailability of MI. The available data suggest that inositol resistance is more likely in moderate/severe obese, insulin-resistant, and hyperandrogenic women with PCOS (86). Compared to a normal-weight woman, the obese had nearly the half probability to ovulate and a quarter of the chance to become pregnant.

In a recent study by Oliva M et al. (87) MI-resistant patients did not show increased plasma levels of MI, raising the question about the role of MI bioavailability in non-responders. MI bioavailability is affected by many different factors, including intestinal absorption, transport from plasma into tissues, endogenous synthesis and catabolism, kidney excretion, etc. The question of inositol bioavailability is suggested by studies in which the intestinal absorption of inositols significantly increases in humans upon co-administration of a-lactalbumin.

α-**lactalbumin (**α-LA) is a protein found in milk (20–25% of whey) that has a role not only as a nutrient but as a factor for the resorption of other nutrients such as vitamins and microelements. The addition of α-LA could play a beneficial role in MI bioavailability by changes in tight junction permeability thus increasing plasma concentration in simultaneous administration In addition, it exerts an anti-inflammatory activity that is beneficial in PCOS (87,88).

Studies demonstrated, both in vivo and in vitro, that α-LA significantly improves MI intestinal absorption and bioavailability. In a different study, PCOS women, who were nonresponsive (inositol-resistant patients) to MI alone, were given 2 g MI plus 50 mg alpha-lactalbumin, twice a day for three months. Ovulation was the primary outcome, whereas some important laboratory parameters were secondary outcomes. At the end of the treatment, 86% of patients ovulated, showing an increase in plasmatic MI levels and a significant improvement in total cholesterol, triglycerides, testosterone, free testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin (SHBG). Also, androstenedione decreased, although it was nonsignificant. Therefore, these studies provide meaningful results to sustain the use of alpha-lactalbumin in combination with MI.

4.8. Inositol in combination with alpha lipoic acid (ALA) and melatonin

Recent therapeutic evidence addressed the importance of the association between alpha lipoic acid and MI or DCI. Alpha lipoic acid (ALA) is a powerful antioxidant that plays a central role in the antioxidant defense network by scavenging reactive oxygen species and regenerating important antioxidants. It is synthesized inside the mitochondria and acts as a cofactor for mitochondrial enzyme complexes involved in oxidative metabolism. The discovery that mammalian cells can synthesize lipoic acid, mainly within the mitochondria, was made relatively recently.

The significance of endogenous lipoic acid is not yet fully understood, although its pharmacological effects have been extensively studied. Lipoic acid administration is beneficial in various metabolic and vascular diseases due to its antioxidant properties. Lipoic acid has also been shown to impact glucose metabolism. It modulates glucose utilization by increasing adenosine monophosphate-activated protein kinase (AMPK) in skeletal muscles. This, in turn, leads to an increase in GLUT-4, a glucose transporter, facilitating glucose uptake into the

cytosol. This indicates that both ALA and MI independently play important roles in activating GLUT-4 vesicles on the cell membrane, thereby promoting glucose uptake (89).

While some studies have shown that the combination of DCI and ALA did not significantly improve clinical and metabolic disturbances in PCOS patients (90), other studies have demonstrated benefits of ALA on glucose uptake in lean PCOS patients (91). For example, one study found that the combination of DCI and ALA (1000mg DCI and 600mg ALA daily) improved menstrual cycle length and restored ovulation in most women with PCOS. However, the improvement in insulin sensitivity, as measured by the HOMA index, was significant only in women with insulin resistance (54,92). A recent study found that combining 500 mg of DCI with 300 mg of ALA in overweight/obese PCOS patients with diabetic relatives undergoing IVF resulted in a lower dose of gonadotropin, shorter stimulation days, and a higher number of mature and fertilized oocytes. This suggests that combination treatment may also improve IVF outcomes in this patient population (93).

A novel combination, used mainly for the treatment of reproductive disturbances in PCOS patients is the one with **melatonin**. Pacchiaroti et al. (94) investigated the combined use of melatonin and myo-inositol in women with PCOS undergoing their first IVF treatment. The study included women divided into three groups: control (folic acid), group A (myo-inositol, folic acid, and melatonin), and group B (myo-inositol and folic acid). Group A showed higher melatonin levels, required lower gonadotropin doses, obtained more mature oocytes, and had a higher percentage of high-quality embryos compared to Group B and the control group. This suggests that the combination of melatonin and myo-inositol may improve oocyte quality and fertilization rates in PCOS patients undergoing IVF.

5. **INOSITOL SAFETY AND OPTIMAL DOSAGE**

Clinical trial data indicate that adverse events related to MI treatment are generally mild and primarily gastrointestinal in nature. These adverse events may include symptoms such as nausea, flatulence, loose stools, and diarrhea. However, it's important to note that these side effects were observed at higher doses of myo-inositol, specifically at a dose of 12 g/day or higher. On the other hand, the commonly used dosage of 4 g/day of inositol, which is often employed in clinical settings, has been reported to be free of side effects. This suggests that the lower dosage of 4 g/day is well-tolerated and does not typically result in adverse gastrointestinal symptoms (95).

A recent study by Bevilacqua et al. (96) investigated the effectiveness of different MI and DCI formulas in PCOS mice. The study revealed that the MI/DCI ratio played a crucial role in restoring a normal phenotype. Mice treated with a 40:1 ratio showed rapid and significant recovery from PCOS symptoms, while other ratios had less efficacy or even negative effects. The study highlights the importance of maintaining the appropriate balance between MI and DCI for optimal functioning of organs. Additionally, high concentrations of DCI can have detrimental effects on follicle function and myo-Ins availability. These findings provide valuable insights into the intricate interplay between MI and DCI in modulating ovarian physiology in PCOS.

CONCLUSION

PCOS is a complex and heterogeneous endocrine disorder influenced by androgen production and a genetic or epigenetic predisposition to hyperinsulinemia. Lifestyle improvements and medical interventions are needed to address its effects on metabolic and reproductive functions. Inositols, such as myo-inositol (MYO) and D-chiro-inositol (DCI), represent a novel therapeutic approach in the management of PCOS. Both play a crucial role in regulating insulin and reproductive pathways. Their optimal ratio is necessary for proper organ function. Impaired MYO-to-DCI conversion and reduced ALA synthesis may contribute to PCOS-related insulin resistance. Inositols offer a safe and natural approach to managing the metabolic impairments of PCOS and enhancing ovarian function. The use of inositols is still experimental and further research is needed to enhance trust in the application of these compounds.

ACKNOWLEDGEMENTS

I would like to extend my gratitude to my mentor, prof. dr. sc. Dinka Pavičić Baldani, for the support and guidance in the process of writing this thesis.
I am forever grateful to my family and friends for always supporting me and believing in me.
To my parents: All that I am or hope to be, I owe to you.

BIBLIOGRAPHY

1. Escobar-Morreale HF. Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. Vol. 14, Nature Reviews Endocrinology. Nature Publishing Group; 2018. p. 270–84.
2. Azziz R. Reproductive endocrinology and infertility: Clinical expert series polycystic ovary syndrome. Obstetrics and Gynecology. 2018;132(2):321–36.
3. Hart R, Hickey M, Franks S. Definitions, prevalence and symptoms of polycystic ovaries and polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol. 2004;18:671–83.
4. Rosenfield RL, Ehrmann DA. The Pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as Functional Ovarian Hyperandrogenism Revisited. Endocr Rev. 2016 ;37(5):467–520.
5. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group.
6. Peña AS, Witchel SF, Hoeger KM, Oberfield SE, Vogiatzi MG, Misso M, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med 2020 Mar 24;18(1).
7. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril. 2018 Aug 1;110(3):364–79.
8. Wang J, Wu D, Guo H, Li M. Hyperandrogenemia and insulin resistance: The chief culprit of polycystic ovary syndrome. Life Sci. 2019 Nov 1;236.
9. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016 Nov 1;22(6):687–708.
10. Palomba S, De Wilde MA, Falbo A, Koster MPH, La Sala GB, Fauser BCJM. Pregnancy complications in women with polycystic ovary syndrome. Hum Reprod Update. 2015 Sep 1;21(5):575–92.
11. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935 Jan 1;29(2):181–91.
12. Zawadzki JK. Diagnostic criteria for polycystic ovary syndrome (a rational approach).

13. Christ JP, Cedars MI. Current Guidelines for Diagnosing PCOS. Diagnostics. 2023 Mar 15;13(6):1113.
14. Lujan ME, Chizen DR, Pierson RA. Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies.
15. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009 Feb;91(2):456–88.
16. Spritzer PM. Polycystic ovary syndrome: reviewing diagnosis and management of metabolic disturbances. Arq Bras Endocrinol Metabol. 2014;58(2):182–7.
17. NATIONAL INSTITUTES OF HEALTH Evidence-based Methodology Workshop on Polycystic Ovary Syndrome. 2012.
18. Lizneva D, Suturina L, Walker W, Brakta S, Gavrilova-Jordan L, Azziz R. Criteria, prevalence, and phenotypes of polycystic ovary syndrome. Fertil Steril. 2016 Jul 1];106(1):6–15.
19. Lauritsen MP, Bentzen JG, Pinborg A, Loft A, Forman JL, Thuesen LL, et al. The prevalence of polycystic ovary syndrome in a normal population according to the Rotterdam criteria versus revised criteria including anti-Müllerian hormone. Human Reproduction. 2014 Apr 1;29(4):791–801.
20. Teede H, Misso M, Tassone EC, Dewailly D, Ng EH, Azziz R, et al. Title: Anti-Müllerian hormone in PCOS: a review informing international guidelines.
21. Ran Y, Yi Q, Li C. The Relationship of Anti-Mullerian Hormone in Polycystic Ovary Syndrome Patients with Different Subgroups. Diabetes Metab Syndr Obes. 2021;14:1419.
22. Gibson-Helm M, Teede H, Dunaif A, Dokras A. Delayed Diagnosis and a Lack of Information Associated With Dissatisfaction in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017 Feb 2;102(2):604.
23. The Lancet Regional Health – Europe. Polycystic ovary syndrome: What more can be done for patients? The Lancet Regional Health - Europe. 2022 Oct 1;21:100524.
24. Riestenberg C, Jagasia A, Markovic D, Buyalos RP, Azziz R. Health Care-Related Economic Burden of Polycystic Ovary Syndrome in the United States: Pregnancy-Related and Long-Term Health Consequences. J Clin Endocrinol Metab;107(2):575–85.
25. Rosenfield RL. Clinical practice. Hirsutism. N Engl J Med. 2005 Dec 15;353(24):2578–88
26. Azziz R, Carmina E, Chen Z, Dunaif A, Laven JSE, Legro RS, et al. Polycystic ovary syndrome. Nature Reviews Disease Primers 2016 2:1]. 2016 Aug 11;2(1):1–18.

27. Mihailidis J, Dermesropian R, Taxel P, Luthra P, Grant-Kels JM. Endocrine evaluation of hirsutism. Int J Womens Dermatol. 2017 Mar 1;3(1):S6–10.
28. Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsutism. Hum Reprod Update. 2010 Jun 30;16(1):51–64.
29. Souter I, Sanchez LA, Perez M, Bartolucci AA, Azziz R. The prevalence of androgen excess among patients with minimal unwanted hair growth. Am J Obstet Gynecol. 2004 Dec;191(6):1914–20.
30. Amiri M, Ramezani Tehrani F, Nahidi F, Bidhendi Yarandi R, Behboudi-Gandevani S, Azizi F. Association between biochemical hyperandrogenism parameters and Ferriman-Gallwey score in patients with polycystic ovary syndrome: A systematic review and meta-regression analysis. Clin Endocrinol (Oxf). 2017 Sep 1;87(3):217–30.
31. Guo Z, Jin F, Chen S, Hu P, Hao Y, Yu Q. Correlation between biochemical and clinical hyperandrogenism parameter in polycystic ovary syndrome in relation to age. BMC Endocr Disord. 2023 Dec 1;23(1):89.
32. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev. 2013 Feb;14(2):95–109.
33. Barber TM. Why are women with polycystic ovary syndrome obese? Br Med Bull. 2022 Sep 22;143(1):4–15.
34. Osibogun O, Ogunmoroti O, Michos ED. Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovascular disease prevention. Trends Cardiovasc Med. 2020 Oct;30(7):399–404.
35. Wild RA, Rizzo M, Clifton S, Carmina E. Lipid levels in polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2011 Mar 1;95(3).
36. Kakoly NS, Khomami MB, Joham AE, Cooray SD, Misso ML, Norman RJ, et al. Ethnicity, obesity and the prevalence of impaired glucose tolerance and type 2 diabetes in PCOS: a systematic review and meta-regression. Hum Reprod Update. 2018 Jul 1;24(4):455–67.
37. Wekker V, Van Dammen L, Koning A, Heida KY, Painter RC, Limpens J, et al. Long-term cardiometabolic disease risk in women with PCOS: a systematic review and meta-analysis. 2020 Nov 1;26(6).
38. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and

Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010;95(5):2038–49.

39. Al Wattar BH, Fisher M, Bevington L, Talaulikar V, Davies M, Conway G, et al. Clinical Practice Guidelines on the Diagnosis and Management of Polycystic Ovary Syndrome: A Systematic Review and Quality Assessment Study. J Clin Endocrinol Metab. 2021 Aug 1;106(8):2436. Available from: /pmc/articles/PMC8830055/
40. Kodipalli A, Devi S. Prediction of PCOS and Mental Health Using Fuzzy Inference and SVM. Front Public Health. 2021 Nov 30 ;9:789569.
41. Deeks AA, Gibson-Helm ME, Paul E, Teede HJ. Is having polycystic ovary syndrome a predictor of poor psychological function including anxiety and depression? Hum Reprod. 2011;26(6):1399–407.
42. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nature Reviews Endocrinology 2011 7:4. 2011 Jan 25;7(4):219–31.
43. Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome in a Dutch twin-family study. J Clin Endocrinol Metab. 2006;91(6):2100–4.
44. Cassar S, Misso ML, Hopkins WG, Shaw CS, Teede HJ, Stepto NK. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic-hyperinsulinaemic clamp studies. Hum Reprod. 2016 Nov 1;31(11):2619–31.
45. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic–hyperinsulaemic clamp. Human Reproduction. 2013 Mar 1;28(3):777–84.
46. Laganà AS, Garzon S, Casarin J, Franchi M, Ghezzi F. Inositol in Polycystic Ovary Syndrome: Restoring Fertility through a Pathophysiology-Based Approach. Vol. 29, Trends in Endocrinology and Metabolism. Elsevier Inc.; 2018. p. 768–80.
47. Moghetti P, Tosi F. Insulin resistance and PCOS: chicken or egg? J Endocrinol Invest. 2021 Feb 1;44(2):233–44.
48. Nestler JE, Jakubowicz DJ, Falcon de Vargas A, Brik C, Quintero N, Medina F. Insulin Stimulates Testosterone Biosynthesis by Human Thecal Cells from Women with Polycystic Ovary Syndrome by Activating Its Own Receptor and Using Inositolglycan Mediators as the Signal Transduction System. J Clin Endocrinol Metab. 1998 Jun 1;83(6):2001–5.

49. Tosi F, Negri C, Perrone F, Dorizzi R, Castello R, Bonora E, et al. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2012 May;97(5):1712–9.
50. O'Reilly MW, Kempegowda P, Walsh M, Taylor AE, Manolopoulos KN, Allwood JW, et al. AKR1C3-Mediated Adipose Androgen Generation Drives Lipotoxicity in Women With Polycystic Ovary Syndrome. J Clin Endocrinol Metab. 2017 Sep 1;102(9):3327-39.
51. Regidor PA, Mueller A, Sailer M, Santos FG, Rizo JM, Egea FM. Chronic Inflammation in PCOS: The Potential Benefits of Specialized Pro-Resolving Lipid Mediators (SPMs) in the Improvement of the Resolutive Response. International Journal of Molecular Sciences 2021, Vol 22, Page 384. 2020 Dec 31;22(1):384.
52. Lim SS, Hutchison SK, Van Ryswyk E, Norman RJ, Teede HJ, Moran LJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews. 2019 Mar 28;2019(3).
53. Dinicola S, Unfer V, Facchinetti F, Soulage CO, Greene ND, Bizzarri M, et al. Inositols: From established knowledge to novel approaches. Vol. 22, International Journal of Molecular Sciences. MDPI; 2021.
54. Kamenov Z, Gateva A. Inositols in pcos. Vol. 25, Molecules. MDPI AG; 2020.
55. Chhetri DR. Myo-inositol and its derivatives: Their emerging role in the treatment of human diseases. Vol. 10, Frontiers in Pharmacology. Frontiers Media S.A.; 2019.
56. Al-Suod H, Ligor M, Rațiu IA, Rafińska K, Górecki R, Buszewski B. A window on cyclitols: Characterization and analytics of inositols. Phytochem Lett. 2017 Jun 1;20:507–19.
57. Bevilacqua A, Bizzarri M. Inositols in insulin signaling and glucose metabolism. Vol. 2018, International Journal of Endocrinology. Hindawi Limited; 2018.
58. Unfer V, Facchinetti F, Orrù B, Giordani B, Nestler J. Myo-inositol effects in women with PCOS: A meta-analysis of randomized controlled trials. Endocr Connect. 2017 Nov 1;6(8):647–58.
59. Facchinetti F, Appetecchia M, Aragona C, Bevilacqua A, Bezerra Espinola MS, Bizzarri M, et al. Experts' opinion on inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes mellitus: a further help for human reproduction and beyond. Vol. 16, Expert Opinion on Drug Metabolism and Toxicology. Taylor and Francis Ltd; 2020. p. 255–74.
60. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med. 1999 Apr 29;340(17):1314–20.

61. Sacchi S, Marinaro F, Tondelli D, Lui J, Xella S, Marsella T, et al. Modulation of gonadotrophin induced steroidogenic enzymes in granulosa cells by d-chiroinositol. Reproductive Biology and Endocrinology. 2016 Aug 31;14(1):1–8.
62. Burghen GA, Givens JR, Kitabchi AE. Correlation of hyperandrogenism with hyperinsulinism in polycystic ovarian disease. J Clin Endocrinol Metab. 1980;50(1):113–6.
63. Dunaif A. Insulin Resistance and the Polycystic Ovary Syndrome: Mechanism and Implications for Pathogenesis*. 1997;
64. Baillargeon JP, Iuorno MJ, Apridonidze T, Nestler JE. Uncoupling Between Insulin and Release of a d-Chiro-Inositol–Containing Inositolphosphoglycan Mediator of Insulin Action in Obese Women With Polycystic Ovary Syndrome. Metab Syndr Relat Disord. 2010 Apr 1;8(2):127.
65. Sun TH, Heimark DB, Nguygen T, Nadler JL, Larner J. Both myo-inositol to chiro-inositol epimerase activities and chiro-inositol to myo-inositol ratios are decreased in tissues of GK type 2 diabetic rats compared to Wistar controls. Biochem Biophys Res Commun. 2002;293(3):1092–8.
66. Heimark D, McAllister J, Larner J. Decreased myo-inositol to chiro-inositol (M/C) ratios and increased M/C epimerase activity in PCOS theca cells demonstrate increased insulin sensitivity compared to controls. Endocr J. 2014;61(2):111–7.
67. Unfer V, Carlomagno G, Papaleo E, Vailati S, Candiani M, Baillargeon JP. Hyperinsulinemia Alters Myoinositol to d-chiroinositol Ratio in the Follicular Fluid of Patients With PCOS. Reprod Sci. 2014;21(7):854–8.
68. Larner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. Molecular Medicine. 2010 Nov 1;16(11–12):543–51.
69. Carlomagno G, Unfer V, Roseff S. The D-chiro-inositol paradox in the ovary. Fertil Steril. 2011 Jun 30;95(8):2515–6.
70. Minozzi M, Costantino D, Guaraldi C, Unfer V. The effect of a combination therapy with myo-inositol and a combined oral contraceptive pill versus a combined oral contraceptive pill alone on metabolic, endocrine, and clinical parameters in polycystic ovary syndrome. Gynecol Endocrinol. 2011 Nov;27(11):920–4.
71. Pkhaladze L, Barbakadze L, Kvashilava N. Myo-Inositol in the Treatment of Teenagers Affected by PCOS. Int J Endocrinol. 2016;2016.

72. Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol Endocrinol. 2009;25(8):508–13.
73. Minozzi M, D'Andrea G, Unfer V. Treatment of hirsutism with myo-inositol: a prospective clinical study. Reprod Biomed Online. 2008;17(4):579–82.
74. Papaleo E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C, et al. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. Gynecol Endocrinol. 2007 Dec;23(12):700–3.
75. Raffone E, Rizzo P, Benedetto V. Insulin sensitiser agents alone and in co-treatment with r-FSH for ovulation induction in PCOS women. Gynecol Endocrinol. 2010 Apr; 26(4):275–80.
76. Ozay AC, Emekci Ozay O, Okyay RE, Cagliyan E, Kume T, Gulekli B. Different Effects of Myoinositol plus Folic Acid versus Combined Oral Treatment on Androgen Levels in PCOS Women. Int J Endocrinol. 2016;2016.
77. Regidor PA, Schindler AE, Lesoine B, Druckman R. Management of women with PCOS using myo-inositol and folic acid. New clinical data and review of the literature. Horm Mol Biol Clin Investig. 2018 Mar 2;34(2).
78. Roseff S, Montenegro M. Inositol treatment for PCOS should be science-based and not arbitrary. Int J Endocrinol. 2020;2020.
79. Monastra G, Vucenik I, Harrath AH, Alwasel SH, Kamenov ZA, Laganà AS, et al. PCOS and Inositols: Controversial Results and Necessary Clarifications. Basic Differences Between D-Chiro and Myo-Inositol. Front Endocrinol (Lausanne). 2021 Apr 6;12.
80. Merviel P, James P, Bouée S, Le Guillou M, Rince C, Nachtergaele C, et al. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. Vol. 18, Reproductive Health. BioMed Central Ltd; 2021.
81. Mendoza N, Diaz-Ropero MP, Aragon M, Maldonado V, Llaneza P, Lorente J, et al. Comparison of the effect of two combinations of myo-inositol and D-chiro-inositol in women with polycystic ovary syndrome undergoing ICSI: a randomized controlled trial. Gynecological Endocrinology. 2019 Aug 3 ;35(8):695–700.
82. Laganà AS, Vitagliano A, Noventa M, Ambrosini G, D'Anna R. Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: a systematic review and meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2018 Oct 1;298(4):675–84.

83. Zheng X, Lin D, Zhang Y, Lin Y, Song J, Li S, et al. Inositol supplement improves clinical pregnancy rate in infertile women undergoing ovulation induction for ICSI or IVF-ET. Vol. 96, Medicine (United States). Lippincott Williams and Wilkins; 2017.
84. Kjerulff LE, Sanchez-Ramos L, Duffy D. Pregnancy outcomes in women with polycystic ovary syndrome: A metaanalysis. Am J Obstet Gynecol. 2011 Jun 1;204(6):558.e1-558.e6.
85. Mustaniemi S, Vääräsmäki M, Eriksson JG, Gissler M, Laivuori H, Ijäs H, et al. Polycystic ovary syndrome and risk factors for gestational diabetes. Endocr Connect. 2018 Jul 1;7(7):859–69.
86. Kamenov Z, Kolarov G, Gateva A, Carlomagno G, Genazzani AD. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. 2015 Feb 1;31(2):131–5.
87. Montanino Oliva M, Buonomo G, Calcagno M, Unfer V. Effects of myo-inositol plus alpha-lactalbumin in myo-inositol-resistant PCOS women.
88. Monastra G, Sambuy Y, Ferruzza S, Ferrari D, Ranaldi G. Alpha-lactalbumin Effect on Myo-inositol Intestinal Absorption: In vivo and In vitro. Curr Drug Deliv. 2018 May 10;15(9):1305–11.
89. Genazzani AD. Expert's opinion: integrative treatment with inositols and lipoic acid for insulin resistance of PCOS.
90. Cianci A, Panella M, Fichera M, Falduzzi C, Bartolo M, Caruso S. d-chiro-Inositol and alpha lipoic acid treatment of metabolic and menses disorders in women with PCOS. Gynecol Endocrinol. 2015 Jun 1;31(6):483–6.
91. Masharani U, Gjerde C, Evans JL, Youngren JF, Goldfine ID. Effects of controlled-release alpha lipoic acid in lean, nondiabetic patients with polycystic ovary syndrome. J Diabetes Sci Technol. 2010;4(2):359–64.
92. Fruzzetti F, Capozzi A, Canu A, Lello S. Treatment with d-chiro-inositol and alpha lipoic acid in the management of polycystic ovary syndrome. Gynecol Endocrinol. 2019 Jun 3;35(6):506–10.
93. Artini PG, Obino MER, Micelli E, Malacarne E, Vacca C, Papini F, et al. Effect of d-chiro-inositol and alpha-lipoic acid combination on COH outcomes in overweight/obese PCOS women. Gynecol Endocrinol. 2020 Sep 1;36(9):755–9.
94. Pacchiarotti A, Carlomagno G, Antonini G, Pacchiarotti A. Effect of myo-inositol and melatonin versus myo-inositol, in a randomized controlled trial, for improving in vitro fertilization of patients with polycystic ovarian syndrome. 2015 Jan 2;32(1):69–73.

95. Carlomagno G. U V. Inositol safety: clinical evidences. Eur Rev Med Pharmacol Sci. 2011;15:931–6.
96. Bevilacqua A, Dragotto J, Giuliani A, Bizzarri M. Myo-inositol and D-chiro-inositol (40:1) reverse histological and functional features of polycystic ovary syndrome in a mouse model. J Cell Physiol. 2019 Jun 1;234(6):9387–98.

BIOGRAPHY

I was born on November 26, 1996 in Mostar, Bosnia and Herzegovina. After finishing primary school and high school in B&H, I decided to enrol in Zagreb School of Medicine to pursue my lifelong dream of becoming a physician. During the clinical years I developed a special interest in the field of Obstetrics and Gynecology, and Endocrinology and Diabetology. This is the reason I chose to write my thesis on a topic that encompasses both fields. My other interests include reading, playing piano, learning new languages and travelling.