

Stringency in polycystic ovary syndrome (PCOS) criteria and application in clinical study recruitment

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Abstract

Background: In this manuscript, we review the various criteria used to diagnosis PCOS, and discuss how the specific diagnostic criteria used can impact recruitment for PCOS studies. PCOS is a common diagnosis, but with a number of differing definitions. We were interested in addressing these differing stringencies and application in clinical trial, such as our group's PCOS diet study.

Methods: For our study on the effects of diets to alter insulin resistance, we adopted the one using more stringent criteria, consisting of biochemical abnormalities, menstrual abnormalities, insulin resistance and abnormal ovarian size and structure. Our study actively recruits from PCOS clinics in the Bay Area. We reported number of women successfully recruited using our PCOS diagnosis stringency, and how these numbers differ from women referred to PCOS clinics in the Bay Area. We also report the reasons patients did not fit our diagnosis criteria to shed insight into how diagnosis differ between healthcare professionals.

Results: To our surprise, the vast majority of subjects seen in the tertiary referral PCOS center at UCSF did not qualify for the study.

Conclusion: The definition of PCOS may be important in study design, and can impact the ability to recruit for the study.

Trial registration: Date of registration: June 20, 2014, NIH ClinicalTrials.gov identifier: NCT02190097

Background

Polycystic ovary syndrome (PCOS) is a common disorder that affects approximately 5-20% of women, though this varies by the criteria used to ascribe the diagnosis¹⁻⁴. Women with PCOS experience a number of symptoms, ranging from insulin resistance to infertility. Despite the high prevalence of symptoms that characterize PCOS, experts worldwide struggle to agree on the proper criteria to be used in both PCOS diagnosis and study⁵. The authors developed a study to further elucidate the influence of diets that impact PCOS symptoms through improving insulin sensitivity; specifically, a paleolithic-type diet and the American Diabetes Association (ADA) recommended diet. Due to the stringency of our study requirements for PCOS diagnosis, our group has struggled to recruit candidates in the Bay Area, despite being a tertiary referral center and recruiting from local PCOS clinics. We also attempted to recruit from the general population in the San Francisco Bay Area through flyers at both the UCSF and UC Berkeley health centers, through Facebook groups, the PCOS clinic study trial page, the UCSF clinical trial recruiting website, local endocrinologist offices, and our listing at clinicaltrials.gov. We therefore decided to investigate the use of varying PCOS criteria in clinical study design, and subsequent subject recruitment. Here, we first discuss PCOS symptoms, to evaluate which subjects would undergo testing for PCOS, the various criteria for PCOS, current treatment options, and finally, we discuss our study outcomes and why we applied the criteria that we did. We hypothesize that depending on what study outcomes are desired, varying definitions of PCOS could be applied. The objective of this study is to measure patient

recruitment under our group's selected PCOS diagnosis criteria. In this study, we reflect on PCOS diagnostic criteria and influence on patient recruitment to clinical trial.

1.1 PCOS Signs and Symptoms

Women with PCOS may experience the following signs and symptoms: 1) elevated androgen levels, 2) insulin resistance, 3) potential to produce ovarian cysts, 4) infertility, 5) irregular menstrual cycles, 6) hirsutism and/or 7) changes in mental health status⁶.

Abnormal release of gonadotropin-releasing hormone (GnRH) disrupts normal luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels, in turn produce increased androgen levels. These disruptions in hormone levels can lead to both oligo- or a-menorrhea (the loss of a regular menstrual cycle) and hirsutism (abnormal hair growth). Without regular menstrual cycles, women can experience difficulties when trying to get pregnant. Both the stress of coping with these symptoms and disruptions in normal hormone levels can lead to changes in mental health status, which can increase risk for depression and/or anxiety⁷.

Aside from the hormone changes experienced, women with PCOS are often insulin resistant and approximately 50% of women are overweight or obese. These metabolic health factors increase risk for high blood sugar, diabetes, stroke, heart disease, high blood pressure, high cholesterol, and sleep apnea⁸. The increased presence of insulin resistance, trouble regulating blood glucose levels, and prevalence of obesity/overweightness in women with PCOS diagnoses led our team to inquire about the influence of diet, specifically diets low in refined carbohydrates (e.g., refined sugars, processed grain cereals, "junk" food), which tends to lower insulin levels, as a method to potentially improve PCOS symptoms⁹⁻¹².

1.2 PCOS Criteria

Since the first documented PCOS patients in 1935, the criteria used for diagnosis has shifted over time. The first PCOS cases were reported by Stein and Leventhal based on seven cases of women with: 1) polycystic ovaries, 2) oligo/amenorrhea with subfertility 3) hirsutism, or 4) lower abdominal pain¹³. In 1990 at a National Institute of Health (NIH) meeting, the following updated criteria was suggested by Zawadski and Dunaif: 1) hyperandrogenism and/or hyperandrogenemia 2) oligo-ovulation 3) exclusion of other known disorders¹⁴. In 2003, the Rotterdam criteria for PCOS were suggested. These criteria are used today by a wide range of medical professionals and researchers and are based on expert meetings, not evidence-based treatment guidance¹⁵. Following these criteria, a PCOS diagnosis is given if two of these three criteria are met: 1) oligo-anovulation, 2) hyperandrogenism or hyperandrogenemia, 3) polycystic ovaries. Although these criteria are the most widely adopted among medical professionals, they remain controversial.

In 2006, the Androgen Excess Society (AES) Task Force members, including Azziz and his team, outlined updated criteria for PCOS diagnosis¹⁶. Considering the four features of 1) ovulatory dysfunction, 2) hirsutism, 3) hyperandrogenemia, and 4) polycystic ovaries, the task force identified nine different

phenotypes that could be considered as being PCOS with currently available evidence. These 9 phenotypes are as follows: A) hyperandrogenemia, hirsutism, oligo-anovulation, and polycystic ovaries B) hyperandrogenemia, hirsutism, and oligo-anovulation C) hyperandrogenemia, oligo-anovulation, and polycystic ovaries D) hyperandrogenemia and oligo-anovulation E) hirsutism, oligo-anovulation, and polycystic ovaries F) hirsutism and polycystic ovaries G) hyperandrogenemia, hirsutism, and polycystic ovaries H) hirsutism and polycystic ovaries I) hyperandrogenemia and polycystic ovaries. Figure 1 outlines the differences between the above discussed criteria.

1.3 Recent Criteria Used in Clinical Study

In recent studies, groups have differed in which set of criteria they use in defining PCOS in their recruitment of candidates. However, it is common to use criteria which address the androgen excess many PCOS patients experience. These criteria recommended by the AES task force may place too much excess on hyperandrogenemia. There are many other syndromes and diseases in which patients suffer from hyperandrogenemia, and it is important to first eliminate these diagnoses before diagnosing a patient with PCOS¹⁷. Elevated levels of another hormone, anti-müllerian hormone, has also been suggested as a potential marker for PCOS, however, further study is needed¹⁸⁻¹⁹. Our group believes the absence of a regular menstrual cycle is a key symptom in PCOS and should not be overlooked, even with the presence of hyperandrogenemia.

Although the above discussed criteria may be sufficient in clinical diagnosis with the goal of patient symptom improvement, more stringent criteria prove useful in specific clinical studies. Clinical studies differ in their goals, which can include treatment reform, providing updated clinical information to patients, and are typically broader scoped than a patient in a doctor's office²⁰⁻²¹. With this in mind, PCOS studies in particular have to proceed with caution when choosing which patients to recruit and which criteria to follow when defining "PCOS"²². Although our team recruits from PCOS clinics in the Bay Area, we have found that many women who have been referred by their doctor to the UCSF clinic do not meet our criteria for PCOS. We know that at least some of the subjects do not have a PCOS diagnosis, and are referred to the clinic by their doctor to find out if they have PCOS.

Methods

2.1 Inclusion/exclusion criteria

Because we were interested in studying if lowering insulin levels would improve hyperandrogenemia, as well as improve menstrual cycle irregularity, our inclusion criteria were: 1) women of reproductive age (18-40 years old), 2) chronic oligo/anovulation, defined as an intermenstrual interval of greater than 45 days and/or less than 8 menstrual cycles per year, 3) evidence of biochemical hyperandrogenemia, which presents as elevation of total or free testosterone above the normal range for women sometimes as hirsutism and/or acne, 4) agreeable to avoidance of pregnancy and to use barrier contraception for

duration of study, and 5) BMI between 18 to 40 kg/m², which spans a healthy weight range to overweight and obese.

We excluded subjects with: 1) other abnormalities which might lead to anovulation, including hyperprolactinemia, thyroid dysfunction and other causes of hyperandrogenemia including late onset congenital hyperplasia, 2) evidence of diabetes based on a fasting glucose of greater than 126 mg/dl or OGTT, use of medications and/or supplements that influence either ovarian function or insulin sensitivity, within 2 months, including oral contraceptive pills, hormonal implants, anti-androgens, antipsychotics, antihypertensives, metformin, glucocorticoids, and health food remedies other than multi-vitamins and calcium, 4) alcohol usage of more than 7 drinks per week, 5) hemoglobin of greater than 10 grams, 6) smokers, 7) inability to understand the study goals and protocols and the consent form 8) any subject, who in the opinion of the investigators, does not qualify for the study, 9) subjects on oral contraception, metformin, or nutritional supplements must agree to discontinue these drugs and undergo an 8-week washout period before the tests are performed.

In any study, it is important to eliminate as many other possible variables that may influence a subject's response to the given diet. These variables may present as: 1) other hormone abnormalities and reasons for anovulation, which may lead to a different response by a subject to a given diet, 2) subjects with diabetes may also provide to be troublesome for the purposes of this study because of their dysregulation of insulin secretion and absorption, and/or 3) other hormone interventions may influence the effect of a diet on PCOS due to their potential disruption in insulin signaling and the menstrual cycle.

2.2 Recruitment strategies

We recruited from patients seen at the PCOS clinic at UCSF, as well as from the San Francisco Bay area, specifically putting up flyers at UCSF medical centers, UC Berkeley health centers, and from local endocrinologist offices. We are listed on clinicaltrials.gov, the UCSF clinical trial recruiting website, the PCOS clinic study trial page, our own Facebook page (<https://www.facebook.com/ucsfpcosdietstudy>) and study webpage (<http://www.pcosdietstudy.org/>), and have links with several PCOS webpages. We publicize our study through these websites in order to reach a broader audience and recruit from the general San Francisco Bay Area population.

Results

3.1 Recruitment for Clinical Study

The number of women we are able to recruit for our study is much lower than the number of women referred to the PCOS clinic. Figure 2 demonstrates the number and percent of subjects with various PCOS diagnostic criteria potentially eligible for our study. These reasons included: 1) subject followed a vegan or vegetarian diet, subject experienced normal menses, subject had normal testosterone levels, subject was using hormonal birth control, subject declined, subject was outside study age range (18-40 years

old), subject was outside study BMI range (18-40 kg/m²). The number of women who qualified for our study was consistently less than 10% of all of the subjects seen at our tertiary referral center for PCOS.

Due to the nature of our dietary study, we had to exclude patients for dietary reasons which further limited our recruitment success. It was important to our group to base our recruitment criteria on our stringent PCOS criteria, which further limited recruitment percentages. We believe this demonstrates women diagnosed with PCOS by their primary care provider and referred to the clinic were often diagnosed under more lenient PCOS diagnostic criteria.

Discussion

Our findings are unique in that no other groups have reported on PCOS recruitment difficulties. Stringency in recruitment criteria is especially important in dietary studies examining metabolic variance among groups due to the impact these recruitment variables can have on study outcome. Our findings suggest that PCOS criteria stringency should be decided upon based on individual study area of focus and design. For example, in our study we look to measure the importance of a whole food, paleolithic-type, diet on PCOS thus require strict diagnosis criteria including biochemical abnormalities, menstrual abnormalities, insulin resistance and abnormal ovarian size and structure.

4.1 Importance of Insulin Resistance as a Marker for PCOS

Although not all women who display symptoms in line with those of PCOS experience insulin resistance, it is an important factor of the overall syndrome. Insulin resistance occurs when higher than usual levels of insulin are required to maintain normal blood glucose levels. As subjects continue to eat a high sugar (or carbohydrate) diet, beta cells continue to secrete more insulin with resultant continuing high blood insulin levels. This cycle occurring over and over again can lead to damage to the beta cells in the pancreas and altered insulin release, thus resulting in insulin resistance²³.

Women with increased blood insulin levels often have increased androgen levels, a hallmark symptom in PCOS. Increased insulin levels can lead to lowered FSH levels, thus causing disruption in the important balance of reproductive hormone levels. With this, androgen levels rise and women with these symptoms may experience a range of symptoms including hirsutism, disruption in normal menstrual cycle, and acne. Thus, targeting improvement of insulin resistance in women with PCOS may offer potential improvement of syndrome symptoms through improving hormone homeostasis²⁴⁻²⁵. Multiple studies have shown insulin resistance is an important contributor to the pathophysiology of PCOS, thus it is not surprising to think that an insulin sensitizing diet may improve the endocrine imbalances associated with PCOS²⁶.

4.2 Obesity

Obesity is also associated with insulin resistance²⁷. A metaanalysis by Behboudi-Gandevani et al. showed that group 1 (obese, PCOS patients) statistically had the highest IR and group 4 (non-obese, non-

PCOS women) have the highest insulin sensitivity. HOMA-IR pooled mean (95% Conf. Interval) of groups 1, 2, 3 and 4 were 5.23 (3.62, 6.85), 2.55 (1.50, 3.59), 3.58 (2.94, 4.21) and 1.32 (0.65, 1.99). Group 2 (non-obese, PCOS patients) and group 3 (obese, non-PCOS women) were between this range and they had lower IR than group 1 (obese, PCOS) and lower insulin sensitivity than group 4 (non-obese, non-PCOS). Weight loss has been shown to improve insulin resistance and PCOS symptoms²⁸.

4.3 Current Treatment Options

The most common current recommendation to improve PCOS prognosis is to follow a healthy lifestyle, which includes a healthy diet and regular exercise. This aids in treating insulin resistance and high blood sugar levels, thus, insulin lowering diets provide a method of potentially treating PCOS. Through a healthy diet and exercise, weight loss is recommended to women with PCOS to aid in alleviating symptoms²⁹.

Although diet, exercise, and weight loss are the most common recommendations by medical professionals to patients with PCOS, there are several methods of drug intervention as well. Birth control can both help in regulating hormone levels, and in turn, provide a regular menstrual cycle. Metformin, a drug commonly used to treat patients with type 2 diabetes mellitus, can be prescribed to women with PCOS in efforts to help lower insulin levels. Spironolactone is often prescribed to assist in preventing excess hair growth. Anti-depressants and anti-anxiety medications can assist in treating potential changes in mental health.

Possibly one of the reasons that so many options are available for PCOS treatment is related to the lack of uniform criteria for PCOS. Without uniform criteria, it's not clear that that we are even treating all the same problem; that is, the diagnosis of PCOS covers a description of a syndrome or final common pathway, with more than one etiology, and hence the failure of any one specific approach. This was our reasoning for the strict criteria used in our study. PCOS is a multifaceted problem and treatment options may change over the course of one's life depending on disease phenotypes that present over time. It is important to manage insulin resistance, as this has been shown to be a contributor to PCOS symptoms.

4.4 Conclusions

Although several groups of criteria have been developed for PCOS diagnosis, our group believes it is important to define PCOS stringency criteria for application in clinical study. Although this has led to difficulties in recruitment of candidates for our clinical study, we remain committed to recruiting candidates of the most consistent criteria to eliminate unnecessary variables which can alter study results. Since our primary outcome variable was improvement in menstrual cycle regularity, we deemed it important to include ovulatory dysfunction. As a co-factor, we also measured ovarian size and number of ovarian cysts. Because our diet study aims to determine the influence of insulin lowering diets on androgen levels, we also required biochemical hyperandrogenemia, (i.e., stricter PCOS subject stringencies as compared to other common diagnosis criteria used in medical practice). We suggest that studies without our specific hypotheses could potentially use other criteria for recruitment. The complexity of the disease makes it difficult to treat, and we hope that by more appropriate diagnoses

criteria for clinical study may help us to parse out the many contributors behind PCOS pathophysiology. In conclusion, we hope that this will help other groups in deciding which criteria to use for application in clinical study, and to not be discouraged by speed of recruitment. Hopefully, our study can provide further insight into the use of diet in PCOS treatment.

Declarations

Ethics approval and consent to participate

All subjects consented to participation in the study and collection and dissemination of data. This study is overseen by the UCSF Office of Ethics and Compliance.

Consent for publication

As an academic study, the group received consent to publish.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All of the authors deny any conflicts of interest.

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Authors' contributions

UM, HH, LF and AM contributed to the design of the study. All of the authors contributed to the writing of this manuscript.

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Abbreviations

PCOS: polycystic ovary syndrome

UCSF: University of California San Francisco

ADA: American Diabetes Association

GnRH: gonadotropin-releasing hormone

LH: luteinizing hormone

FSH: follicle stimulating hormone

AES: Androgen Excess Society

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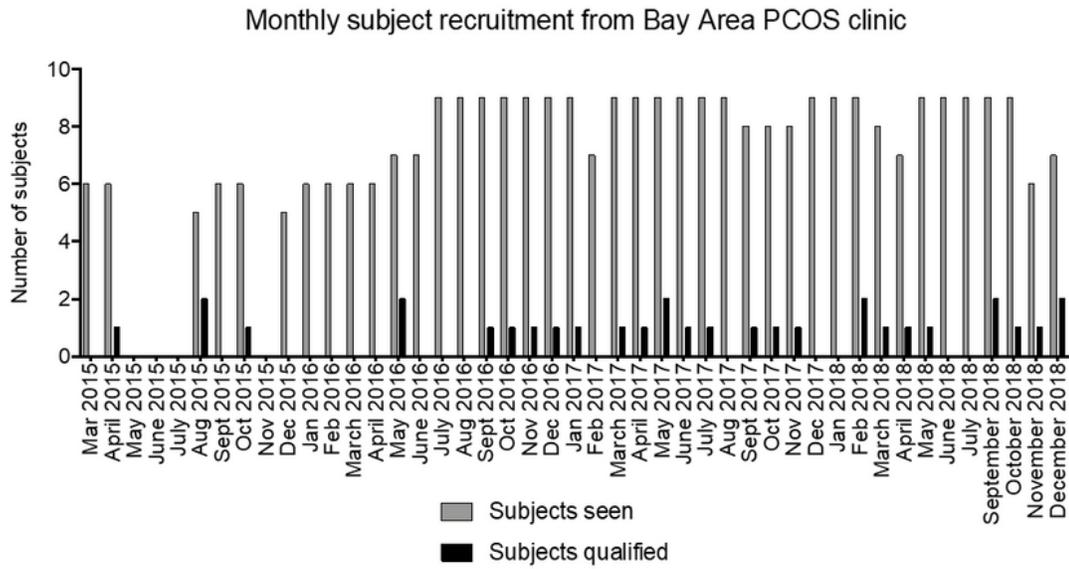
Figures

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligo-anovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	✓	✓	✓	✓	✓	✓										
Rotterdam 2003 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
AES 2006 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓							
Suggested clinical study criteria	✓	✓	✓	✓	✓	✓										

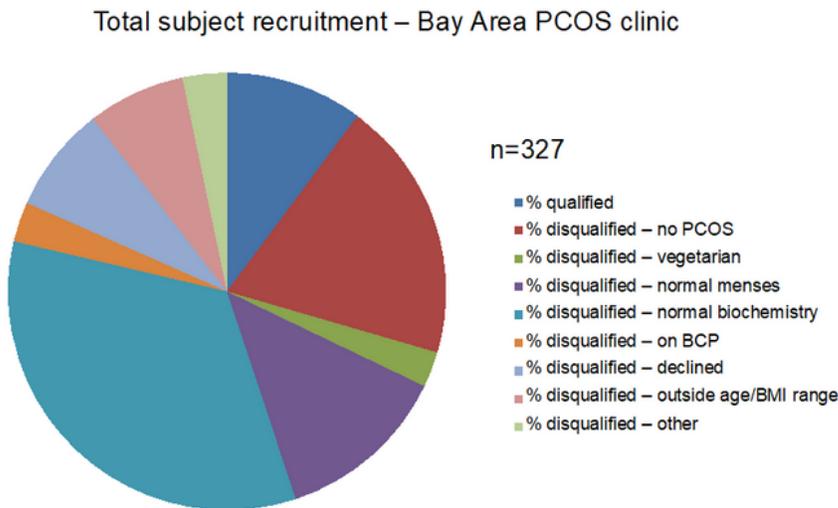
Figure 1

Possible phenotypes of PCOS based on the presence or absence of hyperandrogenemia, oligo-anovulation, hirsutism, and polycystic ovaries. Our suggested stringency of clinical study criteria fits closet to that discussed in 1990 by the NIH.

A.



B.



% qualified	% disqualified							
	no PCOS	vegan/vegetarian	normal menses	normal testosterone or insulin levels	declined - on BCP	declined	outside age/BMI range	other
9	17	3	12	32	3	6	7	2

Figure 2

PCOS subject recruitment for clinical study from Bay Area PCOS clinic: A. Monthly subjects seen in the PCOS clinic as compared to number of candidates recruited for study. B. Representation of the total number of subjects seen as compared to those qualified to participate in our group’s clinical study.