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Psychological characteristics, sexual function and quality of life in infertile women with polycystic ovary syndrome

Iuliia Naumova

PSYCHOLOGICAL CHARACTERISTICS, SEXUAL FUNCTION AND QUALITY OF LIFE IN INFERTILE WOMEN WITH POLYCYSTIC OVARY SYNDROME

Doctoral thesis report presented by:

IULIIA NAUMOVA

To apply for the degree of: Doctor of Medicine from the University of Barcelona

Directed by:

CAMIL CASTELO-BRANCO, Senior Consultant of the Clinical Institute of Gynecology, Obstetrics and Neonatology (ICGON) of the Hospital Clínic de Barcelona and Full Professor of Obstetrics and Gynecology and Head of the Department of Surgery and Surgical Specializations of the University of Barcelona

Tutor: CAMIL CASTELO-BRANCO

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CLÍNIC BARCELONA Hospital Universitari

Dr. Camil Castelo-Branco, Senior Consultant of the Clinical Institute of Gynecology, Obstetrics and Neonatology (ICGON) of the Hospital Clínic de Barcelona and Full Professor of Obstetrics and Gynecology and Head of the Department of Surgery and Surgical Specializations of the University of Barcelona

CERTIFIES:

That the thesis entitled « PSYCHOLOGICAL CHARACTERISTICS, SEXUAL FUNCTION AND QUALITY OF LIFE IN INFERTILE WOMEN WITH POLYCYSTIC OVARY SYNDROME» has been prepared, under his direction, by **Iuliia Naumova**, to apply for the degree of **Doctor of Medicine** from the **University of Barcelona**.

And, for the record, they sign this document, at the request of the petition of interests.

Signatures

Director of Thesis
Dr. Camil Castelo-Branco

Doctoral student
Iuliia Naumova

April, 8th, 2021, Barcelona

To my family and

to those who always accompany me

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Index

Abbreviations

- PCOS: polycystic ovary syndrome
- NIH: National Institute of Health
- ESHRE: European Society for Reproduction and Human Embryology
- ASRM: American Society of Reproductive medicine
- AE-PCOS: Androgen Excess and PCOS Society
- SF-36: Short Form Survey
- PCOSQ: Polycystic Ovary Syndrome Questionnaire
- BDI-II: Beck Depression Inventory
- HAM-A: Hamilton Anxiety scale
- FSFI: Female sexual Function Index
- TFI: tubal factor infertility
- MFI: male factor infertility
- mFG: modified Ferriman-Gallwey scoring method
- PCOM: polycystic ovarian morphology
- BMI: body mass index
- DM2: type 2 diabetes mellitus
- IR: insulin resistance
- CVD: cardiovascular disease
- MAR: medically assisted reproduction

Articles that compose the Doctoral Thesis

Doctoral Thesis is presented in article compendium format. The thesis consists of three articles:

ARTICLE 1

Camil Castelo-Branco & **Iuliia Naumova**

Quality of life and sexual function in women with polycystic ovary syndrome: a comprehensive review.

Gynecol Endocrinol 2020 Feb; 36(2):96-103. doi: 10.1080/09513590.2019.1670788. Epub 2019 Sep 27

Journal Citation Reports (JCR) 2019® Q3 Obstetrics and Gynecology

ARTICLE 2

Iuliia Naumova, Camil Castelo-Branco, Iuliia Kasterina, Gemma Casals

Quality of Life in Infertile Women with Polycystic Ovary Syndrome: a Comparative Study.

Reprod Sci. 2020 Nov 19. doi: 10.1007/s43032-020-00394-1. Online ahead of print.

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ARTICLE 3

Iuliia Naumova, Camil Castelo-Branco, Gemma Casals

Psychological Issues and Sexual Function in Women with Different Infertility Causes: Focus on Polycystic Ovary Syndrome.

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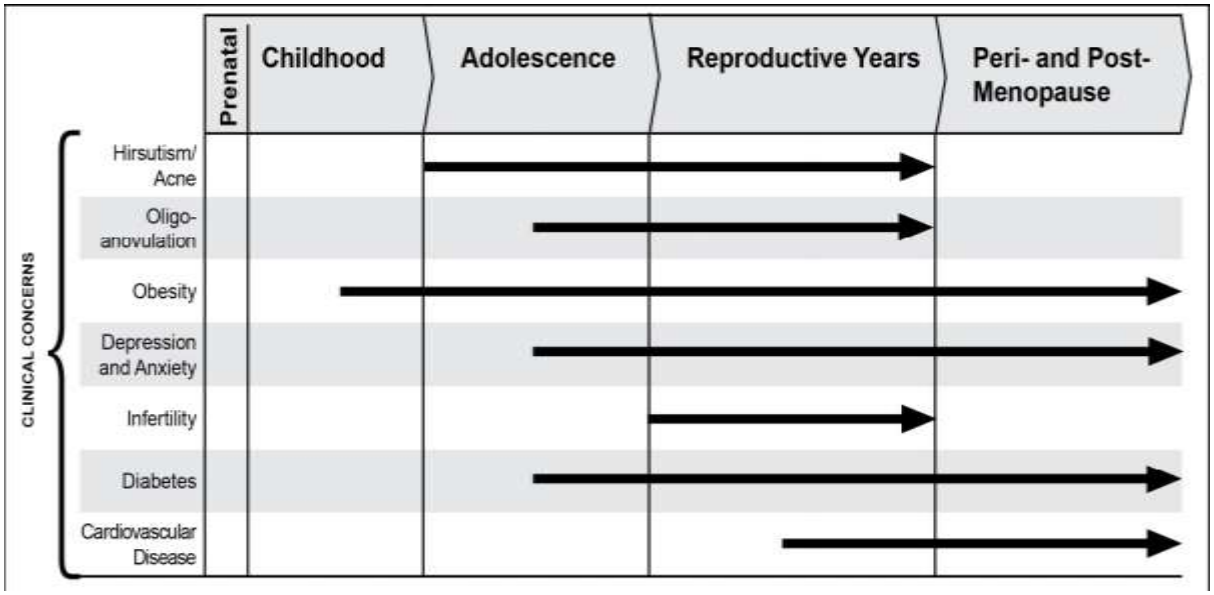
INTRODUCTION

Polycystic ovary syndrome is the most common reproductive disorder causing significant health consequences for women impairing quality of life and increasing morbidity. PCOS affects between 8 to 13 % of reproductive age women and 21% in high-risk groups [1]. Thus, among women with menstrual irregularities, the incidence of PCOS according to various studies ranges from 17.4% to 46.4%. In patients with clinical manifestations of hyperandrogenism, PCOS takes the leading place, reaching 72.1% -82% using various criteria, and in women with anovulatory infertility, PCOS is detected in 55% -91% of cases [2-5].

Women suffering from PCOS present with common features including reproductive (irregular menstrual cycles, infertility and pregnancy complications) [6], metabolic (insulin resistance (IR), metabolic syndrome, prediabetes, type 2 diabetes (DM2) and cardiovascular risk factors) [7,8] and psychological issues [9-11].

Figure 1*. ***Common clinical manifestations associated with the syndrome across the life course***



*(NIH, Evidence-based Methodology Workshop on PCOS, December 3–5, 2012. Final report)

PCOS Classifications

Depending on the criteria for the diagnosis, currently there are several classifications of PCOS:

- criteria of US National Institute of Health (NIH) (1990) [12], revised in 2012;
- criteria of the European Society for Reproduction and Human Embryology (ESHRE) and the American Society of Reproductive medicine (ASRM), adopted in Rotterdam (2003) [13]
- criteria of Society of Hyperandrogenism and PCOS (Androgen Excess and PCOS Society, AE-PCOS) (2006) [14].

The ESHRE/ASRM criteria (2003) suggest the presence of any 2 of 3 signs: oligoanovulation, hyperandrogenism and/or hirsutism, polycystic morphology ovaries according to ultrasound [13].

The AE-PCOS (2006) criteria suggest the presence of 2 of 2 features: hirsutism and/or hyperandrogenemia; oligoanovulation and/or polycystic morphology [14]. Additionally, AE-PCOS criteria (2006) requires the use of accurate androgen level determination methods, which is not always possible.

Following the revision of the NIH criteria (1990) in 2012, the decision of the preferred use of the ESHRE/ASRM (2003) criteria for PCOS diagnosis agreed with mandatory indication of clinical phenotypes was taken. This approach to diagnosing PCOS is supported by the Endocrine Society (USA) [15]

The Rotterdam diagnostic criteria are endorsed by the recent international evidence-based guidelines on the diagnosis and management of PCOS and commonly used globally to diagnose PCOS.

The Rotterdam diagnosis for PCOS requires two of the following features: clinical or biochemical hyperandrogenism, ovulation dysfunction, polycystic ovarian ultrasound; additionally, other endocrine etiologies such as thyroid disease,

nonclassic congenital adrenal hyperplasia, and hyperprolactinemia should be excluded.

However, the recent guideline (2018) refines the advisability of ovarian ultrasound in the diagnosis of PCOS in some conditions, avoiding over diagnosis [16].

Thus, in the accordance with the current recommendations, ultrasound is not a reliable feature to diagnose PCOS in individuals with a gynecologic age <8 years after menarche due to the high incidence of multifollicular ovaries at this stage of life. Besides, in patients with irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not required to diagnose PCOS; however, ultrasound identifies the complete phenotype of PCOS. The threshold values for diagnosing polycystic ovarian morphology have been revised.

Table 1. ***Diagnostic criteria for PCOS.***

US National Institute of Health (NIH) criteria, 1990 [12]	ESHRE/ASRM (Rotterdam) criteria, 2003 [13]	Androgen excess and PCOS society (AE-PCOS) criteria, 2006 [14]	International evidence-based guideline for the assessment and management PCOS, 2018 [16]
• Clinical and/or biochemical hyperandrogenism • Oligo/anovulation	• Clinical and/or biochemical hyperandrogenism • Oligo/anovulation • Polycystic ovaries	• Clinical and/or biochemical hyperandrogenism • Oligo/anovulation and/or polycystic ovaries	• Clinical and/or biochemical hyperandrogenism • Oligo/anovulation • Polycystic ovarian morphology
	Number of follicles in any ovary >12; ovarian volume ≥ 10 ml		Number of follicles in any ovary >20 Ovarian volume ≥ 10 ml
Both criteria are required	2 of 3 criteria are required	Both criteria are required	2 of 3 criteria are required
		The use of accurate androgen level determination methods is required	*Ultrasound is not required if • gynecological age <8 years after menarche • both hyperandrogenism and ovulatory dysfunction are present

*All the Criteria require the exclusion of other medical conditions, including thyroid or pituitary dysfunction, androgen-secreting tumors, Cushing syndrome, or congenital adrenal hyperplasia

Diagnostic criteria of PCOS

Ovulatory Dysfunction and Irregular Menstrual Cycles

Irregular menstrual cycles caused by ovulatory dysfunction is the key feature of PCOS. According to the literature, more than 70% of women affected with PCOS experience menstrual abnormalities [17].

In turn, PCOS is diagnosing in about 85-90% of women with oligomenorrhea and 30-40% of women with amenorrhea [18]. Notably, ovulatory dysfunction can occur in women with regular menstrual cycles [19].

Some studies demonstrate a close relation between the degree of cycle irregularities and the grade of endocrine and metabolic disorders among these women [20,21].

The menstrual disturbances classically have a peripubertal onset. However, menstrual irregularity can be define as normal in the first year post menarche as part of the pubertal transition.

The recent guideline defines irregular menstrual cycle as a cycle shorter than 21 days or longer than 45 days in women between 1 and 3 years post-menarche, and less than 21 or more than 35 days in women over 3 years postmenarche to perimenopause [16].

Oligomenorrhea is the most common menstrual cycle disorder in women suffering from PCOS. According to some authors, it occurs in about 60% of PCOS patients complaining for menstrual irregularity, while amenorrhea is observed in less than 10% of patients [17]. Women with PCOS are more prone to menorrahia than those without. Thus, according to the results of a large population-based retrospective cohort study, women with PCOS had a higher rate of admissions for menorrhagia (14.1 vs 3.6%) [22].

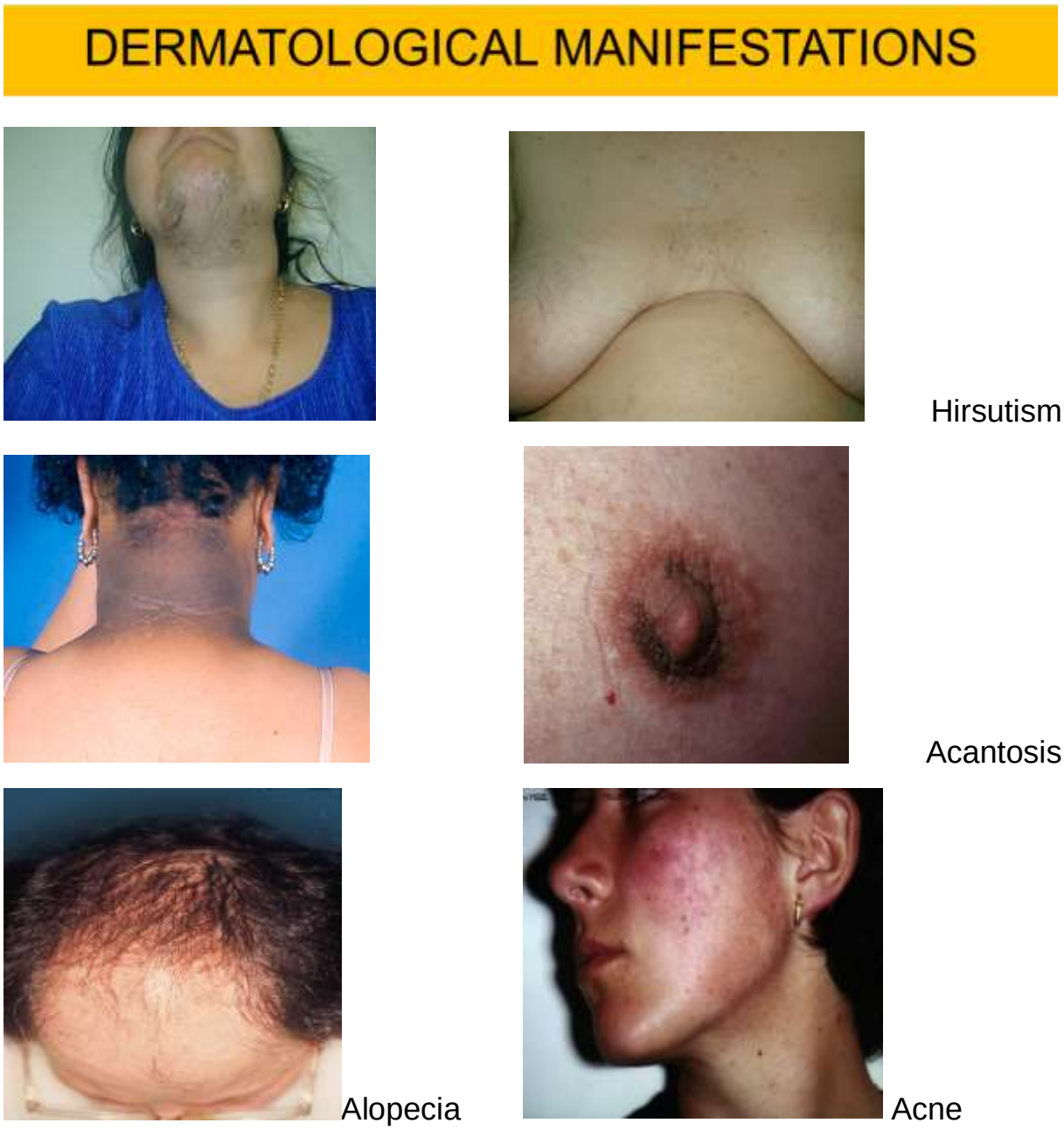
However, the incidence of menstrual cycle irregularity in women with PCOS declines at the end of reproductive age. It is caused by the drop in the ovarian follicle cohort and a decline in androgen levels [18].

Hyperandrogenism

Hyperandrogenism is the most recognizable features of PCOS, with a recent study reporting in 78% of women with PCOS and even higher prevalence in overweight women [23].

Although not always clinically evident, hyperandrogenism is commonly manifested in several cutaneous symptoms including hirsutism, acne, and alopecia (i.e., male pattern baldness).

Figure 2. ***Dermatological manifestations of PCOS***



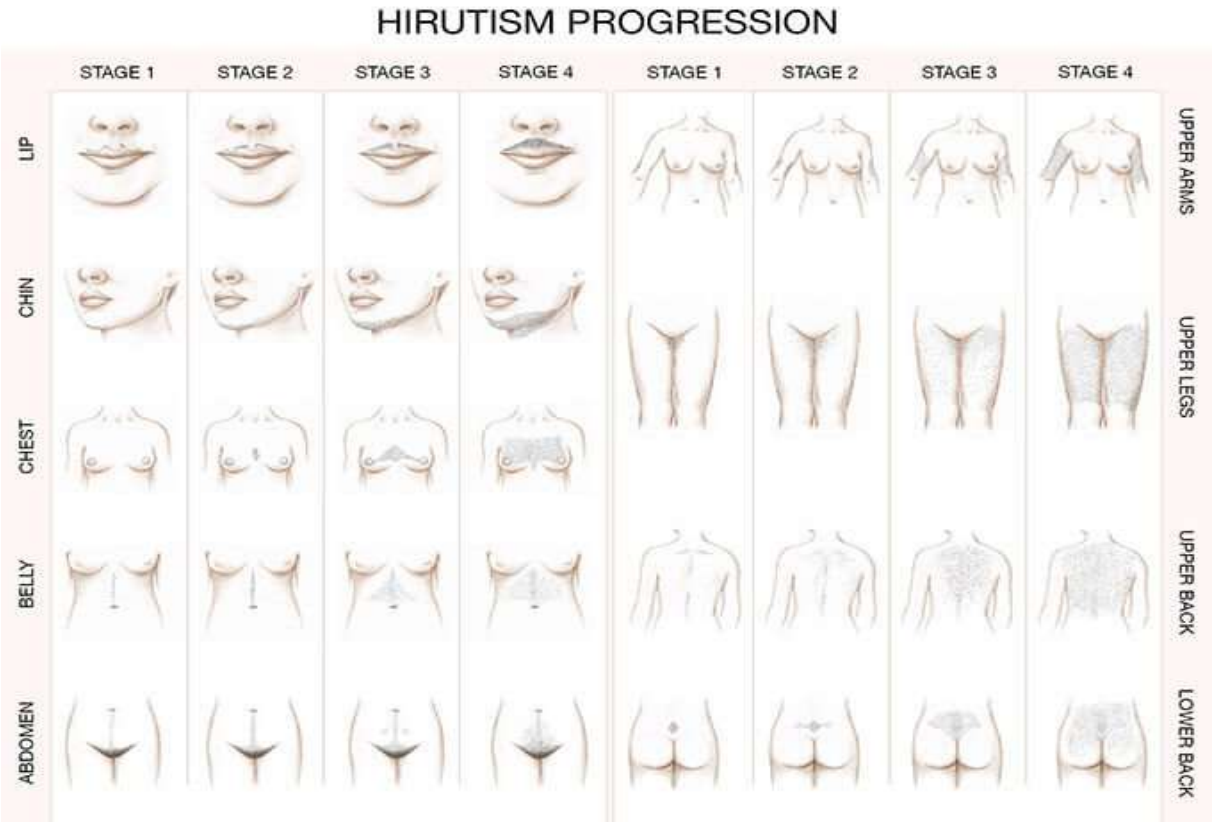
Hirsutism, the presence of terminal (coarse) hair in male pattern distribution, has been documented in up to approximately 70% of patients with PCOS [2]. Hirsutism adversely impacts quality of life and appears to be the most distressing symptom of PCOS [9].

It is widely reported that androgens have significant effects on hair follicle development and growth, stimulating male pattern hair growth via conversion of vellus to terminal hair types [24]. The relationship of androgens to hirsutism is not completely understood, however, the earlier studies have not found clear correlations between androgen levels and presence of hirsutism. Although some studies have shown hirsutism to correlate with free testosterone, others have documented that in women with mild hirsutism, only 50% had elevated free testosterone level; in women with modestly elevated free testosterone, 33% of women had no hirsutism at all, 27% had moderate, and 40% had mild [25]. In another study of over 300 PCOS patients, of those who had evidence of hyperandrogenemia, 63% had clinical hirsutism; of those who were hirsute, 68% were hyperandrogenemic [26].

The prevalence of hirsutism is the same across ethnicities, yet the mFG cut-off scores for defining hirsutism and the severity of hirsutism varies by ethnicity.

In representatives of the Caucasian and Negroid races, an increase in the value of the sum of points on the mFG scale of ≥8 points is pathognomic, although according to some data its increase ≥6 defines as hirsutism [15, 27, 28]. Representatives of Southeast Asia have a diagnostically significant increase in the sum of points on the mFG scale ≥3 [29].

Figure 3. ***The modified Ferriman-Gallwey (mFG) score***



Some authors report that approximately 50% of women with minimal unwanted hair growth and a mF-G score of 5 or less were diagnosed with androgen excess and PCOS [30]

Acne is not particularly specific for PCOS and affects about 30 % of patients with syndrome [16].

Some studies demonstrate the association of acne with biochemical and/or clinical hyperandrogenism in more than 70% of acneic women [31,32], however, the predictive value of acne alone remains unclear [32]. Moreover, there are no universally accepted visual assessments for evaluating acne [33].

Male pattern hair loss (androgenic alopecia) is less frequently seen in PCOS patients, as it generally requires a familial predisposition.

Most studies of women with alopecia reveal a relatively low prevalence of hyperandrogenemia [32, 34] and the predictive value of alopecia alone is unclear.

Polycystic Ovarian Morphology

Polycystic ovarian morphology (PCOM) as a common feature associated with clinical and endocrine features of the syndrome, was incorporated into the diagnosis of PCOS in 2003 in the Rotterdam criteria [13]. The cut-off value for polycystic ovary ultrasound was the presence of 12 or more follicles 2–9 mm in diameter or increased ovarian volume (> 10 ml) in at least one ovary. This threshold of 12 follicles was based on a study published by Jonard S et al; authors demonstrated that follicular number per ovary 12 or more offers the best compromise between specificity (99%) and sensitivity (75%) in detecting hyperandrogenic anovulation [35]. Subsequently, numerous studies have shown a high prevalence of ovaries with more than 12 follicles in healthy young women. Thus, according to Kristensen SL et al. up to 70% of adolescents have PCOM on original criteria due to natural changes in antral follicle count during pubertal transition [36].

The recent guideline recommends using a follicle number of more than 20 follicles (2–9 mm) per ovary and/or an ovarian volume 10 mL to define polycystic ovarian morphology using vaginal transducer frequency 8 MHz; the threshold for PCOM could be an ovarian volume ≥ 10ml, if using older technology. Moreover, due to the high incidence of polycystic ovarian morphology and nonspecificity of the feature in women within 8 years of menarche, ultrasound is not recommended at this life stage for the purposes of diagnosis. The presence of both oligo/anovulation and clinical and/or biochemical hyperandrogenism are required for PCOS diagnosis [37]. Besides, in women with both irregular menstrual cycles and hyperandrogenism, an ovarian ultrasound is not required to diagnose the syndrome, however, it helps to identify the complete PCOS phenotype.

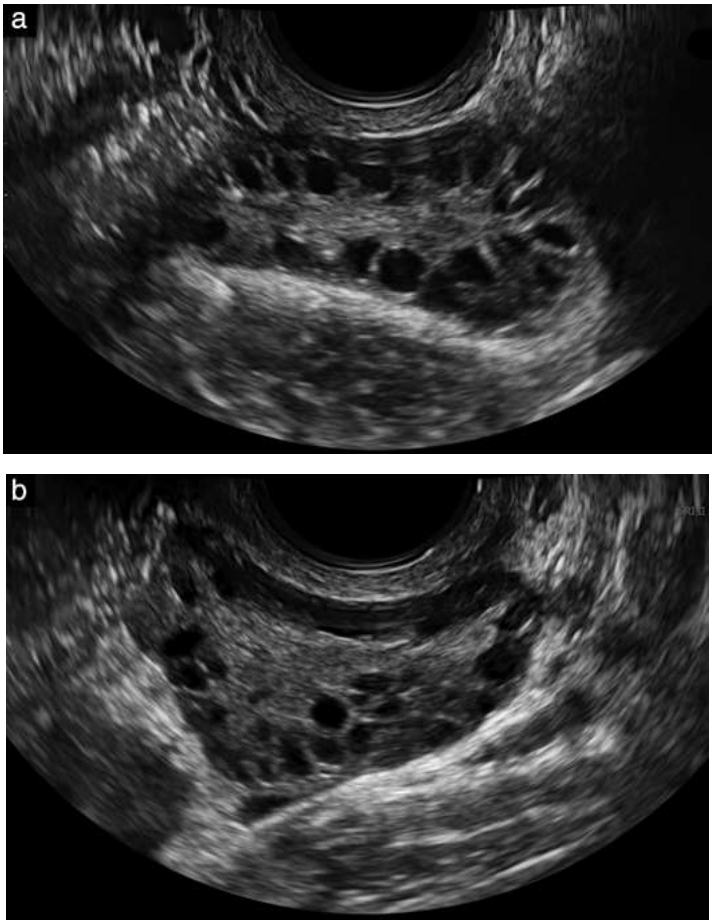


Figure 4. ***Grayscale two-dimensional ultrasound images of right (a) and left (b) ovaries of infertile PCOS patient, showing numerous peripheral antral follicles surrounding a rather hyperechoic central ovarian stroma.)***

PCOS prevalence and PCOS phenotypes

The prevalence of PCOS varies depending on the diagnostic criteria, phenotypes, and populations studied. According to the results of a large meta-analysis conducted by Bozdag G et al, the reported overall prevalence of PCOS (95% CI) according to diagnostic criteria of the NIH, Rotterdam and the AE-PCOS Society is 6%, 10% and 10%, respectively. The range for prevalence on Rotterdam criteria was 8 to 13% [1]. Currently there are four recognized phenotypes of PCOS [15]: (A) phenotype 1, characterized by oligo/anovulation, hyperandrogenism, and polycystic ovarian morphology; (B) phenotype 2, characterized by

oligo/anovulation and hyperandrogenism; (C) phenotype 3, characterized by hyperandrogenism and polycystic ovarian morphology; and (D) phenotype 4, characterized by oligo/anovulation and polycystic ovarian morphology.

Table 2. PCOS adult phenotypes

	ROTTERDAM CRITERIA, 2003	AES criteria, 2006	NIH criteria, 1992	Classic PCOS
1 (A) Phenotype (classic PCOS)				
Clinical and/or biochemical hyperandrogenism				
Oligo/anovulation				
Polycystic ovarian morphology				
2 (B) Phenotype (hyperandrogenic anovulation)				
Clinical and/or biochemical hyperandrogenism				
Oligo/anovulation				
3 (C) Phenotype (ovulatory PCOS)				
Clinical and/or biochemical hyperandrogenism				
Polycystic ovarian morphology				
4 (D) (non-hyperandrogenic)				
Oligo/anovulation				
Polycystic ovarian morphology				

Specification of phenotype was proposed in a workshop convent by the national Institute of Health (NIH) in 2012 [13]. The four phenotypes are listed in table 2 in order of decreasing diagnostic specificity. The hyperandrogenism severity

generally decreases with decreasing phenotype specificity, as does the severity of insulin resistance and obesity.

Prevalence of phenotypes is variable, as this depends greatly on how the population was identified. Thus, in an Indian population, among all PCOS women, 56% presented with phenotype A, 15% with phenotype B, 11% with phenotype C, and 18% with phenotype D [38].

Many studies have shown that PCOS symptom severity as well as IR and other comorbidities occur mostly in women with hyperandrogenic phenotypes (A, B and C), while phenotype D shows a milder form of PCOS [39-41].

According to Guastella E *et al,* the severe PCOS phenotype A (classic PCOS, type I) was the most common phenotype in 53.9% of the patients, while phenotype B (classic, type II) was detected in 8.9% of patients. The two phenotypes of classic PCOS had similar clinical and endocrine characteristics, but the patients with polycystic ovaries had a higher luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio. Ovulatory PCOS phenotype was relatively common (28.8% of PCOS patients) and presented milder clinical and endocrine alterations than the classic PCOS phenotypes. The normoandrogenic phenotype was relatively uncommon. These patients had a normal body mass index, insulin sensitivity, and free androgen index but showed increased levels of LH and LH/FSH ratio [42].

However, in other studies, the differences in IR, glucose intolerance and the prevalence of metabolic syndrome between the four PCOS phenotypes were not clear [43].

Clinical Features

Reproductive problems

Polycystic ovary syndrome (PCOS) is the first common cause of anovulatory infertility and is associated with ~80% of cases of infertility due to anovulation [44]. Of note, spontaneous ovulation occurs in only 32% of cycles on PCOS women [45].

In a large community-based cohort study, infertility was reported in 72% of women with PCOS compared with 16% in those without; its incidence was 15-fold higher in women reporting PCOS, independent of BMI [46].

PCOS patients may also have an increased risk of adverse pregnancy outcomes.

It is still not clear whether women with PCOS have an increased risk of miscarriage compared with women without a fertility disorder. According to the PCOS consensus of 2012 [25], miscarriage rates are suggested to be comparable, although available data show conflicting results.

Recently, a large Australian study demonstrated that the pregnancy loss rate was more frequent in women with PCOS than in controls (20 vs 15%, respectively, $p<0.01$), although PCOS was not an independent risk factor for pregnancy loss but the miscarriage rate was strongly influenced by BMI [47].

The recent retrospective studies found a significantly higher risk of developing gestational diabetes mellitus, pregnancy-induced hypertension, premature delivery in PCOS patients [48].

A large meta-analysis involving 27 studies reported a three to four times increased risk of gestational diabetes, pregnancy-induced hypertension and preeclampsia in women with PCOS compared to controls [49].

Additionally, Swedish population-based cohort study demonstrated a significantly increased incidence of preeclampsia in pregnant women with PCOS after adjusting for BMI and use of assisted reproductive technologies [50].

Notably, maternal complications appear to be frequent in women with hyperandrogenemia vs non-androgenic PCOS women [51,52].

Metabolic Syndrome

Metabolic syndrome and its individual components are common in PCOS, particularly among women with the highest insulin levels and body mass index [1]. PCOS is associated with a variety of metabolic abnormalities including insulin resistance or glucose intolerance, abdominal obesity, dyslipidaemia,

hypertension, obstructive sleep apnoea (OSA) and non-alcoholic fatty liver disease.

Insulin resistance inherent in PCOS, and its associated disturbances are of importance in the pathogenesis of type 2 diabetes, hypertension and coronary heart disease [53]. Thus, impaired glucose tolerance is observed in up to 30% and type 2 diabetes in up to 10% of women with PCOS [8]. When followed up over 10 years, the age-standardized prevalence of diabetes was 39.3% in middle-aged women with PCOS compared with 5.8% of controls of similar age [54].

In a large-scale national epidemiological study, metabolic syndrome was reported in 19.1% women with PCOS [55], while the prevalence of metabolic disturbance in infertile PCOS is even higher and amounts, according to some data, to 27% [56].

Although insulin resistance is not part of the diagnostic criteria, it is highly prevalent, occurring in up to 95% of women with PCOS who are obese and up to 75% of lean women with PCOS [57].

IR and compensatory hyperinsulinaemia contribute to the exacerbation of PCOS symptoms and are critically involved in the development of metabolic syndrome and cardiovascular disease in PCOS women [58].

Approximately 50% of PCOS women are overweight or obese and most of them have the abdominal phenotype. Obesity, particularly the abdominal phenotype, may be partly responsible for insulin resistance and associated hyperinsulinemia in women with PCOS [59].

A large meta-analysis of clamp assessments of insulin action in PCOS found a decrease in insulin sensitivity of 27% in women with PCOS compared with controls, independent of BMI, age, or diagnostic criteria. However, BMI exacerbated insulin resistance by 15% in women with PCOS and had a greater impact on insulin resistance in PCOS than in controls [60].

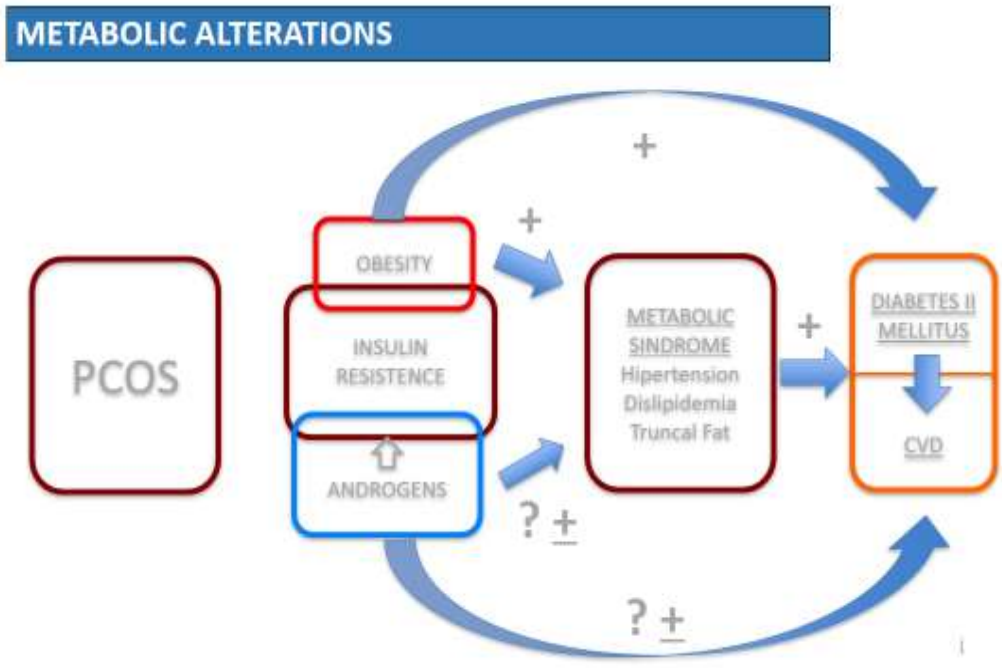
Other recent cross-sectional study showed high prevalence of IR (56.3%) and reduction in insulin sensitivity (IS) by 30.3% in women with PCOS vs controls;

The inherent reduction in IS was 18.8% in lean women with PCOS and BMI independently reduced IS by 37.9% in obese women with PCOS [61].

In the accordance to some studies, body weight status has a greater adverse impact on IR in PCOS than in controls [53] and is the major determining factor for the prevalence of impaired glucose tolerance and metabolic syndrome in women with polycystic ovary syndrome.

In addition, some authors report that IR may be more pronounced in patients presenting with anovulation and hyperandrogenism compared with those who have normal androgen levels or regular menstrual cycles. Thus, Panidis et al reported that in phenotype A, insulin resistance is more prevalent. In women with phenotype C, insulin resistance is not different compared with BMI-matched controls [62].

Figure 5. ***Pathways for the development of cardiovascular disease in women with PCOS*** [63]



Cardiovascular disease (CVD)

Women with PCOS have an adverse cardiovascular risk profile including dyslipidemia, hypertension, and obstructive sleep apnea.

Some studies have found that the prevalence of subclinical CVD markers such as coronary artery calcium scores, C-reactive protein, carotid intima-media thickness, and endothelial dysfunction is more likely to be increased in women with PCOS [64].

Thus, the Coronary Artery Risk Development in Young Adults (CARDIA) study found that women with both hyperandrogenemia and oligomenorrhea (phenotype A) had an increased prevalence of coronary artery calcifications and increased carotid intima-media thickness, but women with isolated oligomenorrhea or hyperandrogenemia did not [64].

A case–control study of 1,550 women with PCOS reported significantly lower levels of HDL and higher levels of total cholesterol, low density lipoprotein, triglycerides, and both systolic and diastolic blood pressure compared with controls, independent of BMI [65]

While the associations between PCOS and cardiometabolic abnormalities have been well described, the evidence around long-term outcomes on cardiovascular events is limited and controversial.

A recent sub-group analysis of 106 women with PCOS and 171 control women within a larger prospective cohort study of women through post-menopause reported no increased risk for stroke or ischemic heart disease compared to the control women [66].

A 2017 meta-analysis of eight studies conducted among 128,977 women aged 36–71 years, with an average follow-up duration of 10–40 years, suggested that PCOS was associated with a significant increased risk for stroke [67]. However, this finding was attenuated and not statistically significant after adjusting for BMI.

In contrast, a large national Denmark study demonstrated a greater risk of incident CVD in PCOS women compared to controls. In this study the CVD event rates

were 22.6 vs. 13.2 per 1000 patient-years for women with PCOS vs. controls [68]. Authors report that obesity, diabetes, and infertility, and previous use of oral contraceptives were associated with increased risk of development of CVD in PCOS women.

In a meta-analysis of 5 studies, women with PCOS had a 2-fold increased risk for coronary heart disease or stroke – an association that remained significant after adjusting for BMI, suggesting the excess risk was not related to a higher BMI in patients with PCOS [69].

Endometrial cancer

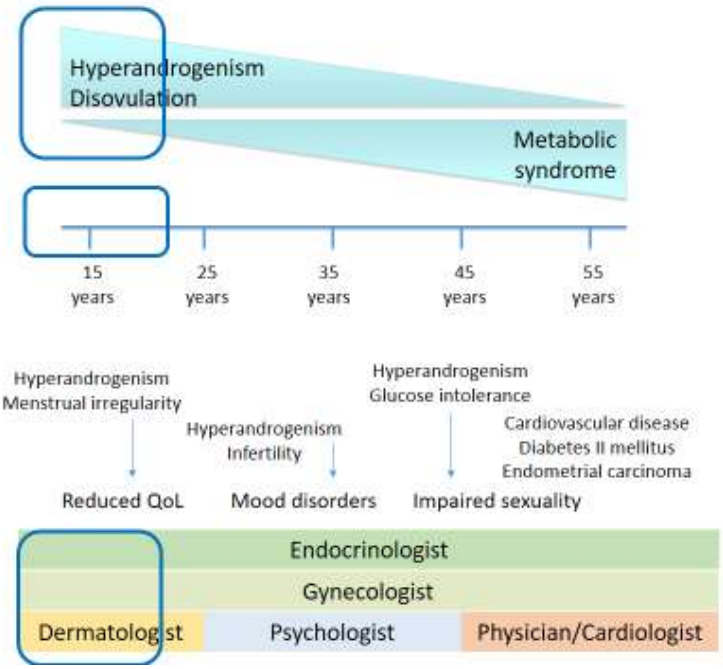
Women with PCOS have several risk factors for endometrial cancer and may be at increased risk of developing it. Some of the clinical, metabolic and molecular risk factors include unopposed estrogen stimulation of the endometrium in anovulatory PCOS women, obesity, insulin resistance, insulin like growth factors, diabetes, nulliparity, progesterone resistance [70].

A large 2012 meta-analysis demonstrated unambiguous link between PCOS and endometrial cancer; Women with PCOS were about three times more likely to develop endometrial cancer compared with those without it. This translates into a 9% lifetime risk of endometrial cancer in Caucasian women with PCOS compared with 3% in women without it [71].

A large Danish cohort study of 12,070 women with PCOS reported a fourfold increased risk for endometrial cancer and two- to fourfold increased risks for colon, kidney, and brain tumors, whereas their risks for breast and ovarian cancer were similar to those of women in the general population. [72].

Similarly, another meta-analysis of 11 studies demonstrated 3-4 fold increased risk of endometrial cancer in PCOS women of all ages [73].

Figure 6. ***Crossing effects of PCOS during life span***



Psychosocial Health, Sexuality and Quality of life

There is increasing evidence that women with PCOS are more likely to suffer from mood disorders. Some studies have reported that women suffering from PCOS are more prone to depression, anxiety, poor self-esteem, negative body image, and psychosexual dysfunction [52, 74].

According to some data, approximately 57% of women suffering from PCOS present with at least one mental disorder [75], that negatively affects their psychological wellbeing and quality of life [76,77]. Of note, more than 65% of women say that PCOS affects everyday life and more than 50% are self-confident that this condition negatively affects their relationships with others [78].

A large German nationwide internet survey with participation of 448 women with PCOS revealed a clinical depression prevalence rate of 21% [79]. Another study demonstrated 23.9% and 25.2% of women with PCOS scored in the mild to moderate and clinically relevant ranges of depression on the Beck Depression Inventory (BDI), respectively [80].

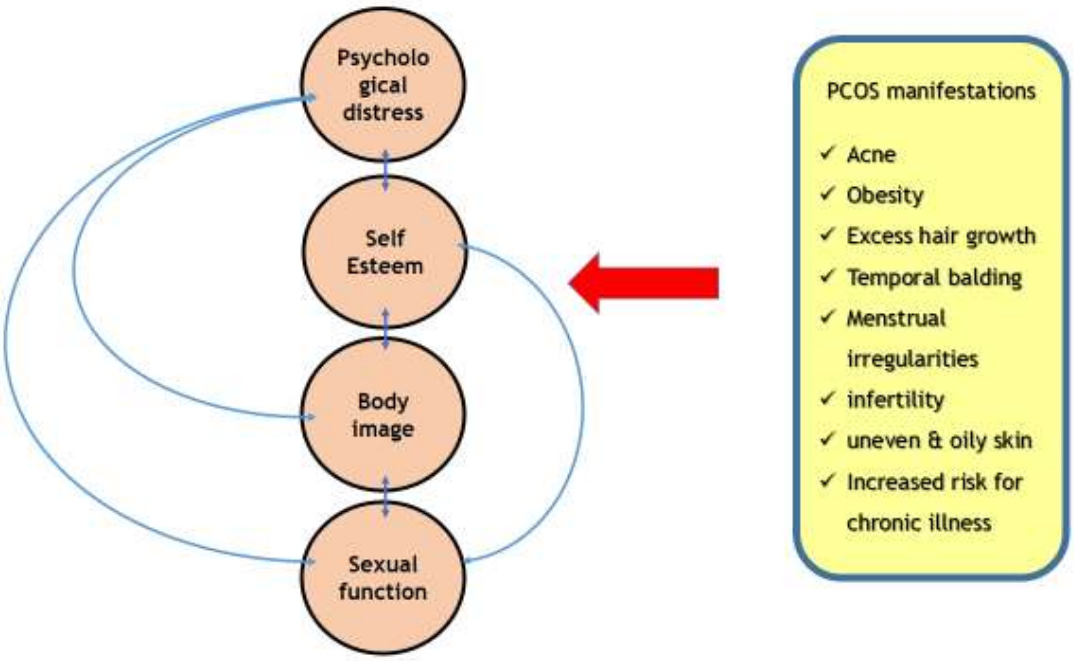
Manifestations of PCOS may result in challenges to body image and feminine identity, compromise quality of life and adversely impact on mood and psychological well-being. The underlying mechanisms are still unclear; however, factors such as insulin resistance, elevated androgens, and clinical features including distress related to hirsutism, weight gain, acne, and infertility are also drivers [81].

Some papers show a correlation between depression scores and insulin resistance, lipid parameters, severity of metabolic syndrome [82]

Numerous clinical studies confirm the role of clinical hyperandrogenism and the consequent social exclusion in various disorders of the psycho-emotional sphere [83-85]. External manifestations of androgens excess (seborrhea, hirsutism, androgen-dependent alopecia, acne) become a significant cosmetic defect and may affect the feminine identity reflecting on the neuropsychological status of women, leading to irritability, depressive states, reducing quality of life and causing social problems [86].

A recent systematic review focusing on moderate and severe symptoms of anxiety and depression reported a 4.18 increased odds of moderate or severe symptoms of depression and a 5.62 increased odds of symptoms of anxiety in women with PCOS compared with controls. The increased risk of depression in women with PCOS persisted after adjustment for BMI. Women with PCOS and symptoms of depression had higher mean values of insulin resistance, BMI, hirsutism, and infertility [87].

Figure 7. ***The relationship between features of PCOS and psycho-sexual health***



The women's sexual function is provided by a balanced interaction of many factors. Endocrine disorders, discomfort in emotional and social sphere can cause sexual dysfunction. Thus, it is known that sexual function can be impaired by androgen levels, obesity, metabolic syndrome, subfertility, mental health, body image and self-esteem [88,89]. These factors are commonly present in women with PCOS and could be contributing to their sexual dysfunction.

Some authors report that problems in the sexual functioning were identified in more than 30% of women with PCOS, and 89% of them presented with weight excess [90].

A recent systematic review and meta-analysis on sexual function in women with PCOS including 18 studies with validated sexual function questionnaires and visual analog scales reported a minor but significant effect on sexual function subscales (arousal, lubrication, satisfaction, orgasm) of the syndrome compared with healthy controls [88]. In addition, excessive body hair growth impaired sexual function, social appearance and sexual attractiveness.

However, some authors suggest that hyperandrogenism does not induce the sense of loss of feminine identity and has no impact on sexual self-worth and sexual satisfaction [91]. Therefore, the role of androgens and its clinical effects on sexual function is still controversial.

The article titled ***«Quality of life and sexual function in women with polycystic ovary syndrome: a comprehensive review»*** has been published in **Gynecological Endocrinology.**

The purpose of an article was to overview scientific sources on the impact of polycystic ovary syndrome on quality of life, psychological state and sexual function in women with this condition.

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Quality of life and sexual function in women with polycystic ovary syndrome: a comprehensive review

Camil Castelo-Branco & Iuliia Naumova

Gynecological Endocrinology, the official journal of the International Society of Gynecological Endocrinology, covers all the experimental, clinical and therapeutic aspects of this ever more important discipline. It includes, amongst others, papers relating to the control and function of the different endocrine glands in females, the effects of reproductive events on the endocrine system, and the consequences of endocrine disorders on reproduction.

- Impact Factor (IF) **1.571 (2019)**
- 5 year Impact Factor **1.615 (2019)**
- It is located in the third quartile of the specialty of Obstetrics and Gynecology (position 61/82), according to the Journal Citation Reports 2019®.

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REVIEW ARTICLE

Quality of life and sexual function in women with polycystic ovary syndrome: a comprehensive review

Camil Castelo-Branco[a]* and Iuliia Naumova[b]*

[a]Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine, University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [b]Faculty of General Medicine, Department of Obstetrics and Gynecology, Saratov State Medical University n.a. V.I. Razumovsky, Saratov, Russia

ABSTRACT

Polycystic Ovary Syndrome (PCOS) is the most common endocrinopathy among women of reproductive age. PCOS is a polysimptomatic disease, the leading manifestations of which are hyperandrogenic dermopathy, menstrual dysfunction, infertility and obesity. Dissatisfaction with one's own appearance, low self-esteem, a feeling of sexual unattractiveness cause chronic psychological discomfort, mood disturbances and problems in the relationship with a partner. The article presents an overview of scientific sources on the effect of polycystic ovary syndrome on the quality of life and the sexual function of women. Data recorded confirm the hypothesis that PCOS is not only an endocrine disorder, but a heterogeneous condition with reproductive, metabolic, and mental manifestations. The association of PCOS manifestations with a decrease in the quality of life and disorders in the sexual sphere of women was well assessed. Data presented in the review ensure the absolute medical and social importance of the study of PCOS.

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KEYWORDS
Hirsutism; polycystic ovary syndrome; sexuality; quality of life

Introduction

Currently, the history of the study of PCOS has more than 80 years [1], but polycystic ovary syndrome remains one of the major challenges in obstetrics and gynecology, due to both the high prevalence of this disorder and the large number of unresolved issues related to pathogenesis, diagnosis and treatment. More than 9000 articles at the National Library of Medicine (PubMed) address different aspects of PCOS. This great interest in different aspects of PCOS is due to the influence of the syndrome on various areas of woman's life, reproductive health, sexual function, and psychological comfort.

The issue of PCOS-associated reproductive problems (hyperandrogenism, anovulation, infertility, pregnancy complications) is particularly acute [2]; however, in recent times increasing importance is given to related metabolic disorders (dyslipidemia, hyperinsulinism, insulin resistance, impaired glucose tolerance), which may result in the development of arterial hypertension, abdominal visceral obesity, early atherosclerosis and coronary heart disease. Thus, the manifestations of PCOS affect the health and quality of life (QoL) of women from adolescence and the reproductive period to the perimenopausal and postmenopausal periods. Therefore, this condition represents a serious medical, social and economic problem [3].

The Rotterdam Resolution (The Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group, 2004) unified the diagnostic criteria for PCOS, and also provided a basis for the existence of several phenotypes, which have differences not only in clinical manifestations, but also in hormonal and metabolic profiles. NIH expert group recommends maintaining Rotterdam diagnostic criteria [3], but focuses on the need to identify a specific phenotype for each patient since may present different complaints and long term complications. Based on the NIH and the ESHRE/ASRM diagnostic criteria the prevalence of PCOS among women of reproductive age in the USA, Europe, Asia and Australia ranges from 6–9% up to 19.9% [4]. PCOS takes a leading place in the population of women with clinical manifestations of hyperandrogenism and is detected in 72.1–82% of cases, while among women with anovulatory infertility, just in 55–91% of cases [5].

Recently, ethnic differences in the phenotypic manifestations of PCOS have been actively studied: being normal body mass index (BMI) and "soft" hyperandrogic phenotype prevalent among women of Asian nationality compared with those from other origins. African American and Hispanic women are more prone to obesity and the development of metabolic syndrome and women in the Middle East and those who were Mediterranean descent have higher levels of hirsutism [6].

Hormonal and metabolic abnormalities in PCOS are well studied and are characterized by impaired ovarian steroidogenesis, gonadotropic dysfunction, impaired concentration of sex steroids, and impaired folliculogenesis [7,8]. Because of the disturbance of steroidogenesis, the synthesis and concentration of androgens increases, causing an excessive effect in androgen-dependent tissues. The more pronounced ovarian dysfunction and the longer the disease, the more severe the clinical manifestations of hyperandrogenism [9]. PCOS complaints such as clinical hyperandrogenism, anovulation, menstrual irregularities can lead to a significant decrease in the quality of life, mood disorders, including depression, marital and social maladjustment and sexual dysfunction. For these reasons, we designed the present

CONTACT Camil Castelo-Branco castelobranco@ub.edu Clinic Institute of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Villarroel 170, Barcelona 08036, Spain
*Both authors contributed equally to the work.

comprehensive review with the aim to systematize data recorded on PCOS and quality of life and sexual function.

Material and methods

Information sources

In March 2019, we searched Embase, Medline, and the Cochrane library for all dates up to and including January 2019 to identify potentially relevant publications. In order to maximize the number of publications meeting selection criteria, the medical departments of companies marketing hormonal contraceptives or fertility drugs were contacted to request publications related to PCOS which were not identified during the electronic search. Reference lists from studies initially selected and from existing reviews were also searched to identify any additional relevant studies not identified by the electronic searches.

Search strategy

Search terms used were: "PCOS", "Polycystic Ovary Syndrome"," quality of life", "sexuality", "sexual function" "sexual dysfunction" and "hormonal contraception". No limits were set in terms of time of publication or study design. The search was performed for publications in English, French, or Spanish. Articles in other languages for which a translation was available in one of the 3 study languages were also included.

Study selection

Titles and abstracts of all the studies retrieved were reviewed by a single reviewer (IN) to initially exclude clearly irrelevant publications. Five per cent of the articles excluded at this point were reviewed by another reviewer (CCB) to confirm irrelevance. The abstracts of the remaining articles were reevaluated and any designated for exclusion were reviewed and confirmed by a second reviewer. The full text of articles selected was obtained and reviewed by both reviewers to ensure they met inclusion criteria. Discrepancies were resolved by consensus or consultation with a third party if no agreement could be reached.

Eligibility criteria

Publications were included if the full text of the article was available and data was reported on quality of life or sexuality. All types of clinical studies were included.

Data extraction

For each study included, one reviewer extracted the data and a second reviewer confirmed the selected data. Any potential discrepancies were resolved by consensus and, if necessary, by referring to a third reviewer. A predeveloped pro-forma was used to extract descriptive data on study design, number of patients included, treatments received, questionnaires on sexuality and on quality of life.

Synthesis of results and data analysis

To establish the effect of PCOS and QoL and Sexuality in each study, we considered the number of patients experiencing related complaints in relation to all subjects included in each study. To ensure that the results were relevant for clinical practice, we conducted a second analysis in which only studies investigating separately sexuality or QoL using multiple languages validated questionnaires were included.

A descriptive analysis of the data obtained was performed. Data were analyzed in terms of general health related QoL and PCOS QoL for all studies and for the subgroup of studies which used sexual function questionnaires.

Results

Study selection

The literature search identified 1131 publications of which 793 citations were initially excluded after a comprehensive evaluation of the abstracts since were repeated manuscripts, congress abstracts or simply did not accomplish inclusion criteria. Of the 338 articles selected for a full text review, 256 were excluded for the reasons indicated in Figure 1. In total, 91 studies met the

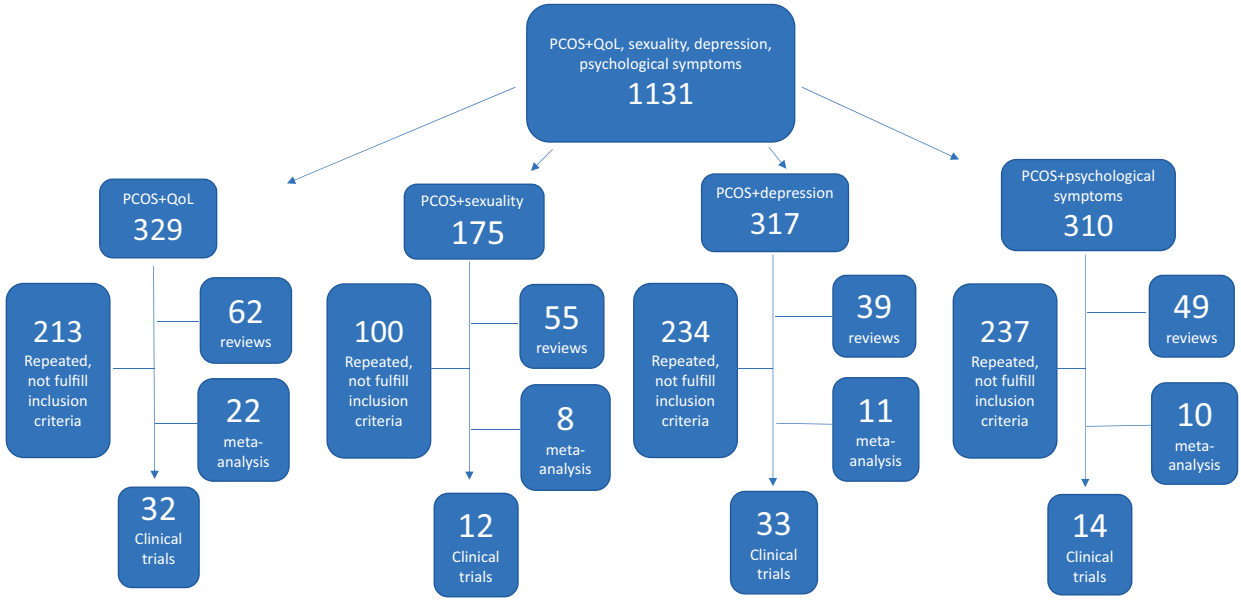

Figure 1. Flow diagram of literature search and selection criteria. Adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [70].

selection criteria for inclusion in this analysis. Of the selected studies, 32 provided data relating to quality of life, 12 to sexuality, 33 to depression and 14 to psychological symptoms.

Study findings

Recent studies have shown that due to the chronic nature and variety of symptoms, PCOS affects almost all stages of patient life. Complaints of women with PCOS, as a rule, are fairly standard: clinical hyperandrogenism including male-type enhanced hair growth, oily skin, acne on the face and back; menstrual cycle abnormalities, and infertility & sterility [10]. Quite often, patients complain of depressed mood, loss of health-related quality of life (QoL) and decreased sexual satisfaction [11–13].

Quality of life in women with PCOS

Manuscripts included in this review evaluated psychological function and quality of life in women with PCOS using appropriate questionnaires or structured interviews (Table 1). To study the health-related QoL, the short form of the questionnaire-36 (Short Form-36 questionnaire, SF-36) has been often used [14]. For patients with PCOS, the PCOSQ (Polycystic Ovary Syndrome Questionnaire) questionnaire should be recommended since includes the analysis of emotions, the impact of hair growth on the body, weight, problems with the menstrual cycle and infertility on the psychological comfort of patients with PCOS [15].

The quality of life of women with PCOS is largely determined by the clinical features of this syndrome and affected by depressive symptoms, anxiety, poor body image and by low self-esteem [16–18].

Numerous studies show reduced QoL scores in women with PCOS, compared with control groups and normative population data [13,19–21]. Coffey et al. reported low scores in all scales of the SF-36 questionnaire (physical and mental component) and in all PCOSQ domains in women with PCOS [22]. According to Stefanaki et al. PCOS creates an important psychological burden throughout the life of women [23]. It is also reported that 57% of women suffering from this syndrome have at least one mental disorder [24], that negatively affects their psychological well-being and quality of life [11,25]. Of note, more than 65% of women say that PCOS affects everyday life and more than 50% are self-confident that this condition negatively affects their relationships with others [26].

Changes in appearance, such as hirsutism and obesity play the greatest role in psycho-social terms [11]. Obesity regardless of the presence of other clinical complaints can significantly impair the quality of life of these women and cause depression [27]. Conversely, for some authors fertility problems (31%) has a greater impact on QoL than obesity (19%) or hirsutism (18%)

Table 1. Influence of PCOS on health-related quality of life (HR-QoL).

Author and year of publication	Sample	Questionnaire	Outcomes	Conclusion
Borghi et al. 2018 [28]	$N = 30$ (PCOS) $N = 30$ (control)	SF-36	Health-related QoL Physical Functioning 90 (PCOS) vs 100 (CG), Mental Health 66 (PCOS) vs 76 (CG)	Significantly less mean scores in PhF and MH domains in PCOS women vs CG ($p < .001$)
Bazarganipour et al. 2015 [19]	$n = 1140$ (PCOS)	PCOSQ, MPCOSQ	Subscales mean scores emotional 4.40; 95% CI 3.77-5.04 infertility 4.13; 95% CI 3.81-4.45 weight 3.88; 95% CI 2.33-5.42 menstruation 3.84; 95% CI 3.63-4.04 hirsutism 3.81; 95% CI 3.26-4.35	HR-QoL affected mostly by menstrual disorders and hirsutism (lowest scores)
Cinar et al. 2011 [40]	$N = 226$ (PCOS) $N = 85$ (control)	PCOSQ	PCOSQ (mean ± SD) Emotion 3.8 ± 1.4 Body hair 3.2 ± 1.6 Menstrual problems 3.5 ± 1.5	HR-QoL affected mostly by menstrual disorders ans hirsutism (lowest scores), $p < .001$
Jones et al. 2010 [21]	$N = 171$ (PCOS, South Asian $n = 42$, Caucasian women, $n = 129$)	SF-36 PCOSQ	PCOSQ (mean scores) Infertility SA 35.3 / Cauc 38.6 (CI -7.7 to 14.3), Weight SA 35.4/ Cauc 42.3 (CI -18.6 to 4.9), SF-36 (mean) Mental Health SA 60.0 / Cauc 57.6 (CI -9.6 to 4.8) p = 0.52 Physical Functioning SA 73.0 / Cau 87.3 (CI 4.5 to 24.1)	NS differences for all domains of PCOSQ in SA and Cauc women (infertility $p = .55$, weight $p = .2$) NS differences for MH domains in SA and Cauc women ($p = .52$) SA women with PCOS have significantly less mean scores in PhF domains vs Cauc women with PCOS ($p = .005$)
Coffey et al. 2006 [22]	$N = 22$ (PCOS) $N = 96$ (controls)	SF-36 PCOSQ	SF-36 (mean scores) PCS 45.1 (PCOS) vs 50.0 (controls), MCS 37.2 (PCOS) vs 45.9 (controls) PCOSQ domains Emotion 3.4 vs 5.8 Hair 3.5 vs 6.8 Infertility 3.2 vs 6.4 Menstruation 3.6 vs 5.6 Weight 2.1 vs 5.2	Significantly less mean scores in PhF and MH domains in PCOS women vs CG ($p < .05$) HR-QoL affected mostly by infertility and obesity (lowest scores), $p < .0001$

N: observations; CG: control group; PCOSQ: Polycystic Ovary Syndrome Questionnaire; MPCOSQ: Modified Polycystic Ovary Syndrome Questionnaire; SF-36: Short Form Questionnaire; SA: South Asian; Cauc: Caucasian, NS: Not Significant; MH: Mental Health, PHF: Physical Functioning; PCS: Physical Component Score, MCS: Mental Component Score.

[26] and for others, the key complaints were hirsutism and menstrual disorders [19] or reproductive and weight concerns [17].

Psycholgical complaints

According to Stapinska-Syniec et al. depression was noted in more than half of the women with PCOS (52%), mild manifestations of depression were diagnosed in 14%, medium-severe forms in 25%, severe depression was detected in 11% of respondents and extremely severe depression in 3% of women suffering PCOS. In this study, patients with PCOS with mood disorders had a significantly greater BMI.

There is no doubt that psychological well-being influences the quality of life. Many studies are devoted to the assessment of psychological disorders associated with PCOS. The most relevant are summarized in Table 2. Some authors exploring psychological complaints in patients with PCOS have suggested a relationship between this disorder and the well-being (particularly for anxiety and quality of life), but failed in demonstrating a reliable relationship between PCOS and the development of depression [28]. The role of hirsutism in the origin of anxiety and negative mood states highlight the connection between psychological distress and the clinical features of the syndrome [28].

Numerous clinical studies confirm the role of clinical hyperandrogenism and the consequent social exclusion in various disorders of the psycho-emotional sphere [29–32]. External manifestations of androgens excess (seborrhea, hirsutism, androgen-dependent alopecia, acne) become a significant cosmetic defect and may influence the feminine identity reflecting on the neuropsychological status of women, leading to irritability, depressive states, reducing quality of life and causing social problems [13,33,34].

According to Sonino et al. in hirsute women, the decline in the quality of life is due to the high level of psychological distress and interpersonal fears that are manifested by social phobias and anxiety-evoking situations such as meeting strangers, partying, shopping [35]. In these patients, significantly higher scores of negative mood and empathy were noted, however, correlations of mood disorders with severity of hirsutism or total testosterone levels had not be found [36].

Most cohort studies have shown that anxiety and depression may be higher than expected. At the same time, women with PCOS experience a higher frequency of depressive episodes, social phobia, eating disorders and suicide attempts compared with controls [37–39].

In a recent systematic review has been suggested that women with PCOS had increased odds of any depressive symptoms (OR: 3.78; 95% CI: 3.03–4.72; 18 studies) and of moderate/severe depressive symptoms (OR: 4.18; 95% CI: 2.68–6.52; 11 studies). Women with PCOS had increased odds of any anxiety symptoms (OR: 5.62; 95% CI: 3.22–9.80, nine studies) and of moderate/severe anxiety symptoms (OR: 6.55; 95% CI: 2.87, 14.93; five studies). The authors conclude that women with PCOS and comorbid depression had higher mean values of age, BMI, hirsutism index, and insulin resistance index [34]. Some papers show a correlation relationship depression scores with insulin resistance, lipid parameters, severity of metabolic syndrome [40].

In a recent study by Tan et al., mental health (MH) was evaluated in 120 women with PCOS and 100 healthy women. The prevalence of anxiety and depression (13.3% versus 2.0% and 27.5% versus 3.0%, respectively) was higher in patients with PCOS compared to controls ($p < .05$) [30]. Obesity, insulin resistance, and elevated androgens may partly contribute to this association [41].

In a study by Barry et al. assessing possible mechanisms of action of hyperandrogenism on the psycho-emotional sphere and the quality of life detected a significantly higher level of anxiety, less resistance to stress, and impaired quality of life in PCOS patients compared with healthy women [42]. Interestingly, there was no correlation between the level of testosterone and the manifestations of neuroticism in patients with PCOS. Increased testosterone levels explained problems in the psycho-emotional sphere only in 4% of scoring in neuroticism, whereas clinical hyperandrogenism (hirsutism, acne, menstrual cycle dysregulation) explained up to 25%. Therefore, the disorders in the psycho-emotional sphere are caused more by the indirect activation effect of testosterone than by its plasma concentration. Therefore, clinical hyperandrogenism itself can directly influence behavioral and emotional processes [43], provoking depression (4 times more often than in the population), emotional lability, anxiety and aggressiveness (7 times higher than the population) [44–46]. In agreement with this concept, Cooney et al. found a positive correlation between depression scores and hirsutism scores [34]. It is noteworthy that the most often reported symptoms of depression in women with PCOS were daily fatigue, sleep disturbances, and diminished interest [47].

PCOS patients are a greater risk for eating disorders such as anorexia nervosa, bulimia nervosa, and binge eating disorder. Some authors have suggested that eating disorders are observed in 21% of women with PCOS [48]. According to Lee et al. women with PCOS and symptoms of depression and anxiety are at higher risk of having eating disorders compared with women with PCOS but without anxiety or depressive symptoms [49].

The issue of the severity of depression manifestation and quality of life among different PCOS phenotypes is a controversial topic. Shi et al. noted significantly higher depression subscales scores in women with PCOS with infertility compared with women with PCOS without infertility [50]. Deeks et al. in turn, did not reveal a significant difference in depression scores in women with PCOS with and without infertility [51].

The relationship of increased BMI and depression scores in women with PCOS is confirmed by several studies [34,52]. Dokras et al. noted a significantly higher prevalence of moderate and severe depressive symptoms in women with PCOS compared with controls. However, they did not find the dependence of increased prevalence of depressive symptoms with BMI [17].

Sexuality in women with PCOS

The women's sexual function is provided by a balanced interaction of many factors. Endocrine disorders, discomfort in emotional and social spheres can cause sexual dysfunction. The feeling of unattractiveness due to hyperandrogenic dermopathy and overweight may lead to a decrease in a woman's self-esteem and cause problems in sexual relations with partners [18]. Problems in the sexual sphere were identified in more than 30% of women with PCOS being obesity largely predominant (89%) among complainers [26]. According to Trent et al., girls with PCOS are 2.8 times less likely to have sex compared with controls [53]. Most recent studies on sexuality and PCOS are recorded in Table 3.

In order to rule out the role of obesity among PCOS, Ferraresi et al., assessed sexual function in women with PCOS with laboratory confirmed hyperandrogenism using the Female Sexual Function Index (FSFI). The two control groups included

Table 2. Psychological morbidity among PCOS women.

Author and year of publication	Sample	Questionnaire	Outcomes	Conclusion
Stapinska-Syniec et al. 2018 [26]	$N = 250$ (PCOS)	BDI	Moderate depression in 25% (62/250) Severe depression 11% (26/250), extreme depression 3%(7/250)	The prevalence of depression is very high in PCOS women
Borghi et al. 2018 [28]	$N = 30$ (PCOS) $N = 30$ (control)	SCL-90-R STAXI-2	Depression 0.70 (PCOS) vs 0.48 (CG) Anxiety 0.45 (PCOS) vs 0.20 (CG)	The prevalence of depression and anxiety is significantly higher in PCOS group, than in CG, $p < .01$
Tan et al. 2017 [30]	$N = 120$ (PCOS) $N = 100$ (control)	BDI GHQ-12 State-Trait Anxiety Inventory	Anxiety 13.3% in PCOS vs. 2.0% CG Depression 27.5% vs. 3.0%	The prevalence of depression and anxiety is significantly higher in PCOS group, than in CG, $p < .05$
Lee et al. 2017 [49]	$N = 148$ (PCOS) $N = 106$ (Control)	EDE-Q NEQ HADS	HADS score, mean ± SD Anxiety 9.41 ± 5.08 PCOS 6.72 ± 3.87 CG, Depression 4.84 ± 4.22 vs 3.09 ± 3.21, Abnormal EDE-Q score 18 (12.16) vs 3 (2.83),	The prevalence of depression, anxiety, eating disorders is significantly higher in PCOS group vs CG, $p < .01$
Asik et al. 2015 [31]	$N = 71$ (PCOS) $N = 15$ (control)	HADS TEMPS-A	Depression 42.3% PCOS vs 14% in CG Anxiety 35.2% vs 12%	The prevalence of depression and anxiety is significantly higher in PCOS group, than in CG, $p < .01$
Annagür et al. 2015 [32]	$N = 88$ (PCOS)	Structured Clinical Interviews for the Diagnostic and Statistical Manual of Mental Disorders	Major depression in 50% of patients, anxiety 13.6%	The prevalence of depression and anxiety is high in PCOS group
Hart et al. 2015 [37]	$N = 2566$ (PCOS) $N = 25660$ (CG))	Hospitalizations by ICD-10-M diagnoses	Stress/anxiety 14.0 % in PCOS vs 5.9% in CG, Depression 9.8% vs 4.3%	The prevalence of depression and anxiety is significantly higher in PCOS group vs CG, $p < .001$
Deeks et al. 2011 [16]	$n = 177$ (PCOS) $n = 109$ (GC)	HADS PCOSQ	Anxiety scores (mean ± SD) PCOS 9.5 ± 3.9 vs CG 6.5 ± 3.6 Depression PCOS 5.7 ± 3.7 vs CG 3.3 ± 3.1,	The prevalence of depression and ʙcanxiety is significantly higher in PCOS group, than in CG, $p < .001$
Cinar et al. 2011 [40]	$N = 226$ (PCOS) $N = 85$ (control)	BDI STAI HADS GHQ	Clinically significant depression in 28.6% of PCOS women vs 4.7% of CG HADS subscales mean scores 9.3 ± 4.3 (PCOS) 6.4 ± 4.1 (control)	The prevalence of depression and anxiety is significantly higher in PCOS group vs CG, $p < .001$
Deeks et al. 2010 [51]	$N = 25$ (PCOS fertile) $N = 22$ (PCOS infertile)	PCOSQ HADS	Anxiety score (mean ± SD) 8.6 ± 3.6 (fertil) vs 10.2 ± 5.1 (infertile), Depression score 3 (1–7) (fertile) vs 6 (3–9) (infertile)	The prevalence of depression is significantly higher in PCOS group with infertility vs fertile PCOS group, $p < .05$ Anxiety – difference NS
Mansson et al. 2008 [48]	$N = 49$ (PCOS) $N = 49$ (control)	MINI	Psychiatric disorders Major depressive episode 67% in PCOS vs 35% CG Suicide attempt: 14% vs 2%, Social phobia: 27% vs 2%, Generalized Anxiety: 13% vs 2%, Any eating disorder: 21% vs 4%,	The prevalence of psychiatric disorders is significantly higher in PCOS group vs CG, $p < .05$
Barnard et al. 2007 [13]	$n = 369$ (PCOS) $n = 860$ (control)	The Zung self-rating depression scale	Depression in PCOS 55% vs CG 45%,	The prevalence of depression is significantly higher in PCOS group, than in CG, $p < .001$
Ching et al. 2007 [20]	$n = 173$ (PCOS) $n = 694$ (control)	GHQ-28 PIQ	Psychological morbidity i PCOS 62.4% (95% CI 55.0–69.3) CG 26.4% (95% CI 23.2–29.7)	Psychological morbidity is significantly higher in PCOS group, than in CG, $p < .0001$
Hollinrake et al. 2007 [47]	$N = 103$ (PCOS) $N = 103$ (control)	PRIME-MD PHQ BDI	BDI mean scores ± SD PCOS 11.9 ± 11.1 vs CG 4.5 ± 5.9,	The prevalence of depression is significantly higher in PCOS group vs CG, $p < .001$

N: observations; CG: control group; HADS: The hospital Anxiety and Depression scale; PCOSQ: Polycystic Ovary Syndrome Questionnaire; GHQ: General Health Questionnaire; PIQ: Personality Inventory Questionnaire; BDI: Beck Depression Inventory; SCL-90-R: Symptom checklist-90-revised; STAXI-2: State-Trait Anger Expression Inventory-2; TEMPS-A: Temperament Evaluation of Memphis, Pisa and san Diego Auto; STAI - State-Trait Anxiety Inventory; ICD-10: International Statistical Classification of Diseases and related Health Problems; PHQ: Patient Health Questionnaire; EDE-Q: Eating Disorder Examination Questionnaire; NEQ: Negative Effects Questionnaire; NS: Not Significant.

obese patients without PCOS and normal weight healthy women. Subjects with PCOS, regardless of body mass index had borderline scores compared to controls, who had normal FSFI. It is to note that no association was found between body mass index, the presence of PCOS, testosterone level, and FSFI scores [54].

In an attempt to evaluate the relationship between hormonal profiles and sexual function, Noroozzadeh et al., determined androgen levels and FSFI in women with and without polycystic ovary syndrome. Although no significant differences were observed in FSFI scores, both in total and specific domains, between women with PCOS and controls a significant positive correlation between dehydroepiandrosterone sulfate level and total FSFI, orgasm and satisfaction domains in controls was found [55].

Table 3. Studies assessing sexual function in women with PCOS.

Author and year of publication	Sample	Questionnaire	Outcomes	Conclusion
Norozzadeh et al. 2017 [55]	$N = 63$ (PCOS) $N = 216$ (Control)	FSFI	Total score PCOS 23.70 (18.20–28.00) CG 25.25 (20.22–28.50), p=.31	No significant difference in sexual function in PCOS group and CG
Shafti et al. 2016 [56]	$N = 129$ (PCOS) $N = 125$ (control)	FSFI WHOQOL-BREF	Subscales mean ± SD scores Desire 6.55 ± 1.68 (PCOS) vs 6.18 ± 1.56 (CG) Arousal13.38 ± 4.73 vs 12.74 ± 3.92 Lubrication 13.92 ± 4.64 vs 13.72 ± 4.13 Orgasm 11.53 ± 4.12 vs 10.81 ± 3.55 Satisfaction 12.19 ± 4.18 vs 11.40 ± 3.75 Pain 10.80 ± 4.16 vs 10.57 ± 3.82	No significant difference in sexual function in PCOS group and CG for all subscales, $p > 0.05$
Lara et al. 2015 [39]	$N = 43$ (PCOS) $N = 51$ (control)	FSFI	Total score mean ± SD PCOS 20.08 ± 9.43 vs Control 21.21 ± 9.64	No significant difference in sexual function in PCOS group and CG
Ferraresi et al. 2013 [54]	$N = 24$ (nonobese PCOS) $N = 24$ obese PCOS) $N = 19$ (nonobese CG) $N = 16$ (obese CG)	FSFI	Total score (mean ± SD) NOPCOS 26.45 ± 4.47 OPCOS 26.57 ± 5.15 NOC 27.18 ± 6.03 OC 23.95 ± 7.17,	No significant difference in sexual function in PCOS group and CG
Battaglia et al. 2008 [59]	$N = 25$ (PCOS) $N = 18$ (controls)	MFSQ BDI	MFSQ > 35 (sexual disfunction) PCOS 4% vs 11% in CG Depression PCOS 20% vs 16% in CG controls	The prevalence of sexual disfunction and depression is significantly higher in PCOS group vs CG, $p < 0.05$

N: observations; CG: control group; BDI: Beck Depression Inventory; FSFI: Female Sexual Function Index; NOPCOS: Non obese PCOS patients; OPCOS: Obese PCOS patients; NOC: Non obese Controls; OC: Obese Controls; MFSQ: McCoy Female Sexuality Questionnaire.

Shafti et al. evaluated the quality of life and sexual function among Iranian women with PCOS and they did not find differences in FSFI subscales comparing with healthy women. However, except for environment domain all quality of life subscales were significantly lower in PCOS group than in controls [56].

A recent systematic review and meta-analysis on sexual function in women with PCOS including 18 studies with validated sexual function questionnaires and visual analog scales reported a minor but significant effect on sexual function subscales (total score: $p = .006$; arousal: $p = .019$; lubrication: $p = .023$; satisfaction: $p = .015$; orgasm: $p = .028$) of this condition compared with healthy controls. In addition, excessive body hair growth impaired sexual function ($p = .006$); social appearance ($p = .007$) and sexual attractiveness ($p < .001$) [57]. Interestingly, in this study satisfaction with the sexual life was observed impaired among PCOS women ($p < .001$) who reported fewer sexual thoughts and fantasies than healthy controls.

The role of androgens and its clinical effects on sexual function is still controversial [58] and some authors suggest that moderate hirsutism and hyperandrogenism do not induce the sense of loss of feminine identity and have no impact on sexual self-worth and sexual satisfaction [59].

Effects of PCOS treatment on quality of life, sexuality and mental health

The different options for PCOS treatment should be individualized depending on clinical manifestations, needs, and preferences of each patient. Goals of such therapies are to improve health outcomes and quality of life as well [60].

Lifestyle change is a priority in the management of PCOS since even moderate changes in the lifestyle and slight weight loss have demonstrated to restore ovulatory cycles, increase fertility and improve quality of life [61,62]. In a recent 24-weeks study by Dokras et al., improvements in quality of life, depressive symptoms, and anxiety disorders among patients with PCOS have been achieved with diet, exercise, and psychological support [12].

The use of hormonal contraception has been related with improvements in specific domains of PCOS QoL questionnaires but not in all. In this sense, one large study assessing the effect of oral contraceptives on emotional distress, anxiety and depression in women with polycystic ovary syndrome after 6 months of use showed an improvement on body hair growth and menstrual irregularities; however, the level of depression remained unchanged [63].

In the clinical picture of PCOS, anxiety and depression symptoms increase the risk of adverse effects on psychological health, which is an important component of self-esteem and a healthy lifestyle for patients in this category [24,64]. Mental disorders, including depression or anxiety, interfere with lifestyle changes, causing chronic process and social maladjustment [64].

Given the importance of mental health, recent studies have suggested that not enough attention has been paid to the mental health of women with PCOS and emphasize the need to assess and manage mental health among this group of women [37–39,65,66].

It is assumed that addressing mental health problems and determining the needs of patients should be a routine part of assessing the complex health status of women with PCOS in a clinical setting [67,68]. For this reason the American Association of Clinical Endocrinologists, the American College of Endocrinology, and the Androgen Excess and PCOS Society in their guide for evaluation and Treatment of PCOS patients recommend that all women with this syndrome should be screened for anxiety and depressive disorders during the initial examination and its use at further stages of treatment and after it [69].

Conclusion

Polycystic ovary syndrome remains one of the most pressing problems and a challenge for many gynecologists. Clinical complaints of androgen excess, problems with the onset of pregnancy, dissatisfaction with appearance and low self-esteem cause

a high prevalence of mood disturbances and reduced quality of life among women with PCOS. Additionally, many authors report impairments in the sexuality of such patients. Recently, evidence has emerged about the relationship between eating disorders and PCOS, as well as the high prevalence of other endocrine disorders in this population group. Further studies on quality of life and psychological comfort in PCOS are necessary to optimize the care of such patients and minimize complications.

Disclosure statement

The authors report no conflicts of interest.

ORCID

Camil Castelo-Branco http://orcid.org/0000-0002-9860-8318
Iuliia Naumova http://orcid.org/0000-0002-4220-1236

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Working Hypothesis

Women with infertility due to PCOS may present with impaired quality of life and are more prone to development of depressive, anxiety symptoms and sexual dysfunction compared with women reporting other infertility cause.

Predisposing factors affecting quality of life and psychological well-being in PCOS patients are still controversial, however, external manifestations of the syndrome may be play the key role.

Objectives

- To investigate general health-related quality of life (QoL) of infertile PCOS patients and women of two reference groups: with tubal factor infertility (TFI) and a group of women with male factor infertility (MFI) (Article 2)
- To evaluate the disease-specific QoL related to PCOS in group of infertile PCOS patients (Article 2)
- To analyze the association between the clinical/biochemical features of PCOS and the physical/psychological well-being of infertile patients with PCOS (Article 2 and 3)
- To assess the prevalence of anxiety and depressive symptoms in infertile PCOS women compared with patients with other infertility cause (Article 3)
- To analyze the contribution of infertility course in adverse psychological state (Article 3)
- To identify factors predisposing to development of anxiety and depressive symptoms in PCOS infertile women (Article 3)
- To assess sexual functioning in women with infertility due to PCOS compared with women presenting with TFI and MFI. If a reducing of sexual function takes place, to identify the predisposing factors (Article 3)

Investigations conducted. Material and Methods. Obtained Results

The study design, the study sample, as well as the methodology used are detailed in the sections of «Material and Methods» of each of the articles that constitute the doctrinal body of this Doctoral Thesis.

These articles are included below as they have been accepted for publication or published in the scientific literature.

Article 2

Quality of Life in Infertile Women with Polycystic Ovary Syndrome: a Comparative Study

Iuliia Naumova, Camil Castelo-Branco, Iuliia Kasterina, Gemma Casals

Article has been accepted for publication in **Reproductive sciences**

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Reproductive Sciences provides a multi-discipline perspective, including all aspects of basic reproductive biology and medicine, maternal-fetal medicine, obstetrics, gynecology, reproductive endocrinology, urogynecology, fertility/infertility, embryology, gynecologic/reproductive oncology, developmental biology, stem cell research, molecular/cellular biology and other related fields.

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Reproductive Sciences is the official publication of The Society for Reproductive Investigation (SRI) whose mission is the advancement of knowledge in reproductive biology.

- Impact Factor (IF) **2.616 (2019)**
- 5 year Impact Factor **2.601 (2019)**
- It is located in the beginning of the second quartile of the specialty of Obstetrics and Gynecology (position 26/82), according to the Journal Citation Reports 2019®.

Article 2 responds to the following objectives:

- To investigate general health-related quality of life of infertile PCOS patients in comparison with women presenting with other infertility causes
- To evaluate the disease-specific quality of life related to PCOS in group of infertile PCOS patients
- To analyze the association between the clinical and biochemical features of the syndrome and the physical/psychological health of infertile patients with PCOS

Reproductive Sciences
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REPRODUCTIVE ENDOCRINOLOGY: ORIGINAL ARTICLE

Quality of Life in Infertile Women with Polycystic Ovary Syndrome: a Comparative Study

Iuliia Naumova[1,2] · Camil Castelo-Branco[3] · Iuliia Kasterina[4] · Gemma Casals[3]

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Abstract

To investigate the quality of life (QoL) of infertile women with polycystic ovary syndrome (PCOS) and analyze the association between the clinical/biochemical features of PCOS and the physical/psychological well-being of patients. An observational study with three independent groups women was designed including 37 infertile PCOS patients, 36 women with tubal factor infertility, and 31 women with male factor infertility referred to the Reproductive Medicine Unit of the Hospital Clinic Barcelona from December 2017 to June 2019. Clinical history, physical examination including Ferriman-Gallwey scores, and vaginal ultrasound were carried out in all patients. All subjects completed the 36-item Short Form Health Survey, and PCOS patients were asked to fill out the Polycystic Ovary Syndrome Questionnaire. The IBM SPSS 23.0 was used for the statistical analysis. Infertile women with PCOS reported significantly worse QoL scores of social functioning ($p = 0.049$), emotional role functioning ($p = 0.041$), mental health ($p = 0.002$), and the mental component summary ($p = 0.002$) compared with women with other causes of infertility. In addition, body pain ($p = 0.006$), general health ($p < 0.001$), and vitality ($p = 0.002$) scores were significantly lower in women with PCOS compared with those with male factor infertility. Infertile PCOS patients showed low scores in all domains of the PCOSQ. Hirsutism and weight gain were the factors most associated with impaired health-related QoL in PCOS. Infertile PCOS women presented worse QoL mainly due to psychological and emotional distress. The main predictors were clinical manifestations of hyperandrogenism and weight gain.

Keywords PCOS · Infertility · Quality of life · Hirsutism · Hyperandrogenemia · PCOSQ, SF-36

Introduction

The widespread prevalence of polycystic ovary syndrome (PCOS) among women of reproductive age [1, 2], as well as the data available on their high risk for developing anxiety and depressive disorders [3–5] highlight the relevance of studying the quality of life (QoL) and the psychological well-being of these women.

PCOS has been the subject of countless scientific studies. More than 10,000 articles in the National Library of Medicine

The study was registered at clinicaltrials.gov; identifier: NCT03306459, https://clinicaltrials.gov/ct2/show/NCT03306459?cond=PCOS&cntry=ES&city=Barcelona&draw=2&rank=3

✉ Camil Castelo-Branco
castelobranco@ub.edu

Iuliia Naumova
jvnaumova@list.ru

Iuliia Kasterina
Julli_s@mail.ru

Gemma Casals
GCASALS@clinic.cat

[1] Faculty of Medicine and Heatlh Sciences, PhD Program, University of Barcelona, Barcelona, Spain

[2] Faculty of General Medicine, Department of Obstetrics and Gynecology, Saratov State Medical University n.a. V.I. Razumovsky, Saratov, Russia

[3] Clinic Institute of Gynecology, Obstetrics and Neonatology. Hospital Clinic Barcelona, Faculty of Medicine-University of Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Villarroel 170, 08036 Barcelona, Spain

[4] Reproductive Health Department, State Institution Clinical Perinatal Centre of the Saratov Region, Saratov, Russia

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(PubMed) address different aspects of PCOS, most of which are devoted to the study of objective clinical manifestations and biochemical parameters. Of note, however, is the scarce information on the QoL, subjective experiences related to the disorder, and psychological complaints of women with this syndrome. Some of the difficulties in studying these circumstances include the intimate nature of this area of research and the insufficient development of a holistic approach for the assessment of these parameters [6].

Along with hormonal, reproductive, and metabolic disorders, in recent years there has been increasing evidence that PCOS is significantly associated with a reduction in health-related QoL and impaired mental health [1, 6–8]. According to several studies, the QoL of women with PCOS is largely determined by the clinical features of this syndrome and is affected by depressive symptoms, anxiety, poor body image, and low self-esteem [7, 9–12].

Subfertility and infertility are serious psychological distress factors. Of note, more than half of women suffering from infertility face the risk of depressive, anxiety disorders, and social dysfunction [13, 14]. Withal in PCOS infertile patients, typical physical manifestations of hyperandrogenism may also negatively affect self-esteem, social functioning, and psychological comfort. It is noteworthy that more than 65% of patients report that PCOS affects their everyday life, and more than 50% report that this condition disturbs their relationships with others [4].

Most of the studies on health-related QoL in patients with PCOS have been carried out in women who do not have immediate plans for pregnancy. As a rule, these women have taken combined oral contraceptives (COCs) for a long time, which, together with lifestyle changes, may improve QoL [15, 16]. Additionally, it should be noted that the possible impact of COCs and other drugs (i.e., those that modulate carbohydrate metabolism) on QoL and psychological status is often neglected, and therefore, many of the surveys carried out do not exclude respondents who take medications, and this may induce data bias. The current investigation was therefore undertaken to investigate the QoL of infertile women with PCOS and analyze the association between the clinical/biochemical features of PCOS and the physical/psychological well-being of patients with PCOS and two comparator groups: one with tubal factor infertility (TFI) and a control group of women with male factor infertility (MFI).

Methods

Sample

In order to avoid the effect of hormonal therapies in women with PCOS, 46 women with this syndrome aged 18 to 40 referring infertility and meeting the Rotterdam criteria were recruited at the Reproductive Medicine Unit of the Hospital Clinic Barcelona from December 2017 to June 2019. The flow chart of participants is shown in Fig. 1. Using a statistical software to calculate sample size used (SPSS SamplePower 3.0.1, Armonk, NY: IBM Corp.) and assuming that the mean difference in SF-36 scores is 20,0 (corresponding to means of 79,0 versus 59,0) and the common within-group standard deviation is 26,6 (based on SD estimates of 30,0 and 23,0) [17] with a maximum acceptable error of 5%, we obtained a sample size of 96 cases for two groups with a 95% confidence. Since infertility and other PCOS-related symptoms have an enormous impact on QoL and psychological well-being, we decided to compare women with PCOS with two control groups: 50 women with TFI and 31 healthy women with

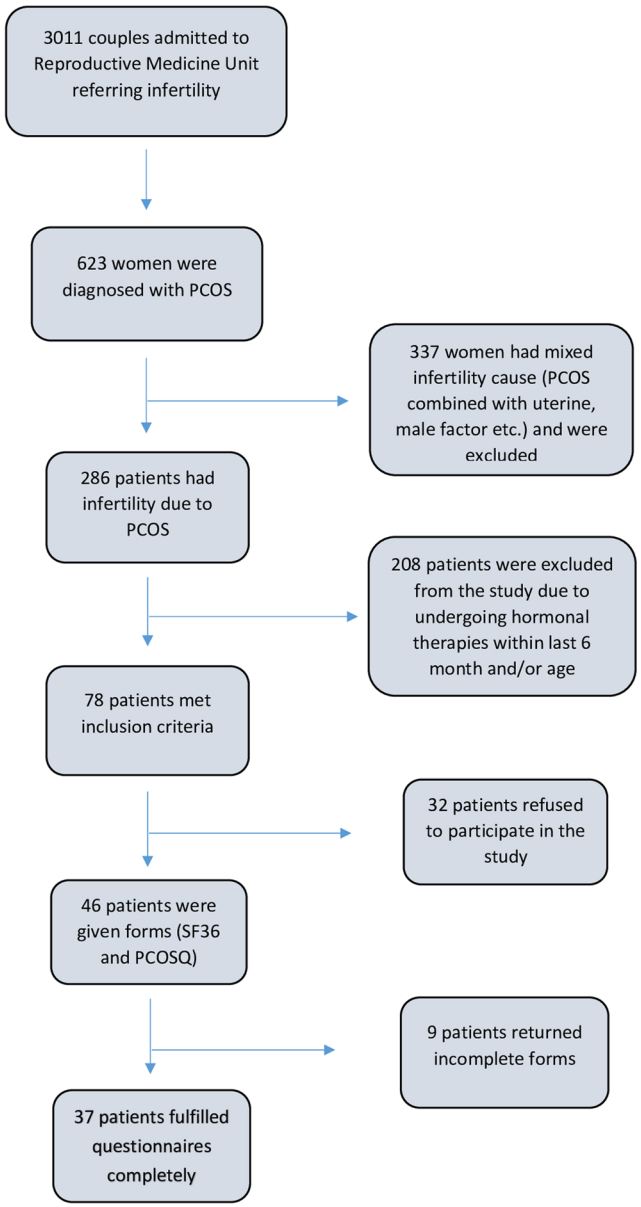

Fig. 1 The flow chart of participants of study group

MFI. These two groups were constituted by women fulfilling inclusion criteria and attending our fertility clinic immediately after PCOS patients. None of the women in the comparator groups had any extragenital pathology.

Methods

A comparative study of three independent groups was designed: PCOS, TFI, and MFI. Anthropometric characteristics, transvaginal ultrasound, and laboratory data, including the free testosterone level, sex hormone-binding globulin in serum and the free testosterone index were recorded in all the participants. The severity of hirsutism was assessed using the Ferriman-Gallwey scoring method (F/G score) with scores ranging from 0 to 36. Scores of 8 or higher were considered as having hirsutism [18].

All participants were asked to complete the Short Form Health Survey (SF-36), and patients with PCOS were also requested to complete the Polycystic Ovary Syndrome Questionnaire (PCOSQ) on health-related QoL in women with PCOS.

Subjects were informed of the study characteristics and that the data obtained from questionnaires would be entered into a database with an identifier code, ensuring patient anonymity. Women who accepted to participate provided written informed consent and completed the questionnaires alone without assistance.

Health-Related Quality of Life Questionnaires

General health-related QoL was assessed using the SF-36 questionnaire that has been adapted for the Spanish-speaking general population [19]. The SF-36 questionnaire consists of 36 self-administered questions that reflect the overall self-esteem of health over the past year. The items are designed to measure health status in eight domains, covering both physical and mental health. The physical component summary (PCS) includes four domains: physical functioning (ten questions), physical role functioning (four questions), body pain (two questions), and general health (five questions). The mental component summary (MCS) includes four domains: vitality (four questions), emotional role functioning (three questions), social functioning (two questions), and mental health (five questions).

Domain scores range from 0 to 100, with higher scores indicating a better health status. The SF-36 was scored according to the equivalence of the SF-36 summary health scores estimated using standard and country-specific algorithms in Spain, according to the results of the International Quality of Life Assessment (IQOLA) Project [20]. The results for each domain were calculated to give an average score for each domain. Afterwards the result of the domain was normalized by subtracting the average of the Spanish population and divided by its standard deviation.

The disease-specific QoL related to PCOS was evaluated with the PCOSQ [21]. This questionnaire consists of 26 items that measure five domains of PCOS-specific symptoms within the previous 2 weeks, including emotions (8 items), body hair (5 items), weight (5 items), infertility problems (4 items), and menstrual problems (4 items). Each question requires an answer on a 7-point Likert scale, with lower scores indicating more impairment.

Statistical Analysis

The IBM SPSS Program (SPSS 23.0, SPSS Inc. Headquarters, 223 South Wacker Drive, Chicago, IL 60606, USA) was used for the statistical analysis. Descriptive analysis was expressed in frequencies and percentages (qualitative variables) or reported as mean and standard deviation (quantitative variables). Normality was assessed by the Kolmogorov-Smirnov test. As data was not normally distributed, non-parametrical tests were used. The Kruskal–Wallis and Mann–Whitney *U*-tests were used for the analysis of quantitative data and the chi-square test was used for the analysis of qualitative data. For correlation analysis, the correlation was used. A p value less than 0.05 was considered statistically significant. Given the need for multiple comparisons, Bonferroni correction was used to control a group error probability. Thus, significance values were adjusted by the Bonferroni correction for multiple tests ($p < 0.0167$ according to Bonferroni correction; 0.05/3 = 0.0167).

Results

The baseline characteristics of the subjects who returned the questionnaires are shown in Table 1. The mean age of the women included in the study was 31.47 ± 5.36 years. No significant differences were found in age ($p = 0.56$) between groups. PCOS patients showed a significantly higher body mass index (BMI) ($p = 0.01$) due to greater proportion of overweight participants (45.9 vs. 19.4 and 12.9%, respectively, $p = 0.019$). Menstrual cycle disorders were reported by 86.5% of respondents in the PCOS group. Approximately, two thirds of the women with PCOS (70.3%) presented clinical features of hirsutism, with mean F/G scores of 11.81 ± 0.52. The mean level of free testosterone in the blood serum of women with PCOS was 37.36 ± 17.3 ng/dl, being significantly higher than that of the women in the other two groups ($p = 0.001$).

PCOS subjects showed significantly worse QoL scores in social functioning ($p = 0.049$), emotional role functioning ($p = 0.041$), mental health ($p = 0.002$), and the MCS ($p = 0.002$) compared to the women with TFI (Table 2). No significant differences were found in either the PCS or in any individual physical domains between PCOS and TFI subjects. On

Table 1 Clinical and anthropometrical characteristics of the three study groups

Characteristics	PCOS	TFI	MFI
Patients completing the questionnaires	37 (80.5%)	36 (72%)	31 (100%)
Mean age (SD)	32 ± 5.05	30.58 ± 6.27	31.87 ± 4.55
Married or with partner	37	36	31
Mean BMI (SD)	24.91 ± 3.59[a,b]	23.12 ± 2.79	22.49 ± 2.95
Patients with BMI > 25	20 (54.1)[a,b]	8 (22.2)	4 (12.9)
Patients with menstrual disorders	32 (86.5)	0	0
Patients with hirsutism	26 (70.3)	0	0
Mean serum testosterone free level, ng/dl (SD)	37.36 ± 17.3[a,b]	26.95 ± 7.3	26.48 ± 7.23
Patients with hyperandrogenemia	7 (18.9)	0	0
Mean F/G scores of hirsute patients	11.81 ± 0.52		

Comparisons between groups were performed using Kruskal–Wallis with Bonferroni correction, while a binomial test was used to compare percentages. Data from completers sample. Results are given as mean ± standard deviation and as total numbers and percentages. p values < 0.0167 are statistically significant

[a] $p < 0.0167$ difference vs TFI group

[b] $p < 0.0167$ difference vs MFI group

the other hand, in comparison with healthy women with MFI, patients with PCOS had significantly lower scores in the domains of body pain ($p = 0.006$), general health ($p < 0.001$), vitality ($p = 0.002$), social functioning ($p = 0.001$), emotional role functioning ($p < 0.001$), mental health ($p < 0.001$), and the MCS ($p < 0.001$).

It should be noted that the scores in the domains characterizing the psychological health of the respondents were significantly worse in women with PCOS compared to those with TFI or MFI, and the women with TFI had worse score than women with MFI (Table 3).

In relation to the PCOSQ scores on health-related QoL among women with PCOS (Fig. 2), it was of note that low scores were found in all PCOSQ domains, the lowest domains being infertility problems (3.51 ± 1.11 out of 7) and emotions (4.36 ± 1.32 out of 7). After adjusting the data for clinical variables, it was found that hirsutism ($p < 0.001$) and weight concerns ($p < 0.001$) had the strongest impact on the patients' health-related QoL. The emotions scores did not depend on the age of the subjects, but were significantly lower in respondents with a BMI > 25 ($p = 0.002$), menstrual

Table 2 Comparison of SF-36 domain outcomes among the PCOS group, tubal factor infertility (TFI) patients, and women with male factor infertility (MFI)

SF-36 domains	PCOS ($n = 37$)	TFI ($n = 36$)	MFI ($n = 31$)	Adj. sig.
Physical functioning	92.6 ± 7.3	92.8 ± 7.8	96.1 ± 4.4	NS
Role-physical functioning	64.2 ± 30.4	76.4 ± 29.2	79.8 ± 26.9	0.047
Bodily pain	78.2 ± 22.3[c]	81.1 ± 21.6	92.4 ± 13.2[a]	0.006
General health	75.4 ± 11.0[c]	79.6 ± 9.1	85.2 ± 9.6[a]	0.0001
Vitality	83.5 ± 9.1[c]	85.3 ± 6.9[c]	90.5 ± 7.7[a,b]	0.002
Social functioning	81.1 ± 18.5[b,c]	90.3 ± 11.6[a]	94.0 ± 9.6[a]	0.001
Role-emotional functioning	58.6 ± 29.8[b,c]	75.9 ± 24.7[a,c]	91.4 ± 14.8[a,b]	0.0001
Mental health	74.9 ± 13.1[b,c]	85.6 ± 12.1[a,c]	93.2 ± 5.8[a,b]	0.0001
Physical component	51.5 ± 5.8	51.3 ± 6.4	52.6 ± 4.7	NS
Mental component	49.0 ± 6.2[b,c]	54.8 ± 5.9[a,c]	58.9 ± 4.0[a,b]	0.0001

Results are given as mean ± standard deviation

Kruskal–Wallis and Mann–Whitney U test, p values < 0.05 are statistically significant

NS not significant

Significance values have been adjusted by the Bonferroni correction for multiple tests

[a] $p < 0.05$ difference vs PCOS group

[b] $p < 0.05$ difference vs TFI group

[c] $p < 0.05$ difference vs MFI group

Table 3 Pairwise comparisons of SF-36 domain outcomes among the PCOS group, tubal factor infertility (TFI) patients, and women with male factor infertility (MFI)

SF-36 domains	Sample	Sig.	Adj. sig.
Role-Physical functioning	PCOS-TFI	NS	NS
	PCOS-MFI	0.021	NS
	TFI-MFI	NS	NS
Bodily pain	PCOS-TFI	NS	NS
	PCOS-MFI	0.002	0.006
	TFI-MFI	0.017	NS
General health	PCOS-TFI	NS	NS
	PCOS-MFI	0.000	0.000
	TFI-MFI	0.023	NS
Vitality	PCOS-TFI	NS	NS
	PCOS-MFI	0.001	0.002
	TFI-MFI	0.015	0.046
Social functioning	PCOS-TFI	0.016	0.049
	PCOS-MFI	0.000	0.001
	TFI-MFI	NS	NS
Role-emotional functioning	PCOS-TFI	0.014	0.041
	PCOS-MFI	0.000	0.000
	TFI-MFI	0.013	0.039
Mental health	PCOS-TFI	0.001	0.002
	PCOS-MFI	0.000	0.000
	TFI-MFI	0.014	0.043
Mental component	PCOS-TFI	0.001	0.002
	PCOS-MFI	0.000	0.000
	TFI-MFI	0.005	0.016

Significance values have been adjusted by the Bonferroni correction for multiple tests

NS not significant

disorders ($p = 0.017$), as well as in women with clinical ($p = 0.004$) and biochemical ($p = 0.029$) manifestations of hyperandrogenism (Table 4).

Correlation analysis showed that the PCOSQ total score was correlated with SF-36 MCS scale and was negatively correlated with the main clinical manifestations of the syndrome ($p = 0.01$ for hirsutism and overweight, $p = 0.05$ for menstrual irregularities) (Table 5). PCOSQ scores in the emotional domain significantly correlated with the SF-36 MCS scale, hirsutism, overweight, and menstrual irregularities.

Discussion

The present study provides a comprehensive exploration of health-related QoL in infertile women with PCOS.

Main Findings

Infertile patients with PCOS have shown significantly worse QoL scores in domains, characterizing mental health, compared with subjects with other causes of infertility. In addition, body pain, general health, and vitality scores were significantly lower in women with PCOS compared with those with male factor infertility. Significant differences in the domains scores, describing physical health were not detected between groups of patients with endogenous infertility. Infertile PCOS patients reported low scores in all domains of the PCOSQ. Correlation analysis showed that hirsutism and weight gain were the factors most associated with impaired health-related QoL in PCOS.

According to previous studies, clinical features associated with PCOS, especially hirsutism and obesity, play the greatest role in reducing QoL and self-perception [22, 23] as they largely interfere with outer appearance and social norms [1].

The relative value of the clinical features of PCOS on QoL is controversial. Weight excess, regardless of other clinical manifestations, can significantly impair the QoL of PCOS women and cause mood disorders [24]. Recent data suggest that the BMI is a good predictor of physical functioning scores measured by the SF-36 [25, 26]. In contrast, according to other authors, fertility problems (31%) have the leading impact on QoL, having a greater impact than obesity (19%) or hirsutism (18%) [4], while other studies report that hirsutism and menstrual irregularities [9] were key complaints affecting the QoL of women with PCOS. On the other hand, some evidence has suggested that poor QoL in these women might be due to reproductive problems and obesity [5]. Additionally, some data confirm the highest effect of PCOS symptoms on HRQOL impairment exerted by self-esteem, body image, and sexual function [27].

One of the main findings of our study is that patients with PCOS had significantly worse scores in the mental health component measured by the SF-36 questionnaire compared with respondents with other infertility causes. Low scores in mental domains indicate impairment of the emotional state of the respondents, inducing a significant limitation of social contacts, a decrease in the level of communication with others, and the possible presence of depressive and anxiety disorders.

Clinical manifestations of androgen excess and weight gain can lead women with PCOS to be dissatisfied with their appearance, make them feel unfeminine, and produce emotional discomfort. Therefore, low scores have been detected in all scales of the SF-36 questionnaire and in all PCOSQ domains in women with PCOS. It is of note that in these women, the mental health component and domains in the SF-36 questionnaire were more affected than the physical dimension [26].

Using the same instrument, Jones et al. reported that in women with PCOS, emotional role functioning was the health domain most affected, with mean scores of 50.4 in the SF-36

Table 4 Dependence of PCOSQ items scores (mean ± SD) on age and clinical manifestations of the syndrome

Age group	*N*	Emotion (PCOSQ)	Hirsutism (PCOSQ)	Weight (PCOSQ)	Infertility (PCOSQ)	Menstruation (PCOSQ)	Total scores
18–24	2	4.63 ± 0.53	5.3 ± 2.12	5.4 ± 1.13	4.25 ± 1.77	4.38 ± 0.18	4.79 ± 1.31
25–29	11	4.02 ± 1.37	4.76 ± 1.82	5.06 ± 1.7	3.25 ± 0.96	4.32 ± 1.44	4.28 ± 1.37
30–34	9	4.57 ± 1.26	5.11 ± 1.5	5.2 ± 1.9	4.0 ± 1.03	4.64 ± 1.05	4.7 ± 1.23
35–44	15	4.44 ± 1.45	4.37 ± 1.8	3.99 ± 1.83	3.32 ± 1.17	4.87 ± 0.93	4.2 ± 1.47
p value		NS	NS	NS	NS	NS	NS
BMI							
< 25	17	5.10 ± 1.12	5.35 ± 1.39	6.34 ± 0.78	4.04 ± 0.88	5.06 ± 1.10	5.18 ± 0.61
25–30	17	3.61 ± 1.17	4.12 ± 1.94	3.16 ± 1.03	2.99 ± 1.14	4.19 ± 0.99	3.61 ± 0.96
> 30	3	4.33 ± 1.06	4.53 ± 0.61	3.8 ± 1.2	3.5 ± 0.90	4.58 ± 1.01	4.15 ± 0.63
p value		0.002	NS	< 0.001	0.017	NS	< 0.001
Hirsutism							
Yes	26	4.02 ± 1.31	3.98 ± 1.40	4.51 ± 1.90	3.14 ± 1.05	4.5 ± 1.24	4.03 ± 1.3
No	11	5.15 ± 1.00	6.47 ± 0.89	5.07 ± 1.56	4.37 ± 0.59	4.90 ± 0.64	5.20 ± 0.43
p value		0.004	< 0.001	NS	< 0.001	NS	< 0.001
Menstrual irregularities							
Yes	32	4.15 ± 0.22	4.63 ± 0.32	4.36 ± 0.31	3.42 ± 0.2	4.44 ± 0.19	4.2 ± 0.2
No	5	5.65 ± 0.4	5.3 ± 0.44	6.68 ± 0.15	4.1 ± 0.22	5.8 ± 0.12	5.51 ± 0.15
p value		0.017	NS	0.006	NS	0.009	0.02
Hyperandrogenemia							
Yes	7	3.57 ± 1.03	3.43 ± 1.34	3.86 ± 1.79	2.89 ± 1.14	4.18 ± 1.42	3.59 ± 0.99
No	30	4.54 ± 1.33	5.02 ± 1.66	4.87 ± 1.79	3.66 ± 1.07	4.72 ± 1.02	4.56 ± 1.24
p value		0.029	0.010	NS	NS	NS	0.045

NS not significant

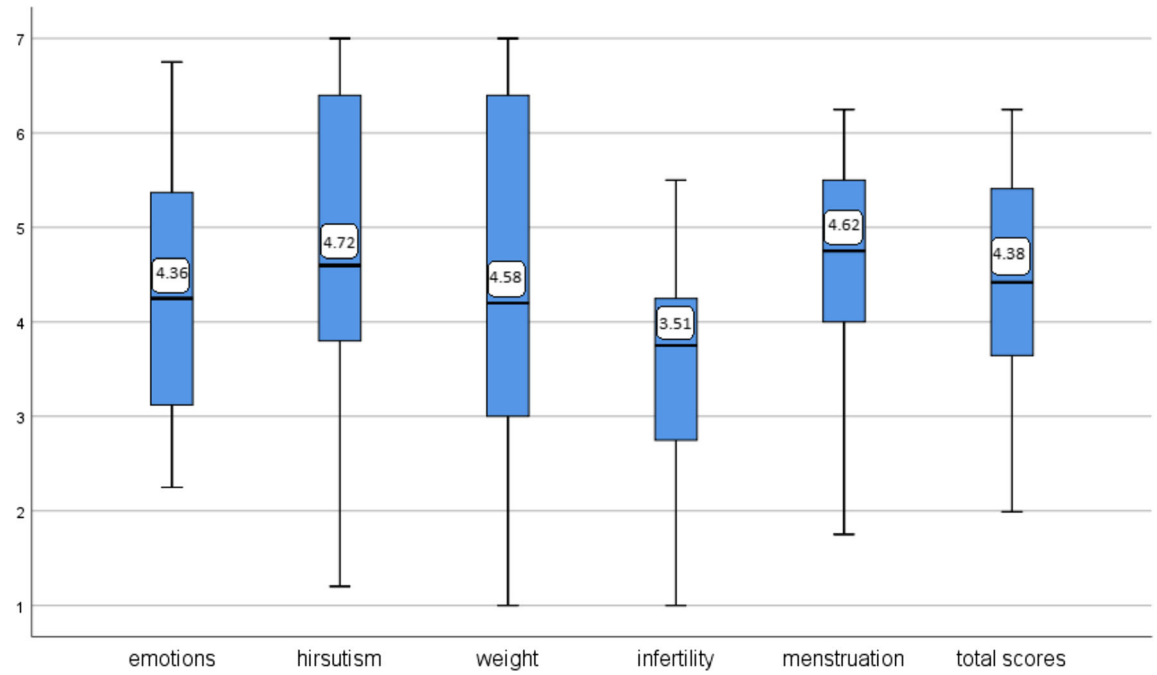

Fig. 2 Boxplots of Polycystic Ovary Syndrome Questionnaire (PCOSQ) domains of PCOS subjects who completed the questionnaires. The middle region of each box plot (box body) covers 50% of the individuals (median), and the region between the upper and the lower transverse lines covers 90% of the individuals. The mean values are presented in small squares inside the box bodies

Table 5 Correlation between PCOSQ/SF-36 and the clinical features of PCOS

	SF36 Physical component (summary scores)	SF36 Mental component (summary scores)	PCOSQ domains (mean scores)					
			Emotion	Hirsutism	Weight	Infertility	Menstruation	Total scores
SF36 Physical component (summary scores)	1	− 0.131	0.045	0.155	0.014	0.126	0.154	0.115
SF36 Mental component (summary scores)	− 0.131	1	0.356*	0.294	0.487**	0.378*	0.157	0.427**
Overweight	− 0.122	− 0.386*	− 0.527**	− 0.346*	− 0.860**	− 0.446**	− 0.371*	− 0.654**
Hirsutism	− 0.177	− 0.479**	− 0.399*	− 0.676**	− 0.145	− 0.518**	− 0.172	− 0.473**
Menstrual irregularity	− 0.104	− 0.332*	− 0.392*	− 0.141	− 0.443**	− 0.211	− 0.429**	− 0.396*
Hyperandrogenemia	− 0.266	− 0.211	− 0.291	− 0.369*	− 0.222	− 0.273	− 0.197	− 0.338

*$p < 0.05$

**$p < 0.01$

questionnaire [21]. Other authors, such as Bazarganipour et al., also found that domains reflecting the psychological state of patients were most affected by PCOS manifestations and had the lowest scores [28]. These results are in agreement with those of the present study, in which the lowest scores were also found in the emotional role domain. Similarly, in a recent meta-analysis by Li et al., women with PCOS had low scores in each dimension of the SF-36, mainly in the emotional role subscale [29]. Notably, Kumarapeli VI et al. found significantly lower mean scores for the physical, psychological, and social relationships domains using WHOQOL-BREF in PCOS women vs controls [30].

Similar data were published by Santoro N et al. Using a specific FertilQOL questionnaire, fertile-related QoL was studied in infertile PCOS patients and in women with an unexplained cause of infertility. Patients with infertility associated with PCOS had significantly lower scores in all domains of the FertilQOL questionnaire (emotional, mind/body, social) except relational domain [31].

We found no significant differences in QoL associated with the physical health component between the PCOS and TFI groups. However, compared with women with non-endogenous causes of infertility (MFI), women with PCOS showed significantly lower scores in the body pain and general health domains as well as in the impaired mental health component. In contrast, on comparing the QoL of women with PCOS with that of women with MFI, Borghi and colleagues found that PCOS patients had significantly lower scores in the SF-36 scales of physical functioning, body pain, and the physical health summary scale, indicating a markedly reduced QoL in the physical health component but not in the other scales or in the mental health summary scale [32]. Interesting data were published by Dokras et al; authors report reduced scores in all domains of SF-36 in PCOS patients. The lowest scores were noted on the general health domain of the SF-36 and the weight and infertility domains on the PCOSQ [33].

In the present study, PCOS patients showed impaired QoL in all domains of the PCOSQ. These results are in accordance with those reported in the study by Böttcher et al. who found that patients with PCOS presented significantly lower total scores and all subscales of the PCOSQ compared with controls [1]. Similar results were published by Turner-McGrievy et al.; respondents with PCOS experiencing infertility reported low scores in all domains of PCOSQ. PCOSQ scores were lowest for infertility and weight domains [34]. Notably, that among PCOS subjects included in this study, the lowest scores were found in the domains of infertility and emotions. However, after adjusting the data for clinical variables, patient' concerns about hirsutism and excess weight had the greatest impact on health-related QoL. The total PCOSQ score was significantly lower in respondents with a BMI > 25 and in those with clinical and biochemical hyperandrogenism. Similar data were described by Angin et al. who assessed the health-related QoL in fertile and infertile women with PCOS and in women with other causes of infertility and found that the lowest SF-36 and PCOSQ scores were observed in infertile PCOS women [23].

The results of the present study suggest that clinical hyperandrogenism has a negative correlation with the scores of the mental health component of the SF-36 questionnaire, and the emotional domain and total PCOSQ scores, resulting in impaired QoL and emotional well-being. However, there were no correlations among biochemical hyperandrogenism and PCOSQ/SF-36 scores. These findings are supported by those described in a study by Barry et al.; authors found no correlation between testosterone levels and manifestations of neuroticism in women with PCOS. Hyperandrogenemia was reported as the cause of problems in the psycho-emotional area in 4% of scores related to neuroticism, whereas clinical

hyperandrogenism (hirsutism, acne, menstrual irregularities) explained up to 25% [35].

The results of our study also allow us to highlight the role of infertility factor in the reduction of patients' QoL. Subjects with tubal (endogenous) infertility factor had significantly lower scores in the domains characterizing mental health, in comparison with women with male infertility factor. Of note, we failed to find the articles on the World Wide Web devoted to the assessment of QoL among women with tubal and male factors of infertility.

The present study has some strengths and limitations; we assessed the QoL in three groups of women with various factors of infertility; two of them had an endogenous cause and one group of women had an exogenous cause of infertility. Patients with tubal factor of infertility and PCOS patients from the position of perceiving themselves as a person responsible for fertile problem were on an equal footing, so that we could study the direct impact of PCOS on woman's physical and mental well-being. However, first, we did not take into account PCOS phenotypes when recruiting subjects for the study group. Therefore, the PCOS group was not heterogeneous since, for obvious reasons, no PCOS participants had the ovulatory phenotype. Nevertheless, patients were divided according to the main clinical manifestations of the syndrome, and health-related QoL was evaluated in each of the subgroups. Second, not all causes of infertility were studied, and therefore, we cannot exclude different possible outcomes if other causes had been considered. Third, the number of patients in each group was small, and only one medical center was involved, which may limit the possibility of generalizing our results; however, in spite of the lower total number of participants, the proposed sample size (of 37, 36, and 31) for the groups has a power near 90%.

Conclusion

The manifestations of PCOS can result in a significant worsening of QoL, mainly affecting psychological and emotional components. The presence of hirsutism and excess weight mainly seems to be associated with the well-being of women with PCOS. Dissatisfaction with self-appearance, a feeling of unattractiveness, and low self-esteem cause chronic psychological discomfort, emotional disturbances, and problems in social relationships. Furthermore, endogenous infertility undoubtedly potentiates deterioration in the QoL and emotional status of women with PCOS.

Finally, among the measures for the examination and treatment of patients with PCOS, it is mandatory to include the study of health-related QoL, since timely assistance from specialists can help to correct psychological problems, reduce social maladaptation, and improve the QoL of these women.

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Contribution to Authorship Contributors: IN and CCB took part in patient recruitment for the study, GC carried out the physical examinations and the SF-36 and the PCOSQ questionnaires. CCB and IN designed the study. IN, CCB, IK, and GC took part in the analysis and interpretation of data, and revision of the draft. IN and CCB wrote the manuscript. All authors approved the final version of the manuscript.

All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the data and accuracy of the data analysis.

Compliance with Ethical Standards

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

Ethical Approval The study protocol was reviewed and approved by the Ethics Committee of the Hospital Clinic of Barcelona (November 29, 2017 HCB/2017/0614) and was performed in accordance with the Declaration of Helsinki II and the ICH Guidelines for Good Clinical Practice.

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Article 3

Psychological Issues and Sexual Function in Women with Different Infertility Causes: Focus on Polycystic Ovary Syndrome

Iuliia Naumova, Camil Castelo-Branco, Gemma Casals

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- It is located in the beginning of the second quartile of the specialty of Obstetrics and Gynecology (position 26/82), according to the Journal Citation Reports 2019®.

Article 3 responds to the following objectives:

- To assess the prevalence of anxiety and depressive symptoms in infertile PCOS women compared with patients with other infertility cause
- To analyze the association between clinical/biochemical features of PCOS, infertility course and the prevalence of depressive/anxiety symptoms in PCOS patients
- To determine the main predictors of anxiety and depression development in PCOS infertile women
- To assess sexual functioning in women with infertility due to PCOS compared with women presenting with tubal and male factor infertility
- To analyze the association between clinical/biochemical features of PCOS, infertility course and sexual functioning in women with PCOS

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REPRODUCTIVE ENDOCRINOLOGY: ORIGINAL ARTICLE

Psychological Issues and Sexual Function in Women with Different Infertility Causes: Focus on Polycystic Ovary Syndrome

Iuliia Naumova[1,2] · Camil Castelo-Branco[1] · Gemma Casals[1]

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Abstract

The objectives of this study are to assess the prevalence of psychological complaints and changes in sexual function in infertile PCOS women compared with patients with other infertility causes (tubal and male infertility factors) and to identify the predisposing factors. An observational study with three cohorts of infertile women was designed including 37 PCOS patients, 36 women with tubal factor, and 31 women with male factor. Clinical history and physical examination were carried out in all patients. All subjects completed the Hamilton Anxiety Rating Scale, the Beck Depression Inventory, and the Female Sexual Function Index questionnaires. Women with infertility due to PCOS showed a significantly higher prevalence of depressive (48.6 vs 19.4 and 12.9%, $p < 0.01$) and anxiety symptoms (21.6 vs 5.6 and 3.2%, $p = 0.041$) than respondents of reference groups. Sexual function in PCOS subjects was impaired in the areas *orgasm* and *satisfaction* ($p < 0.01$ for both) compared to patients of reference groups. Clinical, biochemical hyperandrogenism, and overweight were associated with a higher incidence of depressive and anxiety symptoms in the infertile PCOS group ($p < 0.01$ for all). Besides, the severity of anxiety symptoms was associated with the number of medically assisted reproduction attempts ($p = 0.014$). Weight gain and age ($p = 0.04$ and $p = 0.047$) were associated with impaired sexual functioning. The relation between reduced sexuality and depressive/anxiety symptoms was found ($p = 0.038$ and $p = 0.012$, respectively). Infertile PCOS patients showed the highest prevalence of psychological complaints and some impairment in their sexual functioning. Mental health and sexual functioning need to be part of the routine clinical screening of every PCOS patient. The study was registered at *clinicaltrials.gov* (identifier: NCT03306459) https://clinicaltrials.gov/ct2/show/NCT03306459?cond=PCOS&cntry=ES&city=Barcelona&draw=2&rank=3

Keywords PCOS · Depression · Anxiety · Infertility · Sexual functioning

Introduction

Polycystic ovary syndrome (PCOS) is a multisymptomatic disorder and the most common endocrinopathy among women of reproductive age [1, 2]. The specific physical manifestations of the disease caused by hormonal and metabolic imbalances are associated with no less serious disorders in the psycho-emotional sphere [3–5].

Conception problems, overweight, and features of hyperandrogenic dermopathy are the most bothersome symptoms commonly reported by PCOS women. Poor body image, dissatisfaction with one's appearance, low self-esteem, perception of oneself as not feminine, and unattractive for a partner can markedly affect women's emotional well-being [6].

According to the literature, the frequency of depressive symptoms in patients with PCOS can reach 14–67% [7], while in the general population its prevalence does not exceed 6–

Iuliia Naumova and Camil Castelo-Branco have equal responsibilities.

✉ Camil Castelo-Branco
castelobranco@ub.edu

Iuliia Naumova
jvnaumova@list.ru

Gemma Casals
GCASALS@clinic.cat

[1] Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Villarroel 170, 08036 Barcelona, Spain

[2] Present address: Department of Obstetrics and Gynecology, Faculty of General Medicine, Saratov State Medical University n.a. V.I. Razumovsky, Saratov, Russian Federation

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10% [8]. Besides, PCOS is related to an increased risk of anxiety, eating disorders, sexual dysfunction [9, 10], social phobias, and suicide attempts [11, 12].

Psychopathological problems are a relatively new aspect of PCOS for clinicians. Only about 3.5% of PubMed citations on PCOS address psychological and sexual disorders in PCOS women [4]. Despite the sufficient body of scientific evidence, emphasizing the high prevalence of psycho-emotional problems in patients suffering from PCOS, the underlying factors that make PCOS subjects more susceptible to such disorders are still poorly understood, and data on them are often contradictory [13–15].

The purpose of this study was to assess the prevalence of depressive and anxiety symptoms and sexual dysfunction in infertile PCOS patients in comparison with women with other infertility causes (tubal and male infertility factors), and to identify factors predisposing PCOS subjects to emotional distress and impaired sexual function.

Material and Methods

Sample

To avoid the effect of hormonal therapies on the study topic, 46 PCOS patients aged 18 to 40 who met the Rotterdam criteria and did not receive oral contraceptive pills or medications over the past 6 months were included in the study. Patients were recruited at the reproductive medicine unit of the Hospital Clinic Barcelona from December 2017 to June 2019, where women complained of infertility. The flowchart of participants has been published elsewhere [16].

Using a statistical software to calculate the sample size used (SPSS SamplePower 3.0.1, Armonk, NY: IBM Corp.) and assuming that the mean difference in FSFI scores is 3.2 (corresponding to means of 28.2 versus 25.0) and the common within-group standard deviation is 4.5 (based on SD estimates of 3.3 and 5.4) accepting the type I error as 0.05 with the power of 95%, we obtained a sample size of 102 cases for two groups [17]. The power analysis basing on findings of comparable studies [18, 19] also showed that the sample size of 102 cases for two groups is sufficient for adequate analysis of the variables BDI-II and HAM-A scores. Nevertheless, with the proposed sample size of 37 and 36 for each group, accepting the type I error as 0.05, the study will have the power of 85.6% to yield a statistically significant result, which is acceptable.

As infertility, along with other PCOS-related symptoms, has a significant impact on a woman's psychological well-being and may affect sexuality, we decided to compare PCOS subjects and women with other causes of infertility attended in the reproductive medicine unit during the same period. Since the cause of infertility (exogenous, endogenous) can determine a woman's self-perception as a person solely responsible for the inability to conceive and may differently affect the psychological state, as a control sample, 50 women with tubal factor infertility (TFI) (endogenous cause) and 31 healthy women with male factor infertility (MFI) (exogenous cause) were included in the study. None of the women of the three groups was undergoing medically assisted reproduction (MAR) while participating in the present study. None of the women had any extragenital pathology.

Methods

An analytical study of three independent groups was designed: PCOS, TFI, and MFI. Anthropometric characteristics, a transvaginal ultrasound, and laboratory data, including the level of free testosterone, serum sex hormone-binding globulin (SHBG), and free testosterone index (FTI), were recorded from all participants. The severity of hirsutism was assessed using the modified Ferriman-Gallwey scoring method (mFG); mFG score ranges from 0 to 36, and scores of 8 or higher were considered of having hirsutism [20].

All participants were asked to fill out the Beck Depression Inventory and Hamilton Anxiety Rating Scale questionnaires for assessing the level of mood disorders and the Female Sexual Function Index questionnaire to evaluate sexual functioning. Subjects were informed of the study's characteristics, and the data obtained from questionnaires would be entered into a database with an identifier code, ensuring the patients' anonymity. Women who accepted to participate provided their written informed consent and completed the questionnaires alone without assistance.

The study protocol was reviewed and approved by the Ethics Committee of the Hospital Clinic of Barcelona (November 29, 2017, HCB/2017/0614), was performed in accordance with the Helsinki II Declaration and the ICH Guidelines for Good Clinical Practice, and was registered at clinicaltrials.gov (identifier: NCT03306459).

Questionnaires

The Hamilton Anxiety Rating Scale The Hamilton Anxiety Rating Scale (HAM-A) is a psychological questionnaire used by clinicians to rate the severity of a patient's anxiety. The scale consists of 14 items designed to assess the severity of a patient's anxiety. Each of the 14 items contains a number of symptoms, and each group of symptoms is rated on a scale of zero to four, with four being the most severe.

The items anxious mood, tension, fears, insomnia, intellectual, depressed mood, and behavior at interview characterize the state of mental anxiety; topics somatic (muscular), somatic (sensory), cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and autonomic symptoms characterize somatic anxiety [21].

Upon the completion of the evaluation, the clinician compiles a total, composite score based upon the summation of each of the 14 individually rated items. This calculation will yield a comprehensive score in the range of 0 to 56. It has been predetermined that the results of the evaluation can be interpreted as follows: a score of 17 or less indicates mild anxiety severity, a score from 18 to 24 indicates mild to moderate anxiety severity, and lastly, a score of 25 to 30 indicates moderate to severe anxiety severity.

Beck Depression Inventory (BDI-II) The BDI is a 21-item self-report inventory commonly used to assess the severity of depressive symptoms. The inventory is intended for use in adults and is composed of items related to depressive, as well as physical, symptoms. The severity of depressive symptoms is scored on a scale from 0 to 3 for each item. A higher total score indicates more severe depressive symptoms. The total score is from 0 to 63 and declines by the improvement of a person's condition. The total score is compared to a key to determine the depression's severity. The standard cutoff scores are as follows: 0–13 minimal depression, 14–19 mild depression, 20–28 moderate depression. and 29–63 severe depression [22]. The questionnaire is handed over to the patient and filled out by her independently.

The Female Sexual Function Index (FSFI) FSFI is a multidimensional self-reporting instrument for the assessment of the key dimensions of female sexual function in clinical and non-clinical samples. This questionnaire contains 19 items assigned to six sexual domains: desire (two questions), arousal (four questions), lubrication (four questions), orgasm (three questions), global satisfaction (three questions), and pain (three questions). Every item has multiple-choice answers (ranging from 0 = poor sexual status to 5 = good sexual status), with a maximal total score of 36 points.

The scores of the individual items that comprise the domain are summed up and multiplied by the specific domain factor. The final score is obtained by adding the six domain scores [23].

Statistical Analysis

The IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp.) was used for the statistical analysis. Descriptive analysis was expressed in frequencies and percentages (qualitative variables) or reported as mean and standard deviation (quantitative variables). Normality was assessed by the Kolmogorov-Smirnov test. As data were not normally distributed, non-parametrical tests were used. The Kruskal-Wallis and Mann-Whitney *U* tests were used for the analysis of quantitative data, and Fisher's exact test was used for the analysis of qualitative data. Given the need for multiple comparisons, Bonferroni correction was used to control a group error probability. Significance values have been adjusted for pairwise comparisons. For correlation analysis, Spearman's correlation was used. To determine individual factors that contribute to the development of psychological distress in infertile PCOS, multiple regression analysis was used. Possible predictors (independent variables) and dependent variables (HAM-A scores, FSFI scores, and BDI-II scores) were tested for assumptions; variables HAM-A scores, FSFI scores, and level of serum testosterone free were excluded from the regression analysis as not meeting the assumptions. The interpretation of results involves comparing values of the β coefficient, which is interpreted concerning the strength and direction of the relationship between individual variables. The adjusted R^2 value shows how well the regression model fits the data. A p value less than 0.05 was considered statistically significant.

Results

Of the 46 patients with PCOS initially recruited to the study, 37 patients (80.5%) returned the HAM-A, BDI-II, and FSFI questionnaires completed; in the group of women with tubal infertility, of the 50 patients who received questionnaires, only 36 women returned them filled (72%). All patients (31) of the group of women with male infertility factor returned completed questionnaires.

Clinical and biochemical characteristics of women with infertility caused by PCOS, TFI, and MFI are presented in Table S1.

Mean (SD) age of women who returned the questionnaires was 31.47 (5.36) years. All participants were married or had a stable relationship with a partner. No significant differences in age, duration of infertility, and mean number of MAR attempts were found between groups. There was no significant difference between groups in the proportion of women who underwent MAR attempts. PCOS patients showed a much higher mean value of BMI ($p < 0.01$) due to the larger proportion of overweight participants in the PCOS group compared with TFI and MFI groups (54.1 vs 22.2 and 12.9%, respectively, $p < 0.01$). Seventy percent of the women with PCOS reported mFG score of 8 or more (mean 11.81 ± 4.63) and were defined as hirsute. As expected, the free testosterone level in the blood serum was higher in women with PCOS as against TFI and MFI groups ($p < 0.01$). Menstrual irregularities were reported by 86.5% of respondents in the PCOS group. All respondents of TFI and MFI groups reported a regular menstrual cycle.

Sexual Functioning

In patients with PCOS, considerably lower scores were found in *orgasm* ($p = 0.014$) and *satisfaction* ($p = 0.036$) subscales

compared with subjects of TFI (Table 1). No significant differences were found neither in other subscale scores nor in FSFI *total scores*. At the same time, comparing with healthy women (MFI), patients with PCOS reported much lower scores in all FSFI subscales and FSFI *total scores* except subscale *pain* (Table 2).

Psychological Status

Significant differences in mean values of both HAM-A and BDI-II scores have been observed between PCOS and the other studied groups (Table 3).

Criteria for clinical depression (BDI-II scores > 14) were met in 48.6% of PCOS patients while in respondents with TFI and MFI this figure was 19.4% and 12.9% respectively ($p < 0.01$). Thus, the prevalence of depressive symptoms in women suffering from PCOS was 2.5 times higher than in subjects with TFI and 3.8 times higher compared with MFI respondents.

In the PCOS group, 40.5% of women reported symptoms of mild depression (BDI-II scores 14–19), and 8.1% of them demonstrated symptomatology of moderate depression (BDI-II scores 20–28). In the groups of women with TFI and MFI, only mild forms of depression were observed (in 19.4 and 12.9% of respondents, respectively).

Clinically relevant manifestations of anxiety were detected in 21.6% of respondents with PCOS, which is significantly higher than in groups of women with TFI (5.6%) and MFI (3.2%) ($p = 0.041$). Moderate/severe forms of anxiety were found in only 2 (5.4%) women with PCOS and 1 (2.8%) patient with TFI. Thus, in infertile PCOS patients, anxiety disorders were diagnosed 3.9 and 6.7 times more often than in women with TFI and MFI.

Table 1 Comparison of Female Sexual Function Index (FSFI) subscale outcomes between the PCOS group, tubal factor patients (TFI), and women with male factor as cause of infertility (MFI)

FSFI subscales	PCOS (n=37)	TFI (n=36)	MFI (n=31)	p
Desire	4.87±0.9[c]	4.95±1.0[c]	5.5±0.5[a,b]	<0.01
Arousal	4.95±0.9[c]	5.24±0.7[c]	5.68±0.3[a,b]	<0.01
Lubrication	5.38±0.6[c]	5.48±0.6[c]	5.82±0.3[a,b]	<0.01
Orgasm	4.39±1.0[b,c]	5.01±0.7[a]	5.08±0.6[a]	<0.01
Satisfaction	4.75±0.9[b,c]	5.2±0.7[a]	5.42±0.5[a]	<0.01
Pain	5.69±0.5	5.76±0.5	5.83±0.3	0.304
FSFS total scores	30.02± 0.55[c]	31.63± 0.49[c]	33.32 ±0.23[a,b]	<0.01

Results are given as mean ± standard deviation

Kruskal-Wallis (Mann-Whitney U test), p values < 0.05 are statistically significant

[a] p<0.05 difference vs PCOS group

[b] p<0.05 difference vs TFI group

[c] p <0.05 difference vs MFI group

Table 2 Pairwise comparisons of Female Sexual Function Index (FSFI) subscale outcomes between the PCOS group, tubal factor patients (TFI), and women with male factor as cause of infertility (MFI)

FSFI subscales	Sample	Adj. sig.
Desire	PCOS-TFI	1.000
	PCOS-MFI	0.007*
	TFI-MFI	0.046*
Arousal	PCOS-TFI	0.695
	PCOS-MFI	0.000*
	TFI-MFI	0.016*
Lubrication	PCOS-TFI	1.000
	PCOS-MFI	0.004*
	TFI-MFI	0.039*
Orgasm	PCOS-TFI	0.014*
	PCOS-MFI	0.006*
	TFI-MFI	1.000
Satisfaction	PCOS-TFI	0.036*
	PCOS-MFI	0.001*
	TFI-MFI	0.736
FSFI total scores	PCOS-TFI	0.105
	PCOS-MFI	0.000*
	TFI-MFI	0.038*

*The significance level is 0.05. Significance values have been adjusted by the Bonferroni correction for multiple tests

Correlation analysis showed that scores of BDI-II and HAM-A strongly correlated with the severity of hirsutism, BMI, and the level of serum testosterone in the PCOS group ($p < 0.01$ for all) (Table 4). Besides, HAM-A scores considerably correlated with the mean number of MAR attempts ($p = 0.014$). FSFI total scores negatively correlated with the age of respondents and with BMI in PCOS infertile patients ($p = 0.04$ and $p = 0.047$, respectively). It is worth noting that we found a negative correlation between FSFI total scores and BDI-II/HAM-A scores ($p = 0.038$ and $p = 0.012$, respectively).

Multiple linear regression analysis carried out in the PCOS group revealed that hirsutism (β coefficient = 0.6, $p < 0.001$) and BMI (β coefficient = 0.46, $p < 0.001$) had a strong association with depressive symptoms (Table 5).

Discussion

The goals of this study were to assess the prevalence of depressive and anxiety symptoms and changes in sexual function among infertile PCOS patients compared with subjects with tubal and male factor infertility and to identify key

Table 3 Comparison of depression and anxiety prevalence between the PCOS group, tubal factor patients (TFI), and women with male factor as cause of infertility (MFI)

Characteristics	PCOS	TFI	MFI	*p*
BDI-II scores, mean ± SD	12.3±0.91[b,c]	7.2±0.8[a]	5.8±0.77[a]	<0.01
HAM-A scores, mean ± SD	10.7±1.23[b,c]	5.2±1.01[a,c]	2.7±0.62[a,b]	<0.01
Patients with the absence of anxiety symptoms	29 (78.4)	34 (94.4)	30 (96.8)	0.041
Patients with mild to moderate anxiety symptoms	6 (16.2)	1 (2.8)	1 (3.2)	0.149
Patients with moderate to severe anxiety symptoms	2 (5.4)	1 (2.8)	0	
Patients with depressive symptoms	18 (48.6)[b,c]	7 (19.4)[a]	4 (12.9)[a]	<0.01
Mild depressive symptoms	15 (40.5)[c]	7 (19.4)	4 (12.9)[a]	0.02
Moderate depressive symptoms	3 (8.1)	0	0	
Severe depressive symptoms	0	0	0	

BDI-II Beck Depression Inventory, *HAM-A* Hamilton Anxiety Rating Scale

Comparisons were performed using Kruskal-Wallis (Mann-Whitney *U* test) and Fisher's exact test. Significance values have been adjusted by the Bonferroni correction for pairwise comparisons. Data from completer sample. Results are given as mean ± standard deviation and as total numbers and percentages. *p* values < 0.05 are statistically significant

[a] $p<0.05$ difference vs PCOS group

[b] $p<0.05$ difference vs TFI group

[c] $p<0.05$ difference vs MFI group

features that contribute to their psychological and sexual complaints.

The *principal findings* were the high prevalence of mood disorders in women with infertility due to PCOS. Sexual function was impaired in the areas *orgasm* and *satisfaction*. Hirsutism and overweight were the strongest predictors of the high incidence of depressive and anxiety symptoms, while the weight gain was significantly related to impaired sexuality in the study group. Respondents with infertility caused by PCOS and concurrent depression/anxiety demonstrated a significantly lower index of sexual function.

Psychological State

Our findings correspond with the literature and demonstrate a high prevalence of anxiety and depressive disorders among infertile PCOS patients, significantly higher than respondents with other infertility causes. In fact, almost 50% of the PCOS participants experienced depressive symptoms, which corresponds to 2.5- and 3.8-folds increased prevalence, compared to the TFI and MFI respondents in our sample. Twenty-one percent of PCOS women demonstrated an elevated HAM-A score compared to 5.6 and 3.2% in the reference groups.

Similar results were published by Cooney et al.; based on a meta-analysis, subjects with PCOS had 3.78- and 5.62-folds increased risk of any depressive and anxiety symptoms, respectively [15]. When subjects were matched on BMI, women with PCOS still had higher odds of developing both depressive and anxiety symptoms. Notably, PCOS patients with depression had higher mean values of age, BMI, hirsutism score, and insulin resistance index, while women with PCOS experiencing anxiety had a higher BMI, hirsutism score, and free testosterone level.

The factors underlying the emotional distress in patients with PCOS are still not clear, and the data on this topic is controversial. Therefore, a number of studies consider the

Table 4 Correlation between questionnaires' scores and clinical features/history of infertility of PCOS patients (*N*=37)

	Age	Duration of infertility	Attempt of MAR in history	mFG scores	BMI	Free testosterone level	FSFI total scores
BDI-II scores	0.046	0.224	0.278	0.697**	0.596**	0.425**	−0.342*
HAM-A scores	0.132	0.279	0.400*	0.635**	0.541**	0.418**	−0.409*
FSFI total scores	−0.329*	−0.151	−0.221	−0.113	−0.333*	−0.313	1

BDI-II Beck Depression Inventory, *HAM-A* Hamilton Anxiety Rating Scale, *FSFI* Female Sexual Function Index, *BMI* body mass index, *mFG score* modified Ferriman-Gallwey score, *MAR* medically assisted reproduction

*$p<0.05$

**$p<0.01$

Table 5 Multiple linear regression analysis showing the coefficients of predictive values of independent variables for the dependent variable BDI-II scores in the group of women with infertility due to PCOS ($N = 37$)

		Unstandardized coefficients		Standardized coefficients			Collinearity statistics	
Model		*B*	Std. error	β coefficient	*t*	Sig.	Tolerance	VIF
1	Constant	4.67	1.51		3.1	0.004		
	mFG	0.82	0.146	0.7	5.64	0.000	1.000	1.000
2	Constant	−11.73	3.8		−3.09	0.004		
	mFG	0.72	0.12	0.6	6.02	0.000	0,960	1.040
	BMI	0.7	0.15	0,46	4.55	0.000	0,960	1.040

BDI-II Beck Depression Inventory, *mFG* modified Ferriman-Gallwey score, *BMI* body mass index

Dependent variable: BDI-II scores. Predictors: mFG score, BMI; $R^2 = 0.674$, model p value < 0.01

R^2 and p value are listed for the model 2

poor body image associated with the external manifestations of the syndrome (hirsutism, acne, obesity) and fertility problems the main triggers in the development of mental disorders in patients with PCOS. Thus, according to Stapinska-Syniec et al., 52% of respondents with PCOS presented with depressive symptoms. They had a considerably higher BMI and a lower level of self-perceived attractiveness than the subgroup of PCOS women without depression [10]. Emerkis et al. also confirm a substantially higher prevalence of depression and anxiety, especially a generalized and social anxiety, among patients with PCOS when compared with age- and BMI-matched controls. In this study, BMI was independently associated with depression and generalized anxiety, while an mFG score was associated with panic disorder [24]. On the other hand, Kerchner et al. found a high incidence of mood disorders among subjects with PCOS with a binge eating disorder, and symptoms of depression were identified in 40% of patients. However, there were no differences in body imaging concerns (weight, hirsutism), the frequency of menstrual disorders, and fertile problems in women with, and without, depression [9]. Similarly, Benson et al., in a large meta-analysis, found that women with PCOS are at high risk of developing depressive symptoms regardless of their BMI [14].

Our study emphasized the significant role of clinical/biochemical hyperandrogenism and overweight in the development of anxiety and depressive symptoms ($p < 0.01$ for all), which indicates the importance of poor body image perception in the development of impaired emotional well-being in women with infertility due to PCOS. Likewise, Borghi et al. highlight the negative role of hirsutism in the formation of anxiety disorders; the incidence of anxiety in PCOS patients was directly related to the mFG score. On the other hand, the relationship of biochemical hyperandrogenism and negative mood states was not detected [6]. Nevertheless, Shulman et al. did not find an association between the severity of hirsutism/free testosterone levels and the prevalence of mood disorders [25].

Along with the clinical manifestations of PCOS, infertility and its management negatively affect the psycho-emotional state. The wide range of psychological issues, including depression, anxiety, sexual dysfunction, and social isolation, have been described in infertile couples [26, 27]. Thus, a large online survey conducted among persons with experience of infertility emphasized the significant impact of infertility and MAR attempts on the psychological state, quality of life, and sexual life of respondents [28]. The results of our study confirm the association between severity of anxiety symptoms and the number of MAR attempts in a history of infertility in PCOS patients, but we failed to find a relation between MAR experience and depressive symptoms, or between the duration of infertility and psychological complaints.

Sexual Function

Sexuality has a high impact on overall well-being, but data on the prevalence of sexual dysfunction among patients with PCOS is limited and contradictory, and scientific evidence on the influence of individual factors on sexual function in women with PCOS is mixed. Thus, some authors have reported impairments in such areas as sexual desire [29], orgasm completion [30], and satisfaction [31], while others have failed to find any noticeable worsening in overall sexual functioning [32, 33].

In our study, respondents with PCOS showed much lower scores on the FSFI subscales *orgasm* and *satisfaction* compared with women with TFI, although total scores did not noticeably differ in women with PCOS and TFI. It should be highlighted that FSFI *total scores*, and that of all the subscales scores except for *pain*, were significantly lower in infertile PCOS women, compared to healthy women with a male factor. Similar results were published by Stovall et al.; women with PCOS had a much lower *orgasm completion* score compared with women in the control group [30]. The authors report that, in women with PCOS, an increased BMI was

associated with a significant score reduction in the orgasm/completion subscale, but no substantial associations were found in regard to acne or hirsutism.

The effect of BMI on sexual function in PCOS patients is controversial. Mansson et al., in their study, emphasized the negative association between increased BMI of PCOS patients and the satisfaction with their sexual life [34]. And, Ferraresi et al. found that PCOS women who were overweight had far lower FSFI scores than non-obese women and were at a higher risk of sexual dysfunction [35]. Conversely, Benetti-Pinto et al. found significantly lower FSFI scores in the subscales *stimulation*, *lubrication*, *satisfaction*, and *pain* in patients with PCOS, compared with the control group. However, their BMI did not correlate with sexual function [17].

Numerous studies report that hirsutism, together with obesity, is negatively related to sexual function by causing body dissatisfaction and thus affecting feminine identity [36].

Elsenbruch et al. revealed that both obese and non-obese PCOS women were considerably less satisfied with their sex life, felt themselves less sexually attractive, and reported that excessive body hair concern affected their sexuality, more than the control group [37]. In our study, the results of the correlation analysis in infertile PCOS women showed a marked association of age and BMI with reduced FSFI total scores. However, hirsutism was not related to impaired sexual functioning.

In addition, we found a significant correlation between sexual functioning (FSFI total scores) and an impaired psycho-emotional state in the study group. Similar data was published by Dashti S et al.; respondents with depressive and anxiety symptoms were much more likely to have difficulty in achieving an orgasm than those without mood disorders [38]. Pastoor et al. also noted that anxiety, depression, and poor body image in PCOS patients are psychosocial risk factors for impaired sexual functioning and sexual dissatisfaction [39]. Notably, the World Web contains quite limited data on this topic and requires more investigation.

Strength and Limitations

We assessed the prevalence of depressive and anxiety symptoms, and sexual function in women with endogenous (PCOS and tubal factor) and exogenous (male factor) infertility causes. Data on this topic is quite limited. Nevertheless, our study has some limitations. First, the samples size was rather small, and only one medical center was involved, which may limit the possibility of generalizing our results. However, the proposed sample size (of 37, 36, and 31) for the groups has a power of near 86%. Second, not all PCOS phenotypes were present in sufficient proportion in the study group. Therefore, the PCOS group was not homogeneous, since few PCOS participants had the ovulatory phenotype.

Conclusion

High prevalence of depressive and anxiety symptoms and some impairment of sexual functioning are associated with PCOS. Overweight as well as clinical hyperandrogenism can be seen as important contributors to impaired psychological well-being. Depressive state and weight gain are significant predisposing factors for reduced sexuality. The findings imply that psychological status and sexual functioning need to be part of the clinical screening of every PCOS patient.

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Author Contribution I Naumova: study design, data collection, analysis and interpretation of data, writing manuscript, revision of the draft

C Castelo-Branco: study design, data collection, analysis and interpretation of data, writing manuscript, revision of the draft

G Casals: data collection

All authors approved the final version of the manuscript. All authors had full access to all of the data in the study (including statistical reports and tables) and can take responsibility for the integrity of the data and accuracy of the data analysis.

Data Availability Castelo-Branco, Camil; Naumova, Iuliia (2020), "PCOS and QoL", Mendeley Data, V1, doi: 10.17632/73r7pxtc5d.1; https://doi.org/10.17632/73r7pxtc5d.1

Declarations

Ethics Approval The study protocol was reviewed and approved by the Ethics Committee of the Hospital Clinic of Barcelona (November 29, 2017, HCB/2017/0614), was performed in accordance with the Helsinki II Declaration and the ICH Guidelines for Good Clinical Practice, and was registered at clinicaltrials.gov (identifier: NCT03306459).

Conflict of Interest The authors declare no competing interests.

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Table S1. Clinical and anthropometrical characteristics of the three study groups.

Characteristics	PCOS	TFI	MFI
Patients completing the questionnaires	37 (80.5%)	36 (72%)	31 (100%)
Mean Age (SD)	32±5.05	30.58±6.27	31.87±4.55
Married or with partner	37	36	31
Mean Duration of infertility (SD)	4.7±2.16	4.08±2.8	3.97±2.35
Patients who underwent MAR attempts	14 (37.8)	12 (33.3)	14 (45.2)
Mean number of MAR attempts (SD)	0.7±0.99	0.5±0.78	0.87±1.09
Mean BMI (SD)	24.91±3.59[c]	23.12±2.79	22.49±2.95[a]
Patients with BMI>25	20 (54.1)[c]	8 (22.2)	4 (12.9)[a]
mFG score	11.81±4.63[b,c]	4.36±0.21[a]	4.06±0.25[a]
Patients with hirsutism	26 (70.3)	0	0
Mean Serum Testosterone free level, ng/dl (SD)	37.36±17.3[b,c]	26.95±7.3[a]	26.48±7.23[a]
Patients with hyperandrogenemia	7 (18.9)	0	0
Patients with menstrual disorders	32 (86.5)	0	0

BMI – body mass index; mFG score – modified Ferriman-Gallwey score; TFI – tubal factor of infertility; MFI – male factor of infertility; MAR – medically assisted reproduction

Comparisons were performed using Kruskal-Wallis (Mann–Whitney U test) and the Fisher's exact test. Significance values have been adjusted by the Bonferroni correction for pairwise comparisons. Data from completers sample. Results are given as mean±standard deviation and as total numbers and percentages. P values < 0.05 are statistically significant.

[a] p<0.05 difference vs PCOS group

[b] p<0.05 difference vs TFI group

[c] p <0.05 difference vs MFI group

Discussion

Clinical manifestations of the syndrome and conditions associated with the syndrome may affect QoL and psychological well-being across the life course.

The investigation of QoL and psychological state of patients suffering with PCOS has a number of nuances that should be considered. Thus, PCOS patients commonly take combined oral contraceptive pills (COCs) for a long time as it improves signs of hyperandrogenic dermopathy and menstrual irregularity, and according to some data improves QoL and psychological well-being of such patients [92]. However, there are some evidence about negative impact of COCs on psychological state and increased risk of depression in women using COCs [93].

It's of note, that previous studies focused on evaluation of QoL and psychological complaints in patients with PCOS, commonly involved PCOS women without immediate plans for pregnancy, not excluding those who take contraceptive pills. Therefore, the possible impact of combined oral contraceptives and other medication on QoL and psychological state remain neglected.

Undoubtedly, infertility by itself and its cause (female/male factor) may differently contribute to impairment of life quality and affect psychological health.

In present study we assessed the QoL, psychological state and sexual functioning in three groups of women with various factors of infertility; two of them had an endogenous cause and one group of women had an exogenous cause of infertility.

Patients with tubal factor of infertility and PCOS patients from the position of perceiving themselves as a person responsible for fertile problem were on an equal footing, so that we could investigate the direct impact of PCOS on woman's physical and mental well-being.

Quality of life in infertile PCOS patients

In our study women with infertility due to PCOS demonstrated significantly worse QoL scores in domains, characterizing mental health, compared with patients with tubal and male factor infertility. Low scores in mental domains indicate

impairment of the emotional state of the respondents, inducing a significant limitation of social contacts, a decrease in the level of communication with others, and the possible presence of depressive and anxiety disorders.

However, we did not find significant differences either in the physical component summary (PCS) or in any individual physical domains between PCOS and TFI subjects. On the other hand, in comparison with healthy women with MFI, patients with PCOS had significantly lower scores in the domains of body pain, general health, vitality, social functioning, emotional role functioning, mental health, and the MCS.

Besides, we observed significantly lower scores in domains, characterizing mental health in women presented with tubal factor infertility than women with male factor. In our opinion this scores difference emphasizes the importance of the infertility cause (endogenous/exogenous) in QoL deterioration.

In our study women with infertility due to PCOS demonstrated low scores in all domains of PCOSQ, the lowest scores were reported in domains infertility concern and emotions. However, after adjusting the data for clinical variables, we found that hirsutism and weight concerns had the strongest impact on the patients' health-related QoL. Besides, we noted, that respondents with BMI>25, menstrual disorders, as well as women presenting with hyperandrogenism (clinical/biochemical) had significantly lower emotions domain scores than those with normal weight or without above features. Supposed relationship between impaired QoL of PCOS patients and clinical manifestations of the syndrome was confirmed by correlation analysis: PCOSQ total scores were negatively correlated with the main clinical manifestations of the syndrome (hirsutism, overweight, and menstrual irregularities). Additionally, PCOSQ scores in the emotional domain significantly correlated with the presence of hirsutism, weight excess, and menstrual irregularities. However, we failed to find correlations between biochemical hyperandrogenism and PCOSQ scores.

Psychological complaints

Our findings correspond to the literature and confirm a high prevalence of mood disorders in PCOS patients. We found a significantly higher prevalence of anxiety and depressive symptomatology among PCOS infertile patients vs women with tubal and male infertility cause. Thus, depressive disorders were observed in 48.6% of PCOS patients, and its prevalence was 2.5 times higher than in women with TFI and 3.8 times higher compared with MFI respondents.

However, it should be noted that 40.5% of infertile women suffering from PCOS reported symptoms of mild depression and only 8.1% of them demonstrated symptoms of moderate depression. In the groups of women with tubal and male factors, only mild forms of depression were observed.

The prevalence of anxiety as well was markedly higher in infertile patients with PCOS vs women with other infertility cause and reached 21.6%. Women with infertility associated with tubal and male factor experienced anxiety 3.9 and 6.7 times less often than women with PCOS. Moderate/severe forms of anxiety were found in only 5.4% women with PCOS and 2.8% patient with TFI.

Thus, it can be noted that PCOS women are more prone to development of anxiety and depressive disorders, and mild forms of disturbances prevail.

We failed to find significant difference in anxiety/depression prevalence between women presented with tubal and male infertility cause, however, HAM-A scores were significantly higher in women with tubal infertility vs those with male infertility factor.

Data on the factors underlying the development of depressive and anxiety disorders in literature are still controversial.

In our study we found a significant relationship between depression/anxiety scores and severity of hirsutism, BMI, and the level of testosterone free in the PCOS patients. Besides, anxiety scores considerably correlated with the mean number of MAR attempts.

Thus, hirsutism, weight excess and hyperandrogenemia can be seen as main predisposing factors of impaired psychological state. The interesting finding of our study was a negative impact of infertility course and, in particular, a number of MAR attempts in history of infertility on development of anxiety in PCOS patients that, however, requires for future investigations.

Moreover, we built multiple regression model to identify contribution of few PCOS manifestations in development of depression. We revealed that hirsutism and BMI both were strongly associated with depressive symptomatology in PCOS patients.

Sexual functioning

Undoubtedly, sexuality has a high impact on the overall well-being. However, literature contains quite controversial data on whether PCOS is associated with impaired sexual functioning. Some authors report obesity and hirsutism aversely affect sexuality by causing body dissatisfaction and interfering with the women's feminine self-perception [94], while others have not found any deterioration in sexual functioning in PCOS women [95]. According to some data, infertility by its self can lead to marital problems and sexual dysfunction [96].

It should be noted, in our study all three groups of infertile women demonstrated reduced FSFI total scores.

We found considerably lower scores in the Orgasm and Satisfaction subscales compared with women presenting with tubal infertility factor. However, no significant differences were found neither in other subscales scores nor in FSFI total scores. At the same time, comparing with healthy women (MFI), infertile patients with PCOS reported much lower scores in all FSFI subscales and FSFI total scores, except subscale Pain.

Besides, women with tubal infertility showed significantly lower scores in subscales Desire, Arousal, Lubrication and FSFI total scores than those with MFI.

Analyzing possible predisposing factors, we failed to find an association between hyperandrogenism and sexual dysfunction in PCOS infertile women, however negative correlation between FSFI total scores and BMI was observed.

Moreover, it is worth noting that we found a negative relationship between reduced sexual functioning and depressive/anxiety symptoms.

In our study the difference in FSFI domains scores between women with tubal and male infertility factor indicates a contribution of endogenous infertility in impaired sexuality.

Therefore, overweight, infertility and accompanying psychological distress can be seen as main predictors of impaired sexuality in PCOS patients.

Limitations

The present study has some limitations. First, the number of patients in each group was small, and only one medical center was involved, which may limit the possibility of generalizing our results; however, in spite of the lower total number of participants, the proposed sample size (of 37, 36, and 31) for the groups has a power near 90%.

Second, we did not take into account PCOS phenotypes when recruiting subjects for the study group. Therefore, the PCOS group was not heterogeneous since, for obvious reasons, no PCOS participants had the ovulatory phenotype. Nevertheless, patients were divided according to the main clinical manifestations of the syndrome, and health-related QoL was evaluated in each of the subgroups.

Second, not all causes of infertility were studied, and therefore, we cannot exclude different possible outcomes if other causes had been considered.

Conclusion

- PCOS may result in a significant worsening of QoL, mainly on psychological and emotional components.
- PCOS is associated with high prevalence of depressive and anxiety symptoms
- Weight excess and hirsutism are important predictors for impaired psychological health.
- Weight excess and hirsutism, resulting to dissatisfaction with self-appearance and low self-esteem, may induce a significant limitation of social contacts, a decrease in the level of communication with others, marital problems with a partner
- Impairment of sexual functioning is associated with PCOS
- Anxiety and depressive state, weight gain are significant predisposing factors for reduced sexuality
- Endogenous infertility potentiates deterioration in the QoL, psychological state, and sexual functioning of women with PCOS
- Infertility accompanied by several MAR attempts may be an additional risk factor for the development of anxiety.
- The findings imply that professionals interacting with patients suffering from PCOS should be aware of the high possibility of developing depression and anxiety, reduced QoL, and sexuality in their patients; All patients with PCOS should be mandatory screened for socio-emotional difficulties and sexual problems since timely assistance from specialists can help to correct psychological problems, reduce social maladaptation, and improve the QoL of these women.
- The issues of psychological state and sexuality and should be openly addressed with all patients experiencing infertility regardless its cause.

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Doctoral student

Iuliia Naumova

Dr. Camil Castelo-Branco, Senior Consultant of the Clinical Institute of Gynecology, Obstetrics and Neonatology (ICGON) of the Hospital Clínic de Barcelona and Full Professor of Obstetrics and Gynecology and Head of the Department of Surgery and Surgical Specializations of the University of Barcelona

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