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Clinico-biochemical characteristics of 229 Portuguese infertile women with polycystic ovary syndrome: clinical relevance and relationship with fertility treatment results

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Summary

Purpose: Polycystic ovary syndrome (PCOS) affects 6-20% of reproductive-age women. The authors aimed to evaluate the characteristics of PCOS women and its relationship with fertility treatment outcomes. *Materials and Methods:* The authors reviewed records of PCOS women assisted at Hospital Santa Maria. Fertility treatment results were assessed as pregnancy rate, number of cycles, and miscarriage rate. *Results:* They identified 229 PCOS women, 179 (78.2%) had waist circumference > 80 cm, 72 (31.4%) had type 2 diabetes mellitus (T2DM) familial history and glucose abnormalities, hypertriglyceridemia and low cholesterol-HDL were detected in 23(10.1%), 15 (6.6%) and 103 (45.0%), respectively. Pregnancy was achieved in 164 women. The mean number of cycles to achieve pregnancy was 2.7 (±2.2). Statistical analysis identified factors associated with longer/higher number of treatments: primary infertility, T2DM familial history, hypertriglyceridemia, and low cholesterol-HDL. Waist circumference > 80 cm, older age, and increased LH level were associated with miscarriage. *Conclusions:* Primary infertility, T2DM familial history, hypertriglyceridemia, low cholesterol-HDL, older age, waist circumference > 80 cm, and high LH may confer poorer fertility treatment results.

Key words: Polycystic ovary syndrome; Infertility; Oligomenorrhea; Clinical pregnancy; Spontaneous abortion.

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 6-20% of the reproductive age women [1-3]. The definition of PCOS, according to 2003 ESHRE/ASRM Rotterdam consensus, requires the presence of two out of three diagnostic features: oligomenorrhea or anovulation, clinical or biochemical evidence of hyperandrogenism, and presence of polycystic ovarian morphology [4].

PCOS is a heterogeneous syndrome with ethnicity, geographic region, genetic, and environmental factors contributing to different phenotypes of PCOS and associated comorbidities [5, 6]. Although not necessary for diagnosis of PCOS, obesity, type 2 diabetes mellitus (T2DM), hypertension, cardiovascular disease, dyslipidemia, and infertility are common in this condition. Thus, PCOS adversely affects endocrine, metabolic, cardiovascular, and reproductive health [7].

Women with PCOS have a normal number of primordial follicles and primary/secondary follicles are increased, but due to derangements in factors involved in follicular development, the recruitment and progression of the dominant follicle and ovulation does not occur normally [5, 8]. Menstrual disturbances in PCOS include oligoamenorrhea, anovulation, and prolonged menstrual bleeding. PCOS is the most frequent cause of anovulation, accounting for 75-90% of ovulatory disorders [5, 9]. Nevertheless, up to 30% of women with PCOS may have normal menses [10]. Prolonged periods of anovulation is the primary mechanism of infertility, but there are other subfertility factors in PCOS such as diminished oocyte competence, delay in early embryo kinetics, and endometrial changes interfering with implantation [11]. Moreover, spontaneous abortion occurs more frequently in women with PCOS [12]. Therefore, infertility is highly prevalent in this setting, affecting approximately 40% of PCOS women [5].

The first-line treatment in these women is ovulation induction with clomiphene citrate (CC), which restores ovulation and result in pregnancy in about 50% of PCOS women. Second-line intervention includes either exogenous gonadotropins (Gnd) or laparoscopic ovarian drilling (LOD). Recommended third-line strategy is in-vitro fertilization (IVF) [13]. Some studies have studied the impact of multiple factors that may influence the fertility treatment outcomes, but conclusions are controversial; factors such as overweight/obesity, insulin-resistance, hyperinsulinemia, higher fasting blood glucose, higher systolic blood pressure, and smoking habits may adversely affect cumulative live

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birth rates and increase the risk of spontaneous abortion [14-17]. The authors aimed to evaluate the clinico-biochemical features of a cohort of Portuguese infertile PCOS women and establish their relationship with fertility treatment outcomes.

Materials and Methods

The authors conducted a retrospective study involving infertile women with PCOS referring to the Reproductive Medicine Unit of Hospital de Santa Maria and surveilled within the period of January 2004 to June 2013. Women eligible for inclusion were those with PCOS diagnosis based in the Rotterdam 2003 criteria [4], who either underwent at least one fertility treatment in the present unit and/or reached pregnancy. Patients with other infertility factors, namely endometriosis, male factor (mild to moderate abnormality on spouse semen analysis) or partial tube dysfunction (at least one patent tube) were included. Exclusion criteria were primary ovarian failure (FSH ≥ 40.0 U/L), uncontrolled hypothyroidism (TSH ≥ 4.76 mU/mL), late-onset congenital adrenal hyperplasia (17-hydroxyprogesterone ≥ 3.0 ng/mL), hyperprolactinemia (prolactin ≥ 29.0 ng/mL), hypogonadotropic hypogonadism (low or inappropriate low-normal levels of FSH and LH, plus undetectable or low concentrations of serum estradiol [18]), history of chemotherapy, radiotherapy or pelvic surgery.

Two-hundred twenty-nine infertile PCOS women were identified and their clinical records were reviewed. All records had medical data, physical examination, smoking habits, menstrual irregularities, signs of clinical hyperandrogenism (hirsutism considered for modified Ferriman-Gallwey scores ≥ 8 [19]), familial history, blood pressure, body mass index (BMI), waist circumference (measured on bare skin at the narrowest indentation between the 10th rib and the iliac crest at mid-respiration), transvaginal ultrasonography description of the ovaries (criteria for diagnosing polycystic ovaries were visualization of 12 or more follicles per ovary that were 2-9 mm in diameter and/or an ovarian volume > 10 cm^3) and an extensive biochemical assessment (LH, FSH, estradiol, total testosterone, TSH, prolactin, 17-hydroxyprogesterone, SHBG, measured during the follicular phase following a spontaneous or progestin-induced menses, overnight fast lipid profile, serum insulin, glucose, and 75-g oral glucose tolerance test [OGTT]).

Oligomenorrhea was defined as menstrual cycle interval > 35 days. Biochemical hyperandrogenism was defined by elevated total testosterone (≥ 73 ng/dL, a cutoff level established according to the present laboratory due to the absence of a consensual value [20]; different cutoff values, such 67 or 70 ng/dL, have been proposed [21, 22]). Hypertriglyceridemia was diagnosed for triglycerides level > 150 mg/dL. T2DM was defined as a fasting glucose ≥ 126 mg/dL and/or a two-hour glucose level post 75-g OGTT ≥ 200 mg/dL, while impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) were considered for fasting glucose between 100-125 mg/dL or two-hour glucose post 75-g OGTT between 140-199 mg/dL, respectively [23]. The insulin-resistance was assessed through the homeostasis model assessment for insulin-resistance index (HOMA-IR), calculated with the formula: HOMA-IR= (fasting insulin x fasting glucose [mg/dL])/405; women were considered insulin-resistant for HOMA-IR ≥ 2.5 [24].

In this study, treatment fertility outcomes were assessed according to overall pregnancy rate; number of treatment cycles to achieve clinical pregnancy, and spontaneous abortion rate. Only clinical pregnancies were considered, defined as the presence of a gestational sac on transvaginal ultrasound. Pregnancy rate was calculated as the percentage of pregnant patients per total number of patients. Spontaneous abortions were defined as pregnancy losses up to 20 weeks of gestation after prior detection of a gestational sac. Abortion rate was estimated as the percentage of miscarriages per total number of women. To determine the number of treatment cycles each ovulation induction treatment with CC, CC combined with Gnd or isolated Gnd were individually counted; intrauterine inseminations (IUI), IVF or intracytoplasmatic sperm inseminations (ICSI) were also counted individually; each LOD intervention also counted as one treatment cycle.

Table 1. — *Baseline characteristics in the whole group of infertile women with PCOS.*

Baseline characteristics	PCOS (n=229)
Age (years)	29.7 (±3.9)
Age of menarche (years)	12.8 (±1.9)
Duration of infertility (months)	41 (±29)
Primary infertility	185 (80.8%)
Existence of additional infertility factor	38 (16.6%)
BMI (kg/m^2)	27.8 (±6.4)
Weight excess (BMI ≥ 25 kg/m^2)	134 (58.5%)
Weight (kg)	73.1 (±17.6)
Waist circumference (cm)	93.6 (±14.5)
Waist circumference > 80 cm	179 (78.2%)
Hypertension	12 (5.2%)
Familial history of T2DM	72 (31.4%)
Smoking habits	61 (26.6%)
Polycystic ovarian morphology	213 (93.0%)
Clinical and/or biochemical androgen excess	110 (48.0%)
Oligoamenorrhea	229 (100%)
Biochemical parameters	
FSH *(2.5-10.2 U/L)*	5.0 (±2.1)
LH *(1.9-12.5 U/L)*	9.0 (±5.7)
Estradiol *(19.5-144.0 pg/mL)*	67.9 (±65.0)
Total testosterone *(< 73 ng/dL)*	63.6 (±33.0)
Prolactin *(2.8-29.0 ng/mL)*	12.5 (±6.3)
TSH *(0.55-4.78 mU/mL)*	2.6 (±1.9)
17-hydroxyprogesterone *(0.1-3.0 ng/mL)*	1.5 (±0.7)
SHBG *(18-144 nmol/L)*	43.3 (±38.1)
Insulin *(3-25 mU/L)*	12.1 (±9.6)
Total cholesterol *(<190 mg/dL)*	179.7 (±33.3)
Cholesterol-LDL *(<110 mg/dL)*	111.5 (±33.7)
Cholesterol-HDL *(>50 mg/dL)*	53.4 (±15.1)
Triglyceridemia *(<150 mg/dL)*	86.8 (±42.9)
Fasting glycemia *(<100 mg/dL)*	96.1 (±27.7)
2-h glycemia on 75g-OGTT *(<140 mg/dL)*	96.1 (±27.7)
Hypertriglyceridemia (>150 mg/dL)	15 (6.6%)
Low cholesterol-HDL (<50 mg/dL)	103 (45.0%)
Positive 75g-OGTT	23 (10.1%) [IFG=9; IGT=14]
Biochemical hyperandrogenism	63 (27.5%)
LH/FSH ≥ 2	90 (39.3%)
HOMA-IR	2.6 (±2.1)
HOMA-IR ≥ 2.5	78 (34.1%)

Data is shown as mean (± standard deviation) or n (%).
PCOS: polycystic ovary syndrome; BMI: body mass index; T2DM: type 2 diabetes mellitus; OGTT: oral-glucose tolerance test; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; HOMA-IR: homeostasis model assessment for insulin-resistance index.

Table 2. — *Overview of the fertility treatment results in the 229 infertile women with PCOS.*

Clinical pregnancies (pregnancy rate)	164 (71.6%)
Number of women who had spontaneous abortions (abortion rate)	34 (14.9%)
Total number of spontaneous abortions	43 (3 women had 2 abortions; 2 women had 4 abortions)
Number of treatment cycles to achieve clinical pregnancy	2.7 (± 2.2) [min=1; max=13]
Time between the first treatment and clinical pregnancy (months)	9.9 (± 10.8)
Method of treatment that resulted in clinical pregnancy	
CC	25 (15.2%)
Gnd	60 (36.6%)
CC+Gnd	15 (9.1%)
Spontaneous cycle	16 (9.8%)
Post LOD, spontaneous	17 (10.4%)
Post LOD under IO	7 (4.2%)
Post LOD under IVF or ICSI	6 (3.7%)
IUI	12 (7.3%)
IVF or ICSI	6 (3.7%)

Data is shown as mean (± standard deviation) or n (%).
CC: clomiphene citrate; Gnd: gonadotropins; LOD: laparoscopic ovarian drilling; IO: induction of ovulation; IUI: intrauterine insemination; IVF: in-vitro fertilization; ICSI: intracytoplasmic sperm insemination.

The data analysis and statistical tests were carried out using SPSS (version 20.0). Descriptive statistics were used to summarize the data. Chi-square analysis and Fisher´s exact test were used to compare categorical variables. Student *t*-test, ANOVA, and Wilcoxon tests were used for continuous variables. The Pearson correlation coefficient was used for correlations between continuous variables. A p value < 0.05 was considered statistically significant.

Results

The baseline features of the 229 infertile PCOS women included are summarized in Table 1. The mean age was 30 years. The duration of infertility was 41(± 29) months and 80.8% were primary infertilities. Out of the 229 women, 134 (58.5%) were overweight or obese, 179 (78.2%) had waist circumference > 80 cm, 12 (5.2%) were hypertensive, 61 (26.6%) were smokers, and 72 (31.4%) had familial history of T2DM. Clinical and/or biochemical androgen excess was detected in 110 (48.0%). Glucose abnormalities, insulin-resistance, hypertriglyceridemia, and low cholesterol-HDL were detected in 23 (10.1%), 78 (34.1%), 15 (6.6%), and 103 (45.0%) women, respectively.

Table 2 provides an overview of the fertility treatment outcomes in the infertile PCOS women. Pregnancy was achieved in 164 (71.6%) women. Spontaneous abortion was verified in 34 women (14.9%; five women had more than one abortion) and the mean number of treatment cycles needed to achieve pregnancy was 2.7 (±2.2). The mean duration between the first fertility treatment and pregnancy was 9.9 months. Sixty-one percent of the pregnancies were achieved by pharmacological induced-ovulation methods. Sixteen pregnancies occurred in a non-treatment cycle, 12 of these never submitted to any treatment. LOD was performed in 30 patients, and 17 of

Table 3. — *Mean number of treatment cycles and spontaneous abortion outcomes in the infertile PCOS women who achieved clinical pregnancy.*

PCOS women who became pregnant (n=164)†		Mean number of treatment cycles (n)	Mean number of spontaneous abortions (n)
Age			
< 35 years	150 (91.5%)	2.6 (±2.3)	0.12 (±0.35)
≥ 35 years	14 (8.5%)	2.6 (±1.9)	0.29 (±0.61)
Type of infertility			
Primary	132 (80.5%)	2.9 (±2.3) ‡	0.13 (±0.38)
Secondary	32 (19.5%)	1.8 (±1.4)	0.16 (±0.37)
Clinical and/or biochemical androgen excess			
Yes	82 (50.0%)	3.0 (± 2.5)	0.18 (±0.45)
No	82 (50.0%)	2.3 (± 1.8)	0.09 (±0.28)
Weight excess			
BMI ≥ 25 kg/m²	98 (59.8%)	2.7 (±2.2)	0.17 (±0.43)
BMI < 25 kg/m²	66 (40.2%)	2.5 (±2.3)	0.08 (±0.27)
Waist circumference			
> 80cm	126 (76.8%)	2.6 (±2.1)	0.17 (±0.42) ‡
≤ 80 cm	38 (23.2%)	2.3 (±1.8)	0.03 (±0.18)
Hypertension			
Yes	7 (4.2%)	2.1 (±0.9)	0.14 (±0.38)
No	157 (95.8%)	2.7 (± 2.3)	0.13 (±0.38)
Familial history of T2DM			
Yes	53 (32.3%)	3.4 (±2.5) ‡	0.15 (±0.41)
No	111 (67.7%)	2.3 (±2.0)	0.13 (±0.36)
Smoking habits			
Yes	43 (26.2%)	2.6 (±1.9)	0.19 (±0.39)
No	121 (73.8%)	2.7 (±2.3)	0.12 (±0.37)
Triglyceridemia			
>150 mg/dL	15 (9.1%)	3.6 (±2.9) ‡	0.08 (±0.28)
≤ 150 mg/dL	149 (90.9%)	2.4 (±1.8)	0.12 (±0.35)
Cholesterol-HDL			
< 50 mg/dL	77 (46.9%)	2.9 (±2.1) ‡	0.15 (±0.40)
≥ 50 mg/dL	87 (53.1%)	2.2 (±1.8)	0.09 (±0.29)
75g-OGTT			
Positive	14 (8.5%)	2.5 (±2.3)	0.07 (±0.27)
Negative	150 (91.5%)	2.6 (±1.9)	0.13 (±0.36)
HOMA-IR			
≥ 2.5	55 (33.5%)	2.4 (±2.1)	0.15 (±0.41)
< 2.5	109 (66.5%)	2.6 (±1.8)	0.10 (±0.31)
Biochemical hyperandrogenism			
TT ≥ 73 ng/dL	48 (29.3%)	3.0 (±2.1)	0.15 (±0.41)
TT < 73 ng/dL	116 (70.7%)	2.4 (±1.9)	0.11 (±0.32)

Data is shown as mean (± standard deviation) or n (%).
† For the considered parameters, the women who had clinical pregnancy was compared with women that did not reach pregnancy (n=65) and no statistical significant differences were seen.
‡ Difference with statistical significance ($p < 0.05$).
PCOS: polycystic ovary syndrome; BMI: body mass index; T2DM: type 2 diabetes mellitus; OGTT: oral-glucose tolerance test; HOMA-IR: homeostasis model assessment for insulin-resistance index; TT: total testosterone.

Table 4. — *Correlation coefficients in the infertile PCOS women who achieved clinical pregnancy, regarding the relationship between different clinico-biochemical parameters and the number of treatment cycles and spontaneous abortion.*

PCOS women who became pregnant (n=164)		Mean number of treatment cycles (n)	Mean number of spontaneous abortions(n)
Age (years)	29.3 (±3.8)	-0.11 p=0.15	0.17 p=0.03 ‡
Age of menarche (years)	12.8 (±2.0)	0.46 p=0.56	-0.06 p=0.42
Duration of infertility (months)	40.2 (±29.7)	0.01 p=0.97	0.13 p=0.09
BMI (kg/m^2)	27.7 (±6.6)	0.07 p=0.38	0.02 p=0.83
Waist circumference (cm)	93.1 (±14.7)	0.05 p=0.58	0.05 p=0.55
FSH	4.9 (±1.6)	-0.10 p=0.23	0.04 p=0.59
LH	9.2 (±5.7)	0.01 p=0.88	0.19 p=0.02 ‡
Estradiol	63.7 (±59.5)	-0.03 p=0.68	0.05 p=0.52
Total testosterone	64.1 (±31.0)	0.14 p=0.09	0.01 p=0.88
Prolactin	12.5 (±5.9)	-0.04 p=0.63	-0.04 p=0.65
TSH	2.5 (±1.3)	0.11 p=0.16	0.07 p=0.36
17-hydroxyprogesterone	1.5 (±0.7)	0.08 p=0.36	0.04 p=0.62
SHBG	42.8 (±35.3)	-0.15 p=0.08	-0.10 p=0.26
Insulin	11.7 (±7.9)	0.03 p=0.76	0.04 p=0.63
Total cholesterol	181.8 (±33.8)	-0.02 p=0.81	0.12 p=0.17
Cholesterol-LDL	112.4 (±36.8)	-0.06 p=0.50	0.12 p=0.15
Cholesterol-HDL	53.6 (±15.9)	-0.10 p=0.24	-0.09 p=0.29
Triglyceridemia	89.0 (±45.1)	0.15 p=0.06	0.02 p=0.84
Fasting glycemia	85.9 (±8.9)	0.09 p=0.28	0.01 p=0.91
2-hr glycemia 75-g OGTT	95.6 (±27.3)	0.07 p=0.39	-0.05 p=0.54
HOMA-IR	2.5 (±1.6)	0.01 p=0.90	0.07 p=0.42

Data is shown as mean (± standard deviation) in the second column; the third, fourth, and fifth column includes the Pearson coefficient of correlation and its p value (statistical significance when $p < 0.05$).
‡ Correlations with statistical significance (p<0.05).
PCOS: polycystic ovary syndrome; BMI: body mass index; OGTT: oral-glucose tolerance test; HOMA-IR: homeostasis model assessment for insulin-resistance index.

them reached spontaneous pregnancy postoperatively without additional treatments.

Table 3 summarizes treatment fertility results in the infertile PCOS women who became pregnant, regarding the number of cycles and spontaneous abortion. Coefficients of correlation regarding the relationship between clinico-biochemical parameters and treatment cycles or spontaneous abortion are represented in Table 4. For the considered clinico-biochemical parameters, no statistical significant differences were detected between women who became pregnant and women who did not reach pregnancy (Table 5).

The history of primary infertility, hypertriglyceridemia, clinical and/or biochemical androgen excess, familial history of T2DM, and low cholesterol-HDL were associated with higher number of cycles to obtain pregnancy. Waist circumference > 80 cm was the only feature significantly associated with higher rates of spontaneous abortion. Significant positive correlations were seen only between both mean age/LH and abortion rate.

Table 5. — Distribution of clinico-biochemical parameters within the groups of women that achieved pregnancy and women that did not achieve pregnancy.

	PCOS women who got pregnant (n=164)	PCOS women who did not achieved clinical pregnancy (n=65)	p value
Age			
< 35 years	150 (91.5%)	54 (83.1%)	0.067
≥ 35 years	14 (8.5%)	11 (16.9%)	
Type of infertility			
Primary	132 (80.5%)	53 (81.5%)	0.865
Secondary	32 (19.5%)	12 (18.5%)	
Clinical and/or biochemical androgen excess			
Yes	82 (50.0%)	28 (43.1%)	0.344
No	82 (50.0%)	37 (56.9%)	
Weight excess			
BMI ≥ 25 kg/m^2	98 (59.8%)	36 (55.4%)	0.545
BMI < 25 kg/m^2	66 (40.2%)	29 (44.6%)	
Waist circumference			
> 80cm	126 (76.8%)	53 (81.5%)	0.180
≤ 80 cm	38 (23.2%)	12 (18.5%)	
Hypertension			
Yes	7 (4.2%)	5 (7.7%)	0.294
No	157 (95.8%)	60 (92.3%)	
Familial history of T2DM			
Yes	53 (32.3%)	19 (29.2%)	0.650
No	111 (67.7%)	46 (70.8%)	
Smoking habits			
Yes	43 (26.2%)	18 (27.7%)	0.820
No	121 (73.8%)	47 (72.3%)	
Triglyceridemia			
>150 mg/dL	15 (9.1%)	2 (3.1%)	0.185
≤ 150 mg/dL	149 (90.9%)	63 (96.9%)	
Cholesterol-HDL			
< 50 mg/dL	77 (46.9%)	26 (40.0%)	0.990
≥ 50 mg/dL	87 (53.1%)	39 (60.0%)	
75-g OGTT			
Positive	14 (8.5%)	9 (13.8%)	0.225
Negative	150 (91.5%)	56 (86.2%)	
HOMA-IR			
≥ 2.5	55 (33.5%)	23 (35.4%)	0.387
< 2.5	109 (66.5%)	42 (64.6%)	
Biochemical hyperandrogenism			
TT ≥ 73 ng/dL	48 (29.3%)	15 (27.3%)	0.344
TT < 73 ng/dL	116 (70.7%)	50 (72.7%)	

PCOS: polycystic ovary syndrome; BMI: body mass index; T2DM: type 2 diabetes mellitus; OGTT: oral-glucose tolerance test; HOMA-IR: homeostasis model assessment for insulin-resistance index; TT: total testosterone.

Discussion

The results of the present study suggest that infertile PCOS women with primary type infertility, hypertriglyceridemia, low cholesterol-HDL, and T2DM familial history may have poorer fertility treatment results, possibly requiring more treatment cycles. These features may justify more intensive and effective reproductive approaches in the management of those infertile PCOS women. On the other hand,

the present data suggest that increased ages, waist circumference above 80 cm, and/or higher LH levels may be associated with spontaneous abortion. In the present series, no prognostic significance was found for the other clinico-biochemical features, such age, obesity, insulin-resistance, glucose abnormalities, hypertension or smoking habits.

Dyslipidemia is very common in women with PCOS, with a prevalence of up to 70% [25]. In the present series, the frequency of lipid abnormalities was considerably lower. The most common abnormal lipid profile of these patients includes decreased levels of cholesterol-HDL and increased levels of triglycerides and/or cholesterol-LDL, and it is strongly associated with insulin-resistance and obesity [26]. A recent meta-analysis of lipid levels reported triglycerides levels 26 mg/dL higher in PCOS than in controls; on the other hand, cholesterol-HDL concentrations were six mg/dL lower in PCOS than in controls [27]. Moreover, cholesterol-HDL encompasses different classes of lipoproteins, and it has been reported that PCOS women have not only lower concentrations, but also alterations in their quality [26]. Testosterone has been implicated in lowering the cholesterol-HDL [28]. The association between dyslipidemia and cardiovascular morbidity, which result from the increased atherogenesis, insulin-resistance, oxidative stress, pro-inflammation, and platelet hyperactivity, has been described [25-30]. However, the implication of lipid abnormalities in reproductive life and fertility treatment results are not conclusively established.

In the present study, the presence of hypertriglyceridemia and/or low levels of cholesterol-HDL was significantly associated with poorer fertility treatment results. No relationship with spontaneous abortions was detected for both hypertriglyceridemia and low cholesterol-HDL. Thus, it seems reasonable to control the lipid profile prior fertility treatment as it may interfere negatively with the results. These findings highlight the importance of lipid profile evaluation in infertile women with PCOS seeking pregnancy. Lifestyle modification should be implemented as first-line approach for those who have dyslipidemia. The use of statins in pregnancy is contraindicated; therefore, contraception is obligatory for severe dyslipidemias that implies the use of those drugs [31,32].

The assessment of family history of T2DM should be routinely done in PCOS women, as it allows metabolic risk stratification. T2DM familial history is associated with adverse metabolic profile, namely increased risk for obesity, central fat accumulation, metabolic syndrome, glucose abnormalities, and low cholesterol-HDL [33]. The present study indicates that assessment of T2DM family history may be a valuable prognostic indicator for fertility treatment, with its existence associated to worse results.

In PCOS women, primary infertility is more frequent than secondary infertility [33]. In teh present study, the prevalence of primary infertility was remarkably higher than secondary infertility and the women with primary infertility required more treatment cycles. In this population, other infertility factors were present in 22.9% of the primary infertile women, whereas this was true in only 6.2% of secondary infertilities ($p < 0.05$). By including anovulatory PCOS women with concomitant endometriotic, tubal or spouse sperm abnormalities, the authors believe that these results are more applicable to real-life clinical setting of infertile PCOS women in fertility centers. Thus, fertility workup is required in an important proportion of anovulatory PCOS women, especially those with primary infertility refractory to fertility treatments [13].

Multiple studies have being conducted to address the impact of different factors in the outcomes of fertility treatments. The present study found no impact of overweight/obesity, insulin-resistance and hyperandrogenism on fertility treatment results, although these parameters are frequently reported as relevant adverse factors for fertility treatment [15, 21, 34, 35]. Reduced ovarian responses, suppressed oocyte developmental competence, and lower implantation rates may directly explain the poorer outcomes in this subset of PCOS women [16, 36]. Some reports refer also to negative impact of hypertension or smoking in fertility treatment results in PCOS women [15, 37, 38], which was not confirmed in this series.

Obesity, hyperinsulinemia, and insulin-resistance have being implicated in early pregnancy loss [14, 16, 39]. Moreover, high LH levels and hyperandrogenemia increase the risk of first-trimester abortion [11, 14]. These features are highly prevalent in infertile PCOS women, conferring a high risk for miscarriage. First-trimester abortions may reach 50% in PCOS women, which is threefold higher than the rate of normal women [14, 40, 41]. The present study failed to demonstrate the association between BMI, insulin-resistance or hyperandrogenemia with higher rates of spontaneous abortion. However, the authors found significant associations between older age, waist circumference > 80 cm (a marker of metabolic disturbance and insulin-resistance [42]) and higher LH levels with miscarriage occurrence.

In conclusion, this study demonstrated that infertile PCOS women with primary infertility, hypertriglyceridemia, low cholesterol-HDL, and T2DM familial history may have poorer fertility treatment results, possibly requiring more treatment cycles and longer treatment periods to achieve clinical pregnancy. Older ages, waist circumference above 80 cm, and high levels of LH may be associated with spontaneous abortion. Thus, these features may confer worse prognosis for fertility treatments and should orientate the clinicians for a careful evaluation and management. Preconceptional control of these factors, namely the lipid profile, may positively affect the prognosis of infertility treatments and should be largely stimulated.

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