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COMMENTARY

International evidence-based guideline on assessment and management of PCOS—A Nordic perspective

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Abstract

Polycystic ovary syndrome (PCOS) affects about 12% of women of reproductive age. In 2018, the first evidence-based guideline on assessment and management of PCOS was published, and an updated extended guideline was released in August 2023. These guidelines followed best practice and are endorsed by 39 organizations worldwide, making them the most robust source of evidence to guide clinical practice. In the 2023 guideline, diagnostic criteria have been further refined as polycystic ovary morphology can now be assessed with gynecological ultrasound or elevated anti-Müllerian hormone levels. A healthy lifestyle should be at the focus of care for all women with PCOS; however, with no specific diet or physical exercise recommended. The latest evidence on medical treatments and fertility management are reviewed, including special considerations regarding long-term follow-up of metabolic and psychiatric comorbidities and pregnancy in women with PCOS. Here we summarize the recommendations from a Nordic perspective.

Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; COCP, combined oral contraceptive pill; CPA, cyproterone acetate; EBG, evidence-based guideline; EE, ethinyl estradiol; OR, odds ratio; PCOM, polycystic ovary morphology; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

Maria Forslund and Johanna Melin share first authorship.

KEYWORDS
evidence-based guideline, Nordic guideline, polycystic ovary syndrome

1 | INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women worldwide affecting one out of eight regardless of ethnic background.[1,2] Apart from the symptoms included in the diagnostic criteria (hyperandrogenism and menstrual cycle irregularity), clinical manifestations include reproductive, cardiometabolic, dermatological and psychological features.[3] Unfortunately, the awareness of the syndrome and associated comorbidities has been poor also in the Nordic countries.[4]

In 2018, the first international evidence-based guideline (EBG) for the assessment and management of PCOS, was published, designed to provide evidence-based information, unify and improve patient care. Now, an updated and extended EBG has been developed, to further improve diagnosis and care for this common condition.[5] The EBG was developed in collaboration with over 1000 healthcare professionals, academics, and patients worldwide. A total of 55 prioritized clinical questions were assessed through 52 systematic and three narrative reviews. In total, 39 organizations were involved in the work, including the Nordic Federation of Societies of Obstetrics and Gynecology (NFOG). Here, we summarize the recommendations, from a Nordic perspective.

Key message

The updated evidence-based guideline on assessment and management of polycystic ovary syndrome (PCOS) was released in August 2023, and is here summarized from a Nordic perspective.

2 | PCOS DIAGNOSIS

The revised Rotterdam criteria are now updated to evidence-based criteria. In adults, presence of at least two out of the following criteria of (1) clinical/biochemical hyperandrogenism, (2) ovulatory dysfunction, and (3) polycystic ovary morphology (PCOM) with gynecological ultrasound or elevated anti-Müllerian hormone (AMH) levels are required, after exclusion of differential diagnoses. Most women with PCOS have a combination of hyperandrogenism and irregular cycles, and in these cases there is no need to assess PCOM. In adolescents, both ovulatory dysfunction and hyperandrogenism are mandatory.[5]

Regarding definitions, ovulatory dysfunction is commonly diagnosed by irregular menstrual cycles, defined as <21 or >35 days between cycles when more than 3 years after menarche. The EBG clarifies that irregular cycles are normal the first year after menarche, if >1 to <3 years post menarche, irregular cycles are defined as <21 days or >45 days between cycles. Ovulatory dysfunction may occasionally occur with regular cycles and can be confirmed by measuring serum progesterone levels.

Hirsutism is the most important sign of clinical hyperandrogenism and is best assessed via standardized visual scales such as the modified Ferriman-Gallway score, where a score ≥4–6 indicates hirsutism. This threshold applies to all ethnicities, but we recommend a cutoff of ≥4 in fair-skinned women of Nordic origin. As many women tend to remove hair, the visual scales can be evaluated together with the patient's perspectives. Other signs of clinical hyperandrogenism include acne and female pattern hair loss, but they are less specific.

Biochemical hyperandrogenism should be assessed by measuring total or free testosterone or calculating free androgen index. Liquid chromatography-mass spectrometry (LC–MS) should be used for assessing testosterone, and not direct immunoassays, as their sensitivity and accuracy are too poor, especially at low concentrations.[5] Importantly, despite good availability of LC–MS, many laboratories in the Nordic countries still use direct immunoassays to measure androgen levels in women, thus warranting awareness from the clinicians.

PCOM is defined as ≥20 follicles 2–9 mm on either ovary. As a new criterion, serum AMH can be used as an alternative in adults, noting that AMH is influenced by age, body mass index (BMI), ethnicity, combined oral contraceptive pill (COCP) use, and menstrual cycle day.[5] Cutoffs for AMH are population and assay specific. Neither PCOM nor AMH should be used for diagnosis within 8 years from menarche, as many adolescents have high ovarian reserve. Including AMH in the PCOS diagnosis workup seems to produce reliable PCOS populations also in a Nordic setting.[6] It should also be noted that differently from many other countries, gynecologists perform all ultrasounds themselves thus facilitating ultrasound-based diagnostics for the PCOM in specialized care. However, for general practitioners, measuring AMH-levels is more useful. Indeed, the incorporation of AMH, which is widely available in the Nordic countries, in the diagnostic workup allows a shift towards conducting the evaluation primarily by general practitioners, enabling more effective and continuous overall care, while also saving resources for specialized care. It is important for all healthcare practitioners to be aware of PCOS, to diagnose it, and to inform the patient about the diagnosis.

3 | PSYCHOLOGICAL FEATURES AND MODELS OF CARE

The prevalence of depression and anxiety is increased in adult women with PCOS, odds ratio (OR) 2.6 and 2.7, respectively.[5]

Feedback from consumers and professionals shows that this is often neglected by healthcare professionals.[5] Accordingly, the 2023 EBG recommends routine screening for depressive and anxiety symptoms using regionally validated screening tools. If signs of depression or anxiety are found, the practitioners should further assess and offer treatment or refer to a specialist.[5] In the Nordic setting this is usually managed by the general practitioners.

Negative body image is prevalent in PCOS and is associated with increased anxiety, depression, and decreased health-related quality-of-life.[5] Addressing negative body image offers the potential to manage psychological aspects such as self-esteem and self-acceptance, as well as addressing physical aspects, including hirsutism, overweight, and acne.

The odds for bulimia and binge eating are higher in women with PCOS.[5] Therefore, eating disorders or disordered eating should always be considered in PCOS, independent of weight but especially during weight management and lifestyle interventions. If disordered eating is suspected, qualified practitioners should conduct further assessments and offer appropriate management and support. Psychosexual function are lower in women with PCOS; however, the clinical significance of this finding remains unclear.[5]

The updated EBG strengthens recommendations concerning information resources, models of care, and considerations for cultural and linguistic factors, and recommends that information and education on PCOS should be systematically integrated at all levels of health care professional training.

4 | LIFESTYLE MANAGEMENT

Women with PCOS have an increased prevalence of obesity (around 50%) with adverse impact on reproductive, metabolic, dermatological and psychological health.[5] In the general population, women in the Nordic countries have lower prevalence, around 20%, of obesity compared with many other high income countries.[7] However, lean women with PCOS also have insulin resistance with metabolic risks, exacerbated further by increased weight. There is evidence that lifestyle intervention including exercise alone, or diet combined with exercise and behavioral strategies improves metabolic health in PCOS including central obesity and lipid profile.[5] A healthy lifestyle can therefore be recommended for all women with PCOS to optimize general health, quality of life, body composition, and weight control to prevent weight gain or weight loss in those with overweight/obesity. With current knowledge, there is no specific diet or exercise that is superior to others.[5] The updated EBG recommendations[5] are consistent with population guidelines for physical activity,[8] as well as for diet according to the new Nordic Nutrition Recommendations 2023.[9] When discussing lifestyle management, healthcare professionals should be aware of misinformation on lifestyle advice and of the weight stigma experienced by many women with PCOS.

5 | MANAGEMENT OF NONFERTILITY FEATURES

COCPs are first-line pharmacological treatment for irregular menstrual bleedings and hyperandrogenism.[10] There are marginal benefits of COCPs containing the antiandrogen cyproterone acetate (CPA) combined with ethinyl estradiol (EE) compared with the conventional COCPs; however, EE/CPA-containing pills are not recommended as first-line therapy due to the higher risk of venous thrombotic events after EE/CPA compared with other COCPs in the general population.[11] Lower dose EE therapies have demonstrated efficacy and are recommended. Specific types of COCPs in a context of PCOS cannot currently be recommended; however, COCPs with natural estrogens may offer benefits in effects on metabolism, whilst evidence regarding PCOS is needed on clinical outcomes.[11] In many Nordic countries second generation COCPs are used as first-line treatment due to their beneficial risk profile on venous thrombotic events. Progestin-only preparations can be used for endometrial protection in PCOS, but the data regarding progestin-only preparations on hyperandrogenism is currently limited.[11]

Metformin is recommended for anthropometric and metabolic outcomes, with best evidence in women with BMI ≥25 kg/m^2 but can also be considered in women with normal BMI.[12] Treatment is suggested to start at a low dose, with 500 mg increments once or twice per week, to minimize side effects, with suggested maximum dose 2.5 g in adults and 2 g in adolescents.[5] In cases of pregnancy wish, it has been general practice in the Nordic countries to stop metformin when a pregnancy test is positive/at early ultrasound. This is also supported by the new EBG.

Combination treatment with COCP and metformin may be beneficial in high metabolic risk groups, including women with BMI ≥30 kg/m^2, and those with risk factors for type 2 diabetes (T2D).[13]

Inositol is not recommended but can be considered based on individual preferences. Potential improvement in metabolic measures is noted, but with limited clinical benefits including in ovulation, hirsutism and weight. Considerations need to balance the low potential harm from treatment and moderate cost with limited benefits. Metformin has greater benefits and is recommended over inositol. No recommendation can be made regarding specific types of inositol, doses or combination with other treatments, due to lack of quality evidence.

The glucagon-like peptide-1 receptor agonists used in T2D can be considered as antiobesity treatment in PCOS together with active lifestyle intervention, based on general population recommendations.[5] These treatments are recommended to be used together with effective contraception, as pregnancy safety data are lacking. In the Nordic countries, most of these treatments are currently only approved for the treatment of T2DM. Orlistat is another pharmacological option for anti-obesity treatment. Bariatric/metabolic surgery, available in the Nordic countries, could be considered to improve weight loss[5] based on general population data where it has been shown that in women with BMI ≥35 kg/m^2, bariatric/metabolic

surgery is effective both for weight loss and improved health outcomes. A recent study on women with PCOS showed marked improvements in weight, PCOS symptoms such as hirsutism and irregular periods, but also in lowering the risk for associated comorbidities including T2D and hypertension after surgery.[14] Randomized trials as well as pregnancy and long-term outcome data is limited.

Treatment of hirsutism has been a prioritized area for patients. COCP is first-line treatment, but if not sufficient (given for at least 6 months), an antiandrogen can be added, with mandatory effective contraception.[15] Spironolactone is widely available in the Nordic countries, and doses of 25–100 mg/day seem to have the lowest risk of adverse effects.[15]

The EBG recommends use of laser or mechanical light therapy to treat hirsutism.[5] The guideline highlights that a greater number of sessions might be needed in women with PCOS compared to those with idiopathic hirsutism, and laser is less effective in women with blond, grey or white hair. Intense pulse light (IPL) could be considered, but benefits seem less compared with laser treatment. As laser treatment is an evidence-based therapy, this treatment should be included in the publicly supported treatment options also in Nordic countries.

6 | INFERTILITY

The guideline highlights the good prognosis for live birth for most with PCOS. Indeed, several studies from the Nordic countries have shown that women with PCOS are as likely to have at least one child as non-PCOS controls.[16–19] Women with PCOS should be aware of this to reduce the stress related to this issue and to avoid the stigma of permanent infertility. However, many women with PCOS will need treatment for anovulation and counseling to optimize exacerbating factors such as BMI and maternal age. The EBG recommends age-appropriate education on how to optimize reproductive health in adolescents and women with PCOS including a healthy lifestyle and prevention of excess weight gain without creating weight stigma.

If fertility treatments are needed, letrozole should be considered the first-line pharmacological treatment for anovulation after excluding other causes of infertility In some countries ultrasound monitoring is not performed during the use of these medications, however, in the Nordic setting ultrasound monitoring at least at the first cycle has been part of good clinical practice. Metformin may also be considered as a low threshold infertility treatment, requiring no ultrasound. However, women should be informed that there are more effective ovulation induction agents available. If a woman with PCOS fails to ovulate or responds unfavorably to letrozole, gonadotropin therapy can be used as a second-line treatment, using a low dose gonadotropin protocol and with careful monitoring of follicular development by ultrasound. Nordic clinics are commonly using letrozole and less often gonadotropin treatment. Laparoscopic ovarian drilling can be considered second line as per the EBG. However, due to the invasive nature of the procedure but on the other hand good access to ovulation induction medications and IVF in the Nordics, it is rarely applied.

Finally, if ovulation induction fails, assisted reproductive technology, including in vitro fertilization and intracytoplasmic sperm injection can be offered as a third-line treatment, acknowledging the increased risk for ovarian hyperstimulation syndrome. Options to reduce this risk should be offered (antagonist protocol and agonist trigger). Elective single embryo transfers, endorsed by the EBG, has already been routine clinical practice in the Nordic countries for several decades.

7 | PREGNANCY COMPLICATIONS

Compared to non-PCOS women, women with PCOS have increased risk of miscarriage (OR 1.50), gestational diabetes (OR 2.35), gestational hypertension (OR 2.20), pre-eclampsia (OR 2.28), preterm delivery (OR 1.54) and cesarian section (OR 1.23), also in BMI and age-matched analyses.[5] The PCOS offspring have higher risk for being, small for gestational age, having low birthweight or intrauterine growth restriction, while macrosomia and large for gestational age do not seem to differ.

During pregnancy, PCOS symptoms are difficult to detect, and the condition is seldom considered in everyday obstetric practice. The lack of awareness of the impact of PCOS on pregnancy outcomes and of quality evidence on prepregnancy management of women with PCOS leads to low identification rates and most probably result in suboptimal screening and pregnancy care. Thus, healthcare professionals should identify PCOS status early in pregnancy, indicate this on the health chart, and recognize these pregnancies as being of higher risk. Affected women should have prepregnancy screening for hypertension and diabetes, whereas during pregnancy the high risk for gestational diabetes must be recognized and screened accordingly, preferably in early pregnancy and repeated in mid-pregnancy.

7.1 | Metformin in pregnancy

Metformin should not be routinely used in pregnancy in PCOS but could be considered in some circumstances to reduce risk of preterm delivery or to limit excess gestational weight gain. Metformin does not prevent miscarriage, gestational diabetes, hypertension, preeclampsia, or macrosomia in PCOS.[5,20]

Long-term consequences on offspring remain uncertain. Metformin crosses the placenta, and consequently, the fetus is exposed to therapeutic concentrations;[21] however, teratogenicity has not been reported.[22] Among children exposed to metformin in utero, there may be adverse metabolic outcomes since preliminary data shows more overweight and obesity at 8-years of age.[23]

8 | LONG-TERM CONSEQUENCES

It is well recognized that women with PCOS have increased risk factors/surrogate markers for cardiometabolic disease, and in the

recent guideline, increased cardiovascular disease. A high rate of hypertension has been shown in the Nordic PCOS population,[24] as well as high rates of T2D, although in the Nordic setting, T2D has been mainly associated with overweight and obese women.[25,26] As women tend to gain weight along with aging and PCOS is a high-risk group, it is recommended to assess and monitor for risk factors, including blood pressure and glycemic status, both at time of diagnosis and repeatedly thereafter. Regarding assessment of glycemic status, the 75 g oral glucose tolerance test is recommended as first choice, and whilst fasting glucose and then HbA1c are less accurate they can be used as an informed choice. Moreover, blood lipids should be monitored, with intervals depending on total risk profile and weight status.

Women with PCOS present with different symptoms and they are most often treated by general practitioners, gynecologist and endocrinologists. However, the dissemination and implementation of EBG recommendations outside this group is important, to be able to maintain follow-up throughout life. PCOS is proposed to be included as an independent risk factor both for cardiovascular disease and T2D guidelines in the general population. There is also increased risk for sleep apnea, warranting screening. Endometrial cancer is increased but routine screening is not recommended due to low absolute risk.

9 | FUTURE PERSPECTIVES

PCOS is a lifelong disease, warranting long-term follow up. In adult women who do not have both irregular cycles and hyperandrogenism, the new possibility to use AMH instead of ultrasound, can facilitate diagnosis by the general practitioner office, noting that ultrasound and AMH are not specific or indicated in adolescent diagnosis. Best practice care includes a holistic approach, including nongynecological features such as cardiovascular risk factors and mental health. As for the name, PCOS, reflects only the reproductive side of the syndrome, while leaving out other key elements. Many patients feel that the name is confusing and misleading, and currently an international process over name change is taking place. The guideline will also be translated in several Nordic languages together with the patient materials. The ready tools also include ASKPCOS app that has been generated to facilitate discussion about PCOS between patients and healthcare professionals.

To conclude, evidence in the assessment and management of PCOS has evolved since the first guideline was published. Now it is our responsibility to implement these recommendations in clinical practice to improve the lives of women with PCOS also in the Nordic region.

AUTHOR CONTRIBUTIONS

All authors were involved in developing the original guideline, where HT was the lead. MF and JM in drafted the first version of this review and all authors have contributed in rewriting and revising the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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