

Polycystic Ovarian Syndrome amongst Refugee Populations from Middle Eastern and North African Countries

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Abstract

Polycystic ovarian syndrome (PCOS) affects an estimated 8-13% of premenopausal women yet remains undiagnosed in up to 70% of this population.¹ While few studies have been conducted, it appears there may be an increased prevalence as well as a variable phenotype amongst those from Middle Eastern and North African (MENA) countries. The refugee population at present has a large representation from several countries in this region, including Afghanistan, Iran, Iraq and Syria. Refugee patients coming from MENA countries may have experienced significant stressors or trauma that can exacerbate or increase susceptibility to PCOS.

Intro to PCOS

Polycystic ovarian syndrome is a heterogeneous and prevalent endocrine disorder that affects reproductive aged women. Its features are irregular periods, hyperandrogenism, and at times polycystic ovaries on ultrasound. Elevated androgens can be seen with either clinical signs such as acne, hirsutism, androgenic alopecia, or biochemically on laboratory tests. PCOS has a strong association with metabolic syndrome and those with PCOS are at a heightened risk for developing Type 2 Diabetes.² Anovulatory and irregular cycles can result in reduced fertility. Development of PCOS appears to have a strong genetic component and is highly heritable, but there are numerous other factors, such as environmental, cultural, and epigenetic influences.³

Prevalence amongst MENA Countries

MENA countries include Afghanistan, Algeria, Bahrain, Egypt, Iran (Islamic Republic of), Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, State of Palestine, Qatar, Saudi Arabia, Sudan, the Syrian Arab Republic, Tunisia, Turkey, the United Arab Emirates and Yemen.⁴

A challenge of understanding the prevalence of PCOS is the differing

diagnostic criteria used to diagnose PCOS, including Rotterdam, National Institute of Health (NIH), and Androgen Excess Society (AES). There is varying prevalence based on the criteria used. The NIH definition of 1990 required hyperandrogenism and oligo or anovulation, with polycystic ovaries being a suggestive feature of PCOS but not truly part of diagnosis.⁵ The Rotterdam criteria require 2 out of 3 of the following: clinical or biochemical hyperandrogenism, oligo or amenorrhea, and polycystic appearing ovaries on ultrasound.⁶ This definition broadened the number of people meeting criteria as opposed to the NIH criteria, because it allowed patients to be diagnosed without meeting criteria for hyperandrogenism. The AES guidelines of 2006 again required hyperandrogenism and either anovulation or polycystic ovarian morphology, excluding patients without clinical or biochemical signs of elevated androgens.⁵

The current general prevalence of PCOS according to the Rotterdam criteria is 10% with a possible range of 8-13% among a review of 15 trials.⁷ A meta-analysis of reviews from the Middle East found a pooled prevalence of PCOS diagnosed according to the Rotterdam criteria of 11.9% with a 95% confidence interval of 7.1 to

17.7%⁸. Using the NIH criteria, the prevalence was 8.9% with a much higher prevalence in the Gulf Arab states of 18.8%.⁸ Those studies with the Rotterdam criteria, however, were done only in the Persian (Iran) and Levant (Cyprus, Iraq, Israel, Jordan, Lebanon, Palestine, Syria, Turkey) regions.

Another systematic review used random effect modeling to demonstrate the prevalence of PCOS amongst different ethnicities in general. They found that, using Rotterdam criteria, there was a prevalence of 16% amongst Middle Eastern women, and 6.1% using NIH criteria.⁹ Overall, the results showed lowest prevalence for Chinese women, and then in ascending order Caucasian, Middle Eastern, and Black women with the highest prevalence. Studies from the Middle East were limited to Iranian and Turkish populations. They discussed the large variation using criteria that was most stark in the Middle East population, and concluded that it was evidence of either over or underdiagnosis given the high variation⁹.

Information gathered from the Global Burden of Disease Study, conducted in 2019, was analyzed by Motlagh et al. to explore incidence rates of PCOS in the MENA region. Overall, the rate was 77.2 per 100,000, with a 95% uncertainty interval of 51.6 to 105.4. This was a 33.7% increase since 1990. There was a varying amount of burden on countries, with Kuwait having the highest Years living with Disability (YLD) rate at 25.4 and Afghanistan at 10.8. Highest prevalence was among ages 20-24.⁴

Overall these data seem to show a higher prevalence among Middle Eastern women, even with likely a degree of underdiagnosis. This was seen in a Danish study comparing Caucasian (CA) and Middle Eastern (ME) women that found that Rotterdam criteria for diagnosis of PCOS were met in 56% of both groups, yet 47% of CA had previously been diagnosed, with

only 29% of ME women having been given a diagnosis prior to the study.¹⁰

Genetic Variation

Genetic differences have been suggested as a possible explanation for the variation in both prevalence and phenotype. A study of Iranian women with PCOS concluded there were more polymorphisms in genes related to inflammation and metabolism, but not those related to insulin.¹¹ Other studies have investigated sex hormone binding globulin (SHBG) genes and found there are several variants that may be associated with PCOS.¹² A study of Mediterranean women from Spain and Italy, who are not from the MENA region per se but may share some genetic similarities, showed that there were SHBG variants that influenced SHBG levels and were more common in patients with PCOS.¹³

Diagnosis in Refugee Patients from the Middle East

The Rotterdam criteria are the most widely used, accepted, and affirmed form of diagnosis at present among refugee patients. The presence of multiple diagnostic criteria has led to confusion amongst clinicians and patients, but the Rotterdam criteria have become the consensus amongst the scientific community and should be used. Refugee patients may have been evaluated using NIH guidelines in the past or with an even older criteria requiring the presence of polycystic ovaries. Therefore, patients must be evaluated to meet 2 out of the 3 of hyperandrogenism, oligo/anovulatory cycles, and polycystic ovarian morphology. The following sections will go over possible phenotypic and diagnostic considerations.

Hirsutism

Hirsutism may be present in varying degrees based on ethnicity. For example, the burden of excess hair growth is higher amongst those of Middle Eastern or South Asian origin, while those of Caucasian or East Asian ancestry may have less hair

growth.¹⁴ Middle Eastern women may accept a higher degree of hair growth as normal, looking to family and friends for comparison, and they may in fact be correct in the assumption that they may have a higher baseline. In a study of Danish women with PCOS, Caucasian women were less hirsute but had increased testosterone levels as compared to Middle Eastern women.¹ Therefore, it may be up to the patient to decide what is normal or abnormal for them. In order to understand hirsutism, it may be helpful to discuss with the patient if they have noticed a change in the amount of hair growth or feel it is a higher burden than that of other female relatives in their family.

There are some hypotheses as to why hirsutism levels among Middle Eastern women may be higher while at lower testosterone levels. Androgens increase hair follicle size, diameter of fiber, and time spent during the anagen phase. Testosterone levels overall do not correlate well with the burden of hirsutism. Conversion of testosterone to the more potent form of DHT due to varying levels of the converting enzyme, 5 α reductase, may be a possibility. End organ sensitivity in the form of receptors on hair follicles may also play a role. And finally, sex hormone binding globulin may also influence the amount of free testosterone available to cause effects on hair follicles. Those with lower levels of SHBG may experience more clinical symptoms of hyperandrogenism.¹⁴

The modified Fenway Galliman (mFG) score is a standardized way to evaluate hirsutism. Visually scoring abnormal hair in nine different body areas, grading from 0 (no terminal hair) to 4 (male pattern hair). The mFG cutoff for hirsutism is 8.¹⁵ Some have suggested a higher cutoff score for Middle Eastern women, or generally different cutoffs on the basis of ethnicity.

Hair removal practices are used by patients to treat their hirsutism but may limit diagnosis. For that reason, inquiring about practices of hair removal including shaving, depilatory creams, plucking, threading, waxing, epilating, and sugaring is recommended. Many of these methods involve removing the hair follicle itself and may reduce growth over time. Others turn to more permanent methods such as laser hair removal or electrolysis. These methods can be successful in those with PCOS, but usually require a higher number of sessions, higher energy levels, and maintenance sessions.

It may be more useful to simply move to a biochemical criterion for hyperandrogenism in those patients that are unsure if they have an abnormal amount of hair growth. However, those laboratory tests pose a challenge as well. Androgen levels may fluctuate throughout the day or throughout the menstrual cycle. Additionally, many of the tests available are unreliable and there is a lack of standardization of testosterone assays between institutions.¹⁶

Menstrual Irregularities and Anovulatory Cycles

Menstrual irregularities may be a presenting complaint for many women with PCOS. Besides the inconvenience that irregular menstruation can cause, it may be impactful on religious practices as well for this population. For example, prayers in Islam or communion in the Oriental Orthodox Church may be affected. Inquiring about how these menstrual irregularities are impacting the patient may help direct treatment options as we consider treatment goals.

Note on Over/Underdiagnosis

Overall, it is important that we do not over or under diagnose PCOS. Overdiagnosing may lead to unnecessary and futile treatment, as well as worry and

anxiety. It is not a diagnosis that should be given lightly, as it is associated with a significant amount of distress due to future risk of chronic health issues and fertility concerns. However, underdiagnosing may leave patients to suffer without treatment and be more susceptible to negative sequelae of PCOS, such as depression, anxiety, diabetes, weight gain, and endometrial cancer.

Preventative Healthcare for Patients with PCOS

Patients with PCOS have an increased incidence of metabolic syndrome, Type 2 diabetes, and heart disease. There have been reports of other immigrant populations experiencing an increased amount of metabolic syndrome and its sequelae, but no comprehensive data around Arab American immigrants or those from MENA countries.

Arab American health is overall a difficult area to study. It is a minority group that is often classified as Caucasian or Asian on paperwork and data collection sources, meaning they are difficult to identify on a wider scale in order to study diseases such as diabetes, heart disease, and metabolic syndrome. Research on this group comes from looking at specific ethnic enclaves, rather than population wide sampling. Nevertheless, there appears to be a high prevalence of diabetes, estimated at 4.8-23% of Arab Americans.¹⁷ Vitamin D insufficiency has been identified as a possible contributing factor and is highly prevalent, which appears to be due to diet and lack of sun exposure.¹⁸ Interestingly, acculturation has been found to be associated with an increased diabetes risk, not for men, but for women.¹⁷

A retrospective transectional study of a thousand premenopausal women in Denmark with PCOS, divided by ethnicity, investigated the clinical differences and metabolic risk factors. Caucasian women

had increased body mass index (BMI) compared to Middle Eastern women.¹¹ Another study comparing metabolic characteristics in a Caucasian (UK) and Middle East (Qatar) population showed a few differences. UK women had higher BMI, waist and hip measurements, triglycerides, and systolic and diastolic blood pressure. Middle Eastern women had higher testosterone, high density lipoprotein (HDL), and C-reactive protein (CRP). Glucose, insulin, and hemoglobin A1c were not significantly different, even with the difference in BMI. Middle Eastern women may have a more severe level of hyperandrogenism with fewer metabolic outcomes, but a higher level of CRP that is correlated with increased cardiovascular risk.¹⁹

All of this underscores the importance of identifying those with PCOS in order to assess risk. Annual hemoglobin A1c in patients with PCOS is recommended. In refugee patients, there is already a higher burden of mental health considerations, and women with PCOS are more likely to be affected by depression and anxiety. Women with PCOS should also be screened for mental health concerns and directed to appropriate resources.

Endometrial Cancer

A meta-analysis of gynecological cancers in women with PCOS found that they are 5 times more likely to develop endometrial cancer compared with women without PCOS.²⁰ However, high BMI is a known risk factor, and it is possible the increased incidence of endometrial cancer is at least, in part, due to obesity. Another hypothesized contributor is the chronic anovulation, exposing the endometrium to prolonged estrogen. Results from the Global Burden of Disease study show endometrial cancer as an increasing problem, with age-standardized prevalence rate increasing by 10% in MENA region between 1990 and

2017, which was a greater increase than anywhere else in the world.²¹

There are no guidelines for screening or prevention of endometrial cancer in those with PCOS, and risk mitigation with OCPs does not appear to have been studied in women with PCOS. It could be logically deduced that contraceptive options that address the anovulatory or oligoovulatory states would lead to shedding or thinning of the endometrium, reducing the likelihood of metaplasia. In fact, several studies have demonstrated a risk reduction of about 50% in those using combined oral contraceptives in the general population.²²

Treatment overview for refugee patients with PCOS

With all patients, discussing lifestyle modifications such as diet, exercise, and sleep are a mainstay of the treatment plan. For those who desire menstrual suppression or regularity or treatment of acne and hirsutism, oral contraceptives can be offered. However, some patients may not be interested in this treatment option as it may be stigmatized in their community or culture, especially for unmarried women. If this is chosen as an option for hirsutism, explaining that contraceptives may take around 6 months to affect hair follicles may improve compliance and patient satisfaction. Spironolactone is often used to address hirsutism as well. It is usually prescribed alongside an OCP in sexually active women due to the theoretical risk of feminization of a male fetus in the case of pregnancy. Other options include LARCs for menstrual regularity, especially hormonal IUDs, but it is important to counsel patients that those options will not treat acne or hirsutism. Metformin can result in a modest weight loss and improvement of symptoms, even in patients who are not overweight or prediabetic.²³ GLP-1 agonists have been studied as a treatment for obese women with PCOS and are showing promise as a more

effective treatment than metformin,²⁴ though more research is needed.

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