Archives of Gynecology and Obstetrics (2020) 302:1169–1179
https://doi.org/10.1007/s00404-020-05696-y

GENERAL GYNECOLOGY

Metabolic impact of current therapeutic strategies in Polycystic Ovary Syndrome: a preliminary study

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Received: 5 April 2020 / Accepted: 9 July 2020 / Published online: 8 August 2020

Abstract

Purpose To investigate the metabolic impact of currently used therapies in polycystic ovary syndrome (PCOS).

Methods This is an observational, retrospective and transversal protocol. A small cohort of 133 patients, aged 14–48 years, diagnosed with PCOS was divided into four experimental groups: 1) untreated PCOS patients ($n=51$); 2) PCOS patients treated with one of the following therapies ($n=82$): a) combined oral contraceptives (COC, $n=35$); b) metformin ($n=11$); and c) inositols ($n=36$).

Results Although only < 10% of patients included in this cohort can be strictly encompassed in the development of metabolic syndrome, approximately 20% had insulin resistance. In PCOS patients, COC treatment modified the hormonal profile and worsened lipid parameters (increasing cholesterol and triglyceride levels) and insulin resistance, whereas inositol therapies improved significantly insulin resistance and glycosylated hemoglobin, reducing cholesterol and triglyceride levels. In these women, obesity was associated with greater alterations in lipid and glycemic metabolism and with higher blood pressure levels. PCOS patients with phenotype A presented vaster alterations in lipid metabolism and higher values of glycosylated hemoglobin as well as blood pressure compared to other PCOS phenotypes.

Conclusions Results in this paper suggest that inositol therapies (alone or combined with COC) are the most useful therapies with the best benefits against PCOS symptoms. Thus, integrative treatment may become a more efficient long-term choice to control PCOS symptoms. Furthermore, obesity can be considered as an adverse symptom and calorie restriction a key element of combined treatment in PCOS, not only for fertility management but also in long-term metabolic sequelae.

Keywords Polycystic ovary syndrome · Metabolic syndrome · Chronic anovulation · Oral contraceptives · Inositol · Obesity

Abbreviations

COC	Combined oral contraceptive
BMI	Body mass index
IGFBPs	IGF-1 binding proteins
DHEAs	Dehydroepiandrosterone sulfate
DBP	Diastolic blood pressure
ECLIA	Electrochemiluminescence immunoassay
FSH	Follicle-stimulating hormone
GH	Growth hormone
HDL	High-density lipoprotein
HbA1c	Glycosylated hemoglobin
HOMA	Homeostasis model assessment, common clinical index to estimate insulin resistance
IGF-1	Insulin-like growth factor 1
IR	Insulin resistance
LDL	Low-density lipoprotein
LH	Luteinizing hormone
MBP	Mean blood pressure
MetS	Metabolic syndrome
OSA	Obstructive sleep apnea
PCOS	Polycystic ovary syndrome
SBP	Systolic blood pressure
SHBG	Sex hormone-binding globulin

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SMD Standard mean deviation
TSH Thyroid-stimulating hormone

Introduction

Polycystic ovary syndrome (PCOS) affects nearly 3–10% of women in reproductive age [1–3]. It is a usual endocrine disorder and is associated with hyperandrogenism, chronic anovulation and the appearance of metabolic disturbances that may have serious implications for long-term health. Thus, there are several clinical definitions for PCOS, but the most broadly accepted is the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases in adrenal or pituitary glands [4, 5].

Nowadays, PCOS is the most frequent cause of anovulation, infertility, endometrial hyperplasia and elevated androgen levels leading to hirsutism, alopecia and acne in women in reproductive age [6–8]. Also, PCOS is included within the complex metabolic syndrome (MetS) [9, 10], insulin resistance (IR), obesity and adiposity, obstructive sleep apnea (OSA), hypogonadism, lipodystrophy and microvascular disease [11–23].

Although the etiology of PCOS is not fully understood, it is considered a multifactorial disorder with genetic, metabolic and endocrine abnormalities [24]. IR with compensatory hyperinsulinism are common PCOS features. This IR seems to be the well-known physiopathological link between PCOS and MetS development, but its underlying mechanisms remain unclear.

The present work is a preliminary study in a small cohort of PCOS patients that precedes an ongoing project focused on the investigation of mechanisms involved in the relationship between PCOS development and MetS establishment. In this fashion, the purpose of the present study was to understand and investigate the impact of current therapies (combined oral contraceptives—COC, metformin and inositols) in PCOS metabolic parameters in a small cohort of patients diagnosed with such disorder.

Materials and methods

Participants and ethical procedures

This protocol was previously approved by the Ethics Committee of the "Fundación de Investigación HM Hospitales de Madrid" (14.11.704-GHM), governed by the basic ethical principles contained in the World Medical Declaration of Helsinki [25].

All diagnosed PCOS patients attending to Gynecology consultations at "Puerta del Sur Hospital (HM)" and "Majadahonda Medical Center" in Madrid (Spain) were offered to participate in the present study. Patients were included after obtaining their written informed consent or their parent/guardian written informed consent (in case of minors). Patients who refused to participate in the study were tracked, unless their refusal meant any change in treatment or patient's care.

Diagnose criteria and phenotype characterization

PCOS diagnosis and characterization

PCOS was diagnosed according to the Rotterdam criteria [26], including at least two of the following symptoms: 1) oligo or anovulation; 2) clinical or biochemical signs of hyperandrogenism; 3) polycystic ovaries by ultrasound.

Also, four PCOS phenotypes were established according to the Rotterdam criteria [26]: phenotype A with oligoanovulation, clinical or analytical hyperandrogenism and ultrasound signs of PCOS; phenotype B with oligoanovulation and clinical or analytical hyperandrogenism; phenotype C with clinical or analytical hyperandrogenism and ultrasound images; and/or phenotype D with oligoanovulation and PCOS compatible sonographic images. All of them were considered as qualitative nominal variables.

MetS diagnosis

MetS diagnosis was established according to the criteria set forth by the National Cholesterol Education Program Adult Treatment Panel III (NECP-ATP III) [27], meeting at least three of the following: abdominal circumference > 88 cm, triglycerides > 150 mg/dL, HDL cholesterol < 50 mg/dL, blood pressure > 130/85 mmHg or glucose > 110 mg/dL.

Protocol design

An observational, retrospective and transversal study was made in a small cohort of 133 PCOS patients, aged 14–48 years. This cohort was divided into four experimental groups: 1) untreated PCOS patients ($n = 51$, 38.65%); and 2) PCOS patients treated with ($n = 82$, 61.45%): a) COC ($n = 35$, 25.9%); b) metformin ($n = 11$, 8.25%); and c) inositols ($n = 36$, 27.3%).

This study also included underaged women since it is in the early years of life where all biochemical and hormonal changes associated with the development of PCOS start, and usually is in the adolescence when PCOS is diagnosed.

After the inclusion of patients in one of the experimental groups, a single blood sample (8-h fasting, obtained in the follicular phase of the menstrual cycle) was acquired to determine hormonal and metabolic parameters.

Treatments and follow-up of patients

Treatments were indicated by the clinician, taking into account contraindications for contraceptive treatment. For inositol treatment, two preparations were used: 1) 2 g myo-inositol and 200 µg folic acid ($n=23$); 2) 200 mg myoinositol, 400 mg D-chiro-inositol, 10 mg manganese pidolate and 400 µg folic acid ($n=13$). Several COC treatments were used, such as sustained release vaginal ring with 11.7 mg etonogestrel and 2.7 mg ethinyl estradiol; 2.5 mg nomegestrol acetate and 1.5 mg estradiol; 3 mg drospirenone and 0.02 mg ethinyl estradiol; 3 mg dienogest and 0.03 mg ethinyl estradiol; 100 mg of levonorgestrel and 0.02 mg ethinyl estradiol; being the preparation of 3 mg drospirenone and 0.03 mg ethinyl estradiol the most widely used in the present study. Ultimately, metformin treatment consisted of a standard dose of 850 mg/day of this drug.

Therapies were considered similar for all patients, with the only exception in PCOS patients treated with inositols, where the treatment was prolonged for either more than three months ($n=17$) and less than 3 months ($n=19$).

Serum analytical determinations

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, thyroid-stimulating hormone (TSH), prolactin, 17OH-progesterone, total testosterone, sex hormone-binding globulin (SHBG), androstenedione and dehydroepiandrosterone sulfate (DHEAs) were assessed by electrochemiluminescence immunoassay (ECLIA) using Elecsys and Cobas autoanalyzers. The rate of free androgens was estimated according to the formula: (total testosterone × 3.47/SHBG) × 100; as well as the ratio LH/FSH.

Total cholesterol, HDL, low-density lipoprotein (LDL), triglycerides, glucose, insulin and glycosylated hemoglobin were also determined. HOMA (homeostasis model assessment), an index of IR, was calculated as insulin (µU/ml) for glucose (mmol/L) / 22.5. IR was considered for values greater than 3. Additionally, sodium, potassium, urea and homocysteine serum levels were also determined. All of them were considered as continuous quantitative variables.

Measurement of additional clinical parameters

Body mass index (BMI, a continuous quantitative variable) was estimated according to the following formula: weight (Kg)/height (m^2). BMI was used to classify patients in normal weight (BMI: 5–24.9), overweight (BMI: 25–29.9), obesity grade I (BMI: 30–34.9), obesity grade II (BMI: 35–39.9) and obesity grade III (BMI: > 40) [28].

Blood pressure (a continuous quantitative variable) was determined assessing systolic (SBP) and diastolic blood pressure (DBP) in each patient in sitting position. Mean blood pressure (MBD) was calculated with the formula: 1/3(SBP) + 2/3(DBP).

Statistical analysis

All data are represented as mean ± SMD. Statistical analysis was performed on SPSS 20 (IBM, USA). Qualitative and/or quantitative variables were analyzed with Student T test or χ^2 test. Correlations were evaluated by Spearman test or "r of Pearson". Significance was estimated by the Kruskal–Wallis ANOVA followed by a post hoc test for distribution-free multiple comparisons (Dunnett's test) or Mann–Whitney test for unpaired samples. Differences were considered significant at $p<0.05$.

Results

Clinical features of the population

As mentioned, the small cohort of 133 women (27.80 ± 6.56 years) was diagnosed with PCOS according to the Rotterdam criteria [26]. Regarding body weight and BMI, a total of 63 patients (47%) were overweight or have obesity (Table 1).

Following Rotterdam criteria, patients were classified into four PCOS phenotypes (A, B, C or D). It was found that 50.8% of patients (67 women) belonged to phenotype A, the most frequent PCOS phenotype in this cohort, followed by phenotype D in 27 patients (20.5%), phenotype C in 25 patients (18.9%) and finally phenotype B in 13 patients (9.8%). Considering only obese patients, the most frequent observed PCOS phenotype was phenotype A (75%), followed by phenotype C (11.5%) and phenotype D (7.7%).

Regarding to clinical features, disturbances in menstrual cycle (81%), hirsutism (75.8%) and ultrasonographic alterations (75%) were the predominant clinical symptoms (Table 1).

Metabolic and endocrinological parameters in PCOS patients

PCOS patients included in this protocol were divided into four groups. Despite the limitations of the present study, treatment with COC in PCOS patients modified the hormonal profile reducing significantly FSH, LH and SHBG serum levels. In addition, COC therapies worsened lipid profile and increased circulating cholesterol and triglyceride levels without modulating glycemic metabolism compared to untreated PCOS patients (Table 2, Fig. 1a, b).

However, as compared to untreated patients, inositol therapies improved glucose metabolism parameters (glycemia and insulinemia), including HOMA, a common

Table 1 General and clinical features of the present population

General and clinical features	Total PCOS patients population	PCOS young patients (< 18 years old)	PCOS patients with overweight or obesity (BMI > 25)
n (%)	133 (100%)	10 (7.6%)	63 (43.8%)
Age (years)	27.80 ± 6.56	16.1 ± 1.76	28.2 ± 6.87
Body Weight (Kg)	67.2 ± 15.99	59.10 ± 9.74	80.01 ± 13.34
Body Mass Index (BMI)	25.02 ± 5.36	22.37 ± 4.05	29.87 ± 7.24
PCOS phenotype prevalence (%)			
Phenotype A	50.8%	75%	40%
Phenotype B	9.8%	3.8%	20%
Phenotype C	18.9%	11.5%	30%
Phenotype D	20.52%	7.7%	10%
Main clinical symptoms (%)			
Menstrual irregularities	81%	100%	92%
Hirsutism	75.8%	80%	93%
Ultrasonographic images	75%	80%	96%

Table 2 Metabolic and endocrinological serum parameters in the four experimental groups of PCOS patients

Metabolic and endocrinological parameters	Controls (untreated PCOS patients)	COC group (PCOS patients treated with COC)	Inositol group (PCOS patients treated with inositols)	Metformin group (PCOS patients treated with metformin)
FSH (mUI/mL)	5.84 ± 2.12	**3.77 ± 2.36*****	**5.86 ± 1.64**$^{\&\&\&}$	4.77 ± 2.59
LH (mUI/mL)	8.83 ± 5.33	**5.83 ± 5.79***	**9.21 ± 6.87**$^{\&\&\&}$	7.03 ± 7.66
TSH (µUI/mL)	2.28 ± 1.15	2.27 ± 0.97	2.01 ± 2.01	1.81 ± 0.92
Estradiol (pg/mL)	49.94 ± 38.54	38.39 ± 43.16	57.61 ± 46.16	45.61 ± 32.92
Prolactin (ng/mL)	16.99 ± 9.58	18.22 ± 7.92	17.67 ± 7.03	15.00 ± 7.37
17OH-Progesterone (ng/mL)	0.94 ± 0.71	0.92 ± 0.56	1.19 ± 1.07	0.83 ± 0.44
Testosterone(ng/mL)	0.36 ± 0.23	0.36 ± 0.28	0.36 ± 0.17	1.79 ± 4.58
SHBG (nmol/L)	70.01 ± 42.68	**156.88 ± 101.16*****	**75.37 ± 36.42**$^{\&\&\&}$	85.70 ± 57.33
Androstenedione (ng/mL)	2.77 ± 1.41	2.74 ± 1.92	2.82 ± 1.48	2.52 ± 1.65
DHEAs (µg/mL)	2.26 ± 1.73	1.95 ± 0.94	2.16 ± 1.03	2.45 ± 1.25
Free Androgens	0.71 ± 0.69	0.49 ± 1.10	0.69 ± 0.70	1.46 ± 2.46
LH/FSH	1.58 ± 0.83	1.36 ± 0.95	1.66 ± 1.19	1.46 ± 1.50
Cholesterol (mg/mL)	174.22 ± 30.05	**190.14 ± 32.30****	**178.22 ± 63.0**$^{\&}$	**185.81 ± 23.05**$^{\#}$
HDL (mg/dL)	60.76 ± 17.61	64.87 ± 17.47	62.16 ± 14,62	56.30 ± 16.00
LDL (mg/dL)	99.83 ± 28.11	108.96 ± 30.62	101.22 ± 25.22	112.44 ± 14.84
Triglycerides (mg/dL)	76.02 ± 44.77	**98.38 ± 42.16***	81.74 ± 65.26	**114.72 ± 54.33***
Glucose (mg/dL)	84.98 ± 15.03	84.44 ± 10.37	**79.54 ± 8.88***	79.60 ± 8.22
Insulin (µUI/mL)	10.95 ± 11.21	13.27 ± 10.97	9.36 ± 9.42	14.59 ± 9.10
HbA1c (%)	5.34 ± 0.49	5.21 ± 0.27	**5.11 ± 0.24****	5.21 ± 0.27
HOMA	2.16 ± 2.50	2.88 ± 2.68	**1.64 ± 1.89**$^{*\&\#}$	**2.68 ± 2.02**$^{\#}$
Homocysteine (mmol/L)	9.12 ± 5.59	9.27 ± 4.17	8.36 ± 2.31	10.18 ± 4.78
SBP (mm Hg)	111.94 ± 15.58	115.18 ± 16.66	108.33 ± 12.64	113.82 ± 15.54
DBP (mm Hg)	67.25 ± 10.08	68.03 ± 10.29	66.64 ± 9.24	69.82 ± 11.06
BPM (mm Hg)	82.14 ± 11.24	83.74 ± 11.50	80.53 ± 99.35	84.48 ± 12.04

BMI body mass index; *BPM* blood pressure medium; *DBP* diastolic blood pressure; *DHEAs* dehydroepiandrosterone sulfate; *FSH* follicle-stimulating hormone; *HbA1c* glycosylated hemoglobin; *HDL* high-density lipoprotein; *HOMA* homeostasis model assessment; *LDL* low-density lipoprotein; *LH* luteinizing hormone; *SBP* systolic blood pressure; *SHBG* sex hormone-binding globulin; *TSH* thyroid-stimulating hormone. *p values:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ each group of treated PCOS patients *vs* controls (untreated PCOS patients); $^{\&}p < 0.05$, $^{\&\&}p < 0.01$, $^{\&\&\&}p < 0.001$ inositol group *vs* COC group; $^{\#}p < 0.05$ metformin group *vs* inositol group

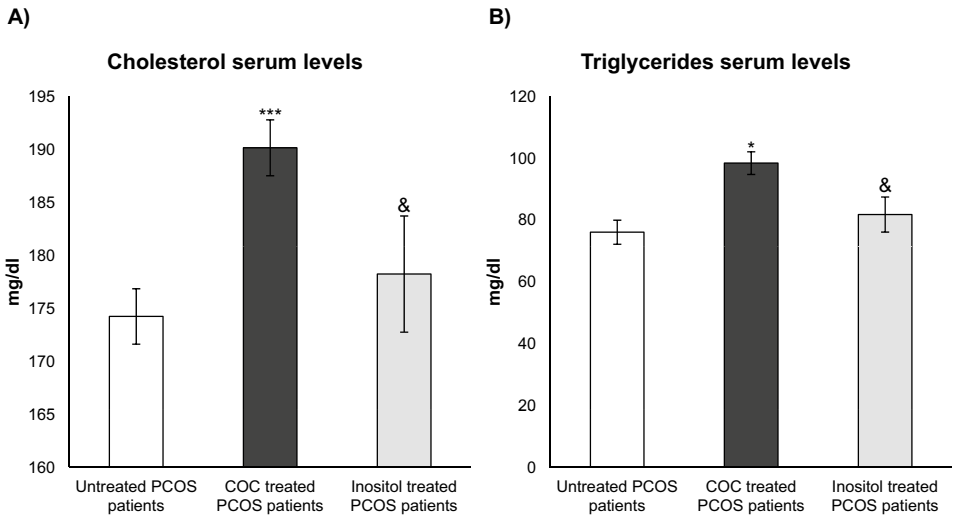


Fig. 1 Cholesterol (**a**) and triglyceride (**b**) serum levels in untreated PCOS patients, COC-treated PCOS patients and inositol-treated patients. $^{*}p<0.05$, $^{***}p<0.001$ COC-treated patients *vs* untreated patients; $^{\&}p<0.05$ inositol-treated patients *vs* COC-treated patients

index of insulin resistance, and glycosylated hemoglobin (Table 2, Fig. 2a–d). In addition, inositol therapies did not increase cholesterol and triglyceride serum levels, but this therapy reduced significantly both parameters as compared to untreated patients (Fig. 1a, b).

Of interest, inositol treatment, administered for more than three months, decreased SBP in PCOS patients (Fig. 3).

Endocrinological and metabolic parameters in obese PCOS patients

47% of patients were overweight or had obesity (Table 1). In the present protocol, obese patients were found in all experimental groups (50% in untreated patients, 26.92% in COC-, 11.53% inositol- and 11.53% metformin-treated patients).

A comparative study of metabolic and endocrinological parameters between obese (BMI > 30) and non-obese (BMI < 25) PCOS patients from the untreated group was performed (Table 3). Significant differences were found in endocrinological profile parameters: obese PCOS patients showed reduced prolactin ($p<0.05$) and SHBG levels ($p<0.01$) and increased free androgen serum levels ($p<0.05$) compared to non-obese PCOS patients. In addition, obese PCOS patients showed reduced HDL ($p<0.01$) and increased triglyceride serum levels ($p<0.05$), as well as altered glucose metabolism parameters, showing hyperinsulinemia ($p<0.05$) and a significant augment in insulin resistance (HOMA, $p<0.05$) and glycosylated hemoglobin levels ($p<0.05$) compared to non-obese PCOS patients (Table 3).

Additionally, untreated obese PCOS patients exhibit a significant increase in blood pressure (both SBP and DBP) compared to untreated non-obese PCOS patients ($p<0.001$) (Table 3).

Finally, these metabolic and endocrinological parameters were compared between non-obese (BMI < 25) and obese (BMI > 30) patients who had received one of the PCOS treatments involved in the present study (COC, metformin and inositols). Most of these parameters were altered in between both groups (Table 4). It is clearly shown that obesity is a sign of poor prognosis that aggravates the progression of PCOS and hinders the effectiveness of any of the studied therapies, particularly in parameters related to dyslipidemia, insulin resistance and blood pressure.

Correlations

Regarding untreated patients, direct and significant correlations were found between insulin serum levels and BMI, free androgens, triglycerides and MBP ($p<0.001$), as well as between circulating glucose levels and glycosylated hemoglobin ($r=0.807$, $p<0.001$), testosterone ($p<0.005$) and MBP ($p<0.03$) (Fig. 4a). A direct significant correlation was found between BMI and MBP in obese PCOS patients (Fig. 4b).

Discussion

Despite the present limitations, results on this paper showed that COC treatment in PCOS patients had a negative metabolic impact, increasing cholesterol and triglyceride serum levels and insulin resistance, whereas inositol therapies did not affect lipid metabolism but improved insulin resistance, reducing glucose and insulin serum levels, particularly insulin resistance (HOMA) and glycosylated hemoglobin, compared to untreated patients.

Interestingly, this study showed that PCOS management in current clinical practice is not enough directed to solve or prevent the complexity of its endocrine and metabolic alterations. Most of the PCOS treatment guidelines suffer from an

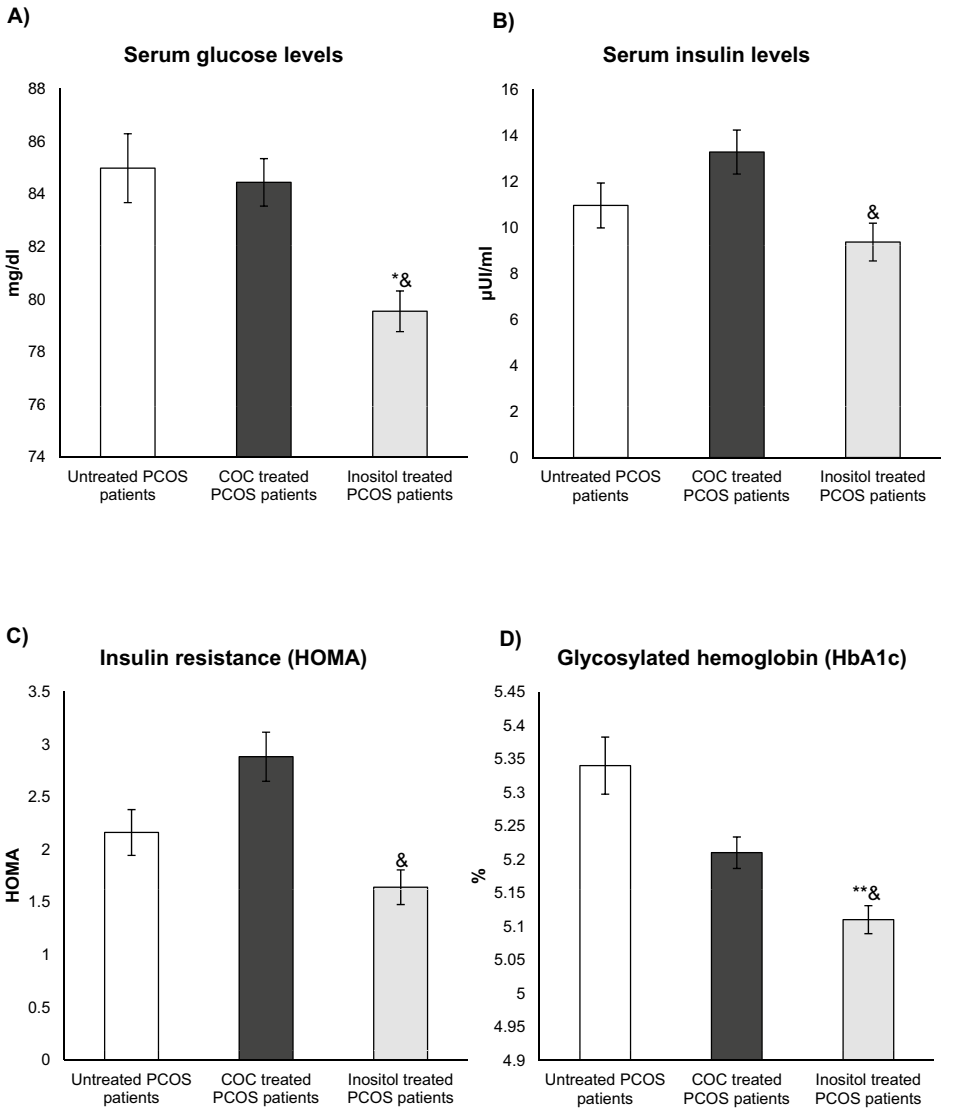


Fig. 2 Serum glucose (**a**), insulin (**b**), HOMA (**c**) and glycosylated hemoglobin (**d**) in untreated PCOS patients, COC-treated PCOS patients and inositol-treated patients. $^{*}p<0.05$, $^{**}p<0.01$ COC both groups of treated patients *vs* untreated patients; $^{\&}p<0.05$ inositol-treated patients *vs* COC-treated patients

integrative view that should address hyperandrogenism and anovulation symptoms, and the vulnerability to metabolic syndrome establishment, overweight/obesity and even type 2 diabetes.

Although < 10% of PCOS patients included in this cohort can be strictly included in MetS, approximately 20% had insulin resistance. Additionally, the comparative study of parameters involved in lipid and glycemic metabolism provide scarce information about the metabolic impact of the different treatments prescribed to PCOS patients, despite the fact that in most patients MetS has not yet been established.

The major finding in this work is that COC treatment in PCOS patients modified the hormonal profile and worsened lipid parameters, and insulin resistance, while inositol therapies improved significantly insulin resistance and glycosylated hemoglobin, reducing cholesterol and triglyceride serum levels as compared to PCOS patients treated with COC. These beneficial effects of inositol therapies are in accordance with those reported by other authors [29–39], some of whom even advise the co-administration of myo-inositol and D-chiro-inositol (40:1) to increase the effectiveness in restoring ovary function and metabolic parameters in PCOS [40, 41]. Thus, inositol therapies could be considered an easy, beneficial and integrative treatment for PCOS patients, due to their better tolerability and their diminished risk of adverse effects, compared to metformin treatments for PCOS patients [42]. In this fashion, inositol therapies in the present small cohort induced a significant increase in LH serum levels compared to values found in COC treatments, accordingly to the described effect of inositol in the stimulation of ovulation [43–45]. However, more clinical studies are needed in order to confirm this hypothesis.

Results in the present work provide evidences that obesity can be considered a bad prognosis since the presence of

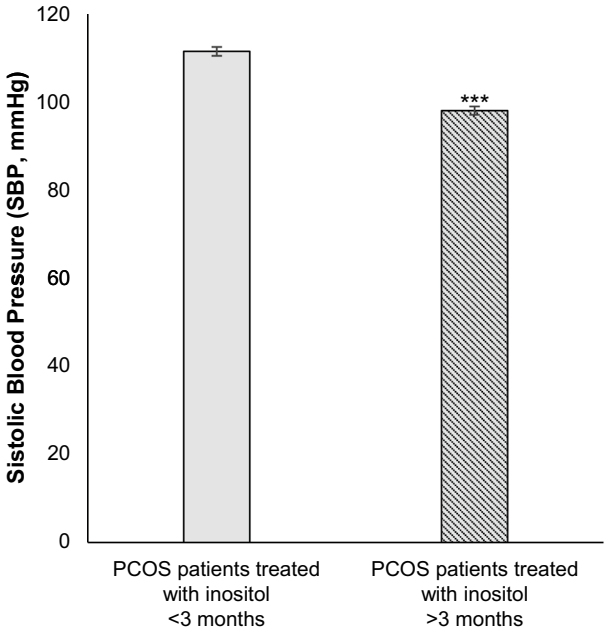


Fig. 3 Systolic blood pressure (SBP, mmHg) in PCOS patients treated with inositol therapies during < 3 and > 3 months. $^{***}p < 0.001$ inositol-treated patients > 3 months *vs* inositol-treated patients > 3 months

obesity (BMI > 30) worsens all parameters of both lipid and glycemic profile as well as blood pressure values (Table 3).

Although it could be considered anecdotal, a COC-treated PCOS patient, included in the present study, only after the loss of 15 kg of body weight became pregnant. These data are in accordance with others previously described where the association of moderate obesity with a poor pregnancy in PCOS was reported, along with the association between weight loss and the correction of gonadotropin and sex steroid alterations in obese anovulatory female [46–51]. The impact of polycystic ovaries on the future reproductive function of these women remains unclear, but evidence suggests that an obesity effective treatment is one key to improve fertility in PCOS patients [48–50, 52, 53].

When metabolic parameters were analyzed according to the phenotype, it was found that PCOS patients with phenotype A presented greater alterations in lipid metabolism and higher values of glycosylated hemoglobin as well as blood pressure, compared with the other phenotypes.

Interestingly, inositol therapies administered for more than three months decreased systolic blood pressure in PCOS patients. In these women, obesity was associated with greater alterations in lipid and glycemic metabolism and with higher blood pressure levels, as mentioned before.

As aforesaid, the etiology of PCOS is not fully understood. This is a multifactorial disorder associated with genetic, metabolic and endocrine abnormalities [24]. To date, PCOS is currently included in the metabolic syndrome

Table 3 Comparative study between untreated PCOS patients without (BMI < 25) and with obesity (BMI > 30)

Metabolic and endocrinological parameters	Non-obese untreated PCOS patients (BMI < 25)	Obese untreated PCOS patients (BMI > 30)
FSH (mUI/mL)	5.75 ± 2.16	6.02 ± 2.65
LH (mUI/mL)	9.53 ± 6.08	8.93 ± 4.92
TSH (µUI/mL)	2.23 ± 1.09	2.69 ± 1.11
Estradiol (pg/mL)	51.38 ± 45.94	57.13 ± 30.01
Prolactin (ng/mL)	18.74 ± 10.58	**13.68 ± 5.87***
17OH-Progesterone (ng/mL)	0.99 ± 0.70	0.98 ± 0.95
Testosterone (ng/mL)	0.34 ± 0.19	0.45 ± 0.31
SHBG (nmol/L)	85.61 ± 46.88	**36.51 ± 12.87****
Androstenedione (ng/mL)	2.78 ± 1.50	3.01 ± 1.60
DHEAs (µg/mL)	2.38 ± 1.89	2.31 ± 1.72
Free Androgens	0.52 ± 0.44	**1.28 ± 1.02***
LH/FSH	1.67 ± 0.90	1.68 ± 0.83
Cholesterol (mg/mL)	173.60 ± 30.40	174.61 ± 31.14
HDL (mg/dL)	64.96 ± 15.92	**50.46 ± 17.02****
LDL (mg/dL)	99.09 ± 27.28	103.69 ± 28.89
Triglycerides (mg/dL)	63.92 ± 25.66	**101.84 ± 63.62***
Glucose (mg/dL)	83.07 ± 6.40	90.53 ± 26.36
Insulin (µUI/mL)	6.92 ± 2.86	**21.44 ± 18.54***
HbA1c (%)	5.24 ± 0.30	**5.59 ± 0.82***
HOMA	1.30 ± 0.69	**4.22 ± 4.22***
Homocysteine (mmol/L)	9.512 ± 7.13	8.94 ± 2.14
SBP (mm Hg)	106.38 ± 11.71	**127.77 ± 14.51*****
DBP (mm Hg)	63.66 ± 6.93	**77.23 ± 10.97*****
BPM (mm Hg)	77.90 ± 7.73	**94.08 ± 11.19*****

BMI body mass index; *BPM* blood pressure medium; *DBP* diastolic blood pressure; *DHEAs* dehydroepiandrosterone sulfate; *FSH* follicle-stimulating hormone; *HbA1c* glycosylated hemoglobin; *HDL* high-density lipoprotein; *HOMA* homeostasis model assessment; *LDL* low-density lipoprotein; *LH* luteinizing hormone; *SBP* systolic blood pressure; *SHBG* sex hormone-binding globulin; *TSH* thyroid-stimulating hormone. *p values:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ non-obese untreated PCOS patients *vs* obese untreated PCOS patients

(MetS) alterations [10]. In this way, PCOS patients have higher risks to suffer certain diseases compared to the general population, e.g., type II diabetes, cardiovascular disease, endometrial carcinoma and several gestational complications. These risks expose PCOS patients to high morbidity, being associated with an increase in economic and healthcare impact.

In this context, another potential factor involved in the pathophysiology of PCOS that deserves special mention is insulin-like growth factor 1 (IGF-1) deficiency, which still remains controversial. However, in the last decade several studies have been conducted, revealing the relevant role of IGF-1 deficiency in the development of MetS. Succinctly, an inverse correlation between IGF-1 (IGF-1/IGFBP-3 ratio)

Table 4 Comparative study of endocrine and metabolic parameters between patients without (BMI < 25) and with obesity (BMI > 30) treated for PCOS with combined oral contraceptives, metformin and inositols

Metabolic and endocrinological parameters	Non-obese patients treated for PCOS (BMI < 25)	Obese patients treated for PCOS (BMI > 30)
FSH (mUI/mL)	5.04 ± 2.34	3.55 ± 2.08*
LH (mUI/mL)	7.43 ± 6.97	5.65 ± 5.58
TSH (µUI/mL)	1.96 ± 1.03	2.51 ± 1.17
Estradiol (pg/mL)	41.74 ± 40.02	70.00 ± 67.92
Prolactin (ng/mL)	17.01 ± 8.35	17.12 ± 7.35
17OH-Progesterone (ng/mL)	0.95 ± 0.78	0.82 ± 0.70
Testosterone (ng/mL)	0.72 ± 2.39	0.25 ± 0.19
SHBG (nmol/L)	125.38 ± 92.21	97.68 ± 60.67
Androstenedione (ng/mL)	2.56 ± 1.53	2.04 ± 1.34
DHEAs (µg/mL)	1.99 ± 1.00	1.52 ± 0.40**
Free Androgens	0.80 ± 1.66	0.48 ± 0.58
LH/FSH	1.39 ± 1.13	1.46 ± 1.07
Cholesterol (mg/mL)	183.75 ± 28.51	198.76 ± 38.96
HDL (mg/dL)	70.19 ± 13.96	46.15 ± 9.06***
LDL (mg/dL)	102.65 ± 22.83	122.58 ± 30.77*
Triglycerides (mg/dL)	67.60 ± 24.58	149.38 ± 74.26***
Glucose (mg/dL)	79.47 ± 10.31	88.61 ± 6.38***
Insulin (µUI/mL)	8.29 ± 8.48	19.00 ± 8.93***
HbA1c (%)	5.17 ± 0.26	5.27 ± 0.26
HOMA	1.57 ± 2.02	4.17 ± 1.94***
Homocysteine (mmol/L)	8.44 ± 2.52	8.19 ± 3.64
SBP (mm Hg)	106.69 ± 11.39	129.92 ± 18.27***
DBP (mm Hg)	65.33 ± 9.13	77.62 ± 9.17***
BPM (mm Hg)	79.11 ± 8.78	95.05 ± 11.46***

BMI body mass index; *BPM* blood pressure medium; *DBP* diastolic blood pressure; *DHEAs* dehydroepiandrosterone sulfate; *FSH* follicle-stimulating hormone; *HbA1c* glycosylated hemoglobin; *HDL* high-density lipoprotein; *HOMA* homeostasis model assessment; *LDL* low-density lipoprotein; *LH* luteinizing hormone; *SBP* systolic blood pressure; *SHBG* sex hormone-binding globulin; *TSH* thyroid-stimulating hormone. *p values:* $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ non-obese untreated PCOS patients *vs* obese patients treated for PCOS

circulating levels and several markers for obesity, MetS, type II diabetes, and cardiovascular disease has been found, indicating that low IGF-1 circulating levels can result in MetS, raising the risk for cardiovascular disease and type II diabetes. Nonetheless, more studies are needed to describe the exact mechanism by which IGF-1 deficiency impacts and interacts with other factors and hormones to develop MetS, type II diabetes and its cardiovascular consequences [9].

Accumulated evidence suggests how the GH/IGF-1 axis, together with insulin and IGF-1 binding proteins (IGFBPs), act in a synchronized manner to regulate energy metabolism. Possibly, when this whole system becomes altered by obesity, genetics or environmental factors, several adverse consequences may develop, such as insulin resistance, steatosis, MetS and type II diabetes. A recent review about MetS suggests that IGF-1 acts as the keystone maintaining homeostasis in this system [9].

In summary, PCOS is a gynecological condition in which etiopathogenesis is not fully understood. Until now, therapeutic standard strategies for PCOS have been focused on hirsutism treatment and ovulation restoration. However, it should be taken more into account the prevalence of hyperinsulinemia and insulin resistance, which are often involved in the pathogenesis of this syndrome, in order to establish a better therapeutic strategy for PCOS.

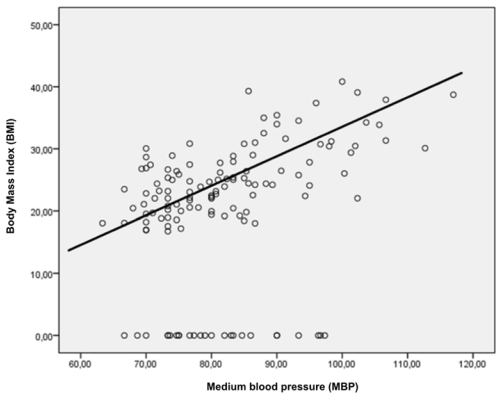
Fig. 4 **a** Direct or inverse correlations between circulating levels of glucose or insulin and other studied parameters in untreated PCOS patients. **b** Direct correlation between Body mass index (BMI) and medium blood pressure (MBP)

A)

Serum Insulin	r Pearson	*p value*
BMI	0,595	***0,001***
SHBG (nmol/L)	-0,294	*0,04*
Free Androgens	0,516	***0,001***
HDL (mg/mL)	-0,435	*0,03*
Triglycerides (mg/mL)	0,48	***0,001***
MBP (mmHg)	0,621	***0,001***
Serum Glucose	**r Pearson**	***p value***
Testosterone (ng/mL)	0,485	***0,005***
Glycosylated hemoglobin (%)	0,807	***0,001***
Homocisteine (mmol/L)	-0,301	*0,04*
MBP (mmHg)	0.293	***0,03***

BMI, body mass index; *HDL*, high density lipoprotein; *HOMA*, homeostasis model assessment; *SHBG*, sex hormone-binding globulin.

B)



Acknowledgements The authors wish to express their gratitude to Dr. Mª Teresa Blanco Guillén, Cristina Alonso Gracia, María Cabrera Salinas, Raquel Romero Fernández, Alicia Guntiñas Castillo, Izaskun Méndez García, Alba Miranda Calvo, Antonio Ierullo, Carolina Cantos and Virginia Rodríguez Tabares, all of these MD of our team, for their generous help. This work was possible thank to the financial help of "Fundación de Investigación HM Hospitales".

Author contributions MVDD: project development, data collection, data analysis; OGP: data collection; JKG: data collection; ALE: data collection; IME: manuscript writing/editing; ICC: project development, data analysis; MARZ: project development. All authors read and approved the final manuscript.

Funding This work was supported by Fundación de Investigación HM Hospitales.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Committee of the "Fundación de Investigación HM Hospitales de Madrid" (14.11.704-GHM).

References

1. March WA, Moore VM, Willson KJ et al (2010) The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 25:544–551. https://doi.org/10.1093/humrep/dep399
2. Wolf W, Wattick R, Kinkade O, Olfert M (2018) Geographical prevalence of polycystic ovary syndrome as determined by region and race/ethnicity. Int J Environ Res Public Health 15:2589. https://doi.org/10.3390/ijerph15112589
3. Ding T, Hardiman PJ, Petersen I et al (2017) The prevalence of polycystic ovary syndrome in reproductive-aged women of different ethnicity: a systematic review and meta-analysis. Oncotarget 8:96351–96358. https://doi.org/10.18632/oncotarget.19180
4. Bani Mohammad M, Majdi Seghinsara A (2017) Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. Asian Pac J Cancer Prev 18:17–21. https://doi.org/10.22034/APJCP.2017.18.1.17
5. Ebersole AM, Bonny AE (2020) Diagnosis and treatment of polycystic ovary syndrome in adolescent females. Clin Obstet Gynecol. https://doi.org/10.1097/GRF.0000000000000538
6. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R (2011) Polycystic ovary syndrome: etiology, pathogenesis and diagnosis. Nat Rev Endocrinol 7:219–231. https://doi.org/10.1038/nrendo.2010.217
7. Sirmans SM, Pate KA (2013) Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol 6:1–13. https://doi.org/10.2147/CLEP.S37559
8. Dumesic DA, Oberfield SE, Stener-Victorin E et al (2015) Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 36:487–525. https://doi.org/10.1210/er.2015-1018
9. Aguirre GA, De Ita JR, de la Garza RG, Castilla-Cortazar I (2016) Insulin-like growth factor-1 deficiency and metabolic syndrome. J Transl Med 14:3. https://doi.org/10.1186/s12967-015-0762-z
10. Khorshidi A, Azami M, Tardeh S, Tardeh Z (2019) The prevalence of metabolic syndrome in patients with polycystic ovary syndrome: a systematic review and meta-analysis. Diabetes Metab Syndr 13:2747–2753. https://doi.org/10.1016/j.dsx.2019.06.008
11. Grundy SM (2006) Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. J Am Coll Cardiol 47:1093–1100. https://doi.org/10.1016/j.jacc.2005.11.046
12. Ford ES, Li C, Sattar N (2008) Metabolic syndrome and incident diabetes: current state of the evidence. Diabetes Care 31:1898–1904. https://doi.org/10.2337/dc08-0423
13. Wolk R, Somers VK (2007) Sleep and the metabolic syndrome. Exp Physiol 92:67–78. https://doi.org/10.1113/expphysiol.2006.033787
14. Ip MSM, Lam B, Ng MMT et al (2002) Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 165:670–676. https://doi.org/10.1164/ajrccm.165.5.2103001
15. Alberti KGMM, Eckel RH, Grundy SM et al (2009) Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; american

heart association; world heart federation; international. Circulation 120:1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644
16. Kim HJ, Kim HJ, Lee KE et al (2004) Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med 164:2169–2175. https://doi.org/10.1001/archinte.164.19.2169
17. Kotronen A, Westerbacka J, Bergholm R et al (2007) Liver fat in the metabolic syndrome. J Clin Endocrinol Metab 92:3490–3497. https://doi.org/10.1210/jc.2007-0482
18. Parish JM, Adam T, Facchiano L (2007) Relationship of metabolic syndrome and obstructive sleep apnea. J Clin Sleep Med 3:467–472
19. Gami AS, Somers VK (2004) Obstructive sleep apnoea, metabolic syndrome, and cardiovascular outcomes. Eur Heart J 25:709–711. https://doi.org/10.1016/j.ehj.2004.03.008
20. Gruber A, Horwood F, Sithole J et al (2006) Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. Cardiovasc Diabetol 5:22. https://doi.org/10.1186/1475-2840-5-22
21. Tasali E, Van Cauter E (2002) Sleep-disordered breathing and the current epidemic of obesity: consequence or contributing factor? Am J Respir Crit Care Med 165:562–563. https://doi.org/10.1164/ajrccm.165.5.2201001b
22. Cizza G, Skarulis M, Mignot E (2005) A link between short sleep and obesity: building the evidence for causation. Sleep 28:1217–1220. https://doi.org/10.1093/sleep/28.10.1217
23. Vgontzas AN, Bixler EO, Chrousos GP (2005) Sleep apnea is a manifestation of the metabolic syndrome. Sleep Med Rev 9:211–224. https://doi.org/10.1016/j.smrv.2005.01.006
24. Franks S, McCarthy MI, Hardy K (2006) Development of polycystic ovary syndrome: involvement of genetic and environmental factors. Int J Androl 29:278–285. https://doi.org/10.1111/j.1365-2605.2005.00623.x **(discussion 286-90)**
25. World Medical Association (2013) World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310(20):2191–2194. https://doi.org/10.1001/jama.2013.281053
26. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group (2004) Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 19:41–47
27. National Institutes of Health (2002) High Blood Cholesterol Evaluation Treatment Detection National Cholesterol Education Program Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report.
28. Nuttall FQ (2015) Body mass index. Nutr Today 50:117–128. https://doi.org/10.1097/NT.0000000000000092
29. La Marca A, Grisendi V, Dondi G et al (2015) The menstrual cycle regularization following D-chiro-inositol treatment in PCOS women: a retrospective study. Gynecol Endocrinol 31:52–56. https://doi.org/10.3109/09513590.2014.964201
30. Nestler JE, Jakubowicz DJ, Iuorno MJ (2000) Role of inositolphosphoglycan mediators of insulin action in the polycystic ovary syndrome. J Pediatr Endocrinol Metab 13(Suppl 5):1295–1298
31. Costantino D, Minozzi G, Minozzi E, Guaraldi C (2009) Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci 13:105–110
32. Dinicola S, Chiu TTY, Unfer V et al (2014) The rationale of the myo-inositol and D-chiro-inositol combined treatment for polycystic ovary syndrome. J Clin Pharmacol 54:1079–1092. https://doi.org/10.1002/jcph.362
33. Unfer V, Porcaro G (2014) Updates on the myo-inositol plus D-chiro-inositol combined therapy in polycystic ovary syndrome. Expert Rev Clin Pharmacol 7:623–631. https://doi.org/10.1586/17512433.2014.925795
34. Facchinetti F, Bizzarri M, Benvenga S et al (2015) Results from the international consensus conference on myo-inositol and d-chiro-inositol in obstetrics and gynecology: the link between metabolic syndrome and PCOS. Eur J Obstet Gynecol Reprod Biol 195:72–76. https://doi.org/10.1016/j.ejogrb.2015.09.024
35. Pizzo A, Laganà AS, Barbaro L (2014) Comparison between effects of myo-inositol and D-chiro-inositol on ovarian function and metabolic factors in women with PCOS. Gynecol Endocrinol 30:205–208. https://doi.org/10.3109/09513590.2013.860120
36. Matarrelli B, Vitacolonna E, D'Angelo M et al (2013) Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: a randomized controlled trial. J Matern Fetal Neonatal Med 26:967–972. https://doi.org/10.3109/14767058.2013.766691
37. Nestler JE, Jakubowicz DJ, Reamer P et al (1999) Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med 340:1314–1320. https://doi.org/10.1056/NEJM199904293401703
38. Gerli S, Papaleo E, Ferrari A, Di Renzo GC (2007) Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. Eur Rev Med Pharmacol Sci 11:347–354
39. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM (2008) Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol 24:139–144. https://doi.org/10.1080/09513590801893232
40. Monastra G, Unfer V, Harrath AH, Bizzarri M (2017) Combining treatment with myo-inositol and D-chiro-inositol (40:1) is effective in restoring ovary function and metabolic balance in PCOS patients. Gynecol Endocrinol 33:1–9. https://doi.org/10.1080/09513590.2016.1247797
41. Genazzani AD (2016) Inositol as putative integrative treatment for PCOS. Reprod Biomed Online 33:770–780. https://doi.org/10.1016/j.rbmo.2016.08.024
42. Facchinetti F, Orrù B, Grandi G, Unfer V (2019) Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials. Gynecol Endocrinol 35:198–206. https://doi.org/10.1080/09513590.2018.1540578
43. Nordio M, Basciani S, Camajani E (2019) The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios. Eur Rev Med Pharmacol Sci 23:5512–5521. https://doi.org/10.26355/eurrev_201906_18223
44. Laganà AS, Garzon S, Casarin J et al (2018) Inositol in polycystic ovary syndrome: restoring fertility through a pathophysiology-based approach. Trends Endocrinol Metab 29:768–780. https://doi.org/10.1016/j.tem.2018.09.001
45. Tanbo T, Mellembakken J, Bjercke S et al (2018) Ovulation induction in polycystic ovary syndrome. Acta Obstet Gynecol Scand 97:1162–1167. https://doi.org/10.1111/aogs.13395
46. He Y, Tian J, Blizzard L et al (2020) Associations of childhood adiposity with menstrual irregularity and polycystic ovary syndrome in adulthood: the childhood determinants of adult health study and the bogalusa heart study. Hum Reprod 35:1185–1198. https://doi.org/10.1093/humrep/deaa069
47. Cena H, Chiovato L, Nappi RE (2020) Obesity, polycystic ovary syndrome and infertility: a new avenue for GLP-1 receptor agonists. J Clin Endocrinol Metab. https://doi.org/10.1210/clinem/dgaa285

48. Hamilton-Fairley D, Kiddy D, Watson H et al (1992) Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. Br J Obstet Gynaecol 99:128–131. https://doi.org/10.1111/j.1471-0528.1992.tb14470.x
49. Pasquali R, Antenucci D, Casimirri F et al (1989) Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. J Clin Endocrinol Metab 68:173–179. https://doi.org/10.1210/jcem-68-1-173
50. Naderpoor N, Shorakae S, Joham A et al (2015) Obesity and polycystic ovary syndrome. Minerva Endocrinol 40:37–51
51. Loh HH, Yee A, Loh HS et al (2020) Sexual dysfunction in polycystic ovary syndrome: a systematic review and meta-analysis. Hormones (Athens). https://doi.org/10.1007/s42000-020-00210-0
52. Woodward A, Klonizakis M, Broom D (2020) Exercise and polycystic ovary syndrome. Adv Exp Med Biol. https://doi.org/10.1007/978-981-15-1792-1_8
53. Javed Z, Papageorgiou M, Madden LA et al (2020) The effects of empagliflozin versus metformin on endothelial microparticles in overweight/obese women with polycystic ovary syndrome. Endocr Connect. https://doi.org/10.1530/EC-20-0173