POLYCYSTIC OVARY SYNDROME

PCOS

A Practical Guide For Health Care Professionals

PAKISTAN ENDOCRINE SOCIETY

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EDITED BY

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Foreword

Practicing medicine is an “art “, and practicing Endocrinology is “fine art”. I feel Endocrinology is and was one of the least addressed field of medicine at least in Pakistan, and although lately many endocrine diseases like diabetes and thyroid disorders got attention and are being addressed by the Endocrinologists but still there is a huge gap in the knowledge of physicians regarding endocrine diseases which needs to be filled in .

Polycystic ovarian syndrome (PCOS) is definitely one of the many endocrine diseases which need due attention. The prevalence of PCOS is increasing world over and Pakistan is no exception. Diagnostic and therapeutic challenges which any physician may come across and the diversity with which disease presents is evident by different criteria for diagnosis since this disease was added to medical literature. As disease presents with many faces, it needs holistic approach when making diagnosis and management plan.

Pakistan is generally a recourse limited country particularly when it comes to investigating a disease and hence reliance on clinical presentation is ever so important which than need to be understood by majority of practicing physicians. For the last 28 years since I have been practicing Endocrinology in Pakistan, I have seen many faces of PCOS which at times frustrated both me and my patients when we didn't get the desired outcome management goals. But with experience and knowledge one learns how to tailor course for the benefit of our patients and this is where one needs minute details to be practiced.

This book, which is probably the only book on the subject being authored by so many experienced endocrinologists of Pakistan as well as young and energetic contributors, who have undoubtedly covered most relevant topics of the disease and dissected the disease for readers in an effective way. This book not only covers the most relevant topics related to PCOS but also addresses the neglected issues related to the disease like mental health and role of diet in the management of the disease. I can easily say this book being a new and important innovation in the subject.

I congratulate all the authors on their remarkable effort and I am sure this will be a treat for the readers interested to know about this disease and its management aspects particularly relevant to our local population.

I would also like to congratulate Dr. Ibrar Ahmed, the current President of Pakistan Endocrine Society for taking this very pertinent initiative and making it possible to publish this book .
My best wishes,

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Preface

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in reproductive-aged women. The etiology of the syndrome is multifactorial, with genetic susceptibility, androgen exposure in early life and adiposity related dysfunction leading to perturbance in hypothalamicovarian function. The clinical features are varied, with manifestations arising even in early adolescence, developing into multisystem reproductive, metabolic and psychological manifestations in adulthood.

As women with PCOS consult different medical Specialities like Gynecology, dermatology and/or endocrinology according to the clinical manifestations, it is important to highlight this important topic so as to avoid unnecessary tests and to manage these women properly. In this booklet by Pakistan Endocrine Society, we have tried to highlight the natural history and various challenges faced by health care professionals in the diagnosis and management of PCOS.

Topics covered in this booklet include overview of PCOS including diagnostic criteria, challenges in diagnosing PCOS, endometrial, dermatological and reproductive disorders, cardio metabolic effects of PCOS, as well as psychological aspects. Importance of dietary modifications is covered in a separate chapter. Throughout the book we have tried to use a simple easy to understand language focusing on practical aspects. We are very grateful to all the contributors for their valuable time and contribution and hope that this booklet will help clinicians in managing their patients with PCOS in a better way. We are also grateful to Dr. Saima Askari for helping us in the Final Editing of the Book.

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Chapter 1

An overview of PCOS

DR. ZAREEN KIRAN

Case Summary:

21 years old female, single, presented in the outpatient department, at a tertiary hospital, with chief complaints of irregular periods and weight gain for 2 years. Menarche was attained at the age of 15 years. She gradually developed scanty menstrual flow, with around 2-2.5 month's interval in between each cycle. She had weight gain of 10kg in 9-10 months along with acne and hirsutism. Her past history was unremarkable. Prior to her presentation, she had been diagnosed with Polycystic ovary syndrome (PCOS)-spectrum disease for which she took Tab. Diane-35 for 1.5 years, and left 4 months back. She was on topical creams, regular waxing and also took laser therapy for hirsutism. Her mother is hypertensive and paternal aunt is diabetic. There is no history of similar disorders in the family. At the time of presentation, she was not on any regular medications, and there was no history of addiction. On examination: she was overweight with B.P. of 150/96 mmHg, Pulse: 76bpm, Weight: 62kg, Height: 154cm, BMI: 26.1 kg/m^2. She had evidence of acanthosis nigricans and acne on chin, forehead, back and chest. Her Ferriman-Galloway score was 17. Secondary sexual characteristics were normal with Tanner's stage 5. There were no signs of virilization. She did not have any evidence of central adiposity or striae, moon face, easy bruising, skin thinning or proximal myopathy. Systemic examination was unremarkable.

Key Points:

* The current understanding of polycystic ovarian syndrome diagnosis is controversial.
* Key features of the clinical findings include hyperandrogenism and ovulatory dysfunction, which are shared by many other endocrine and metabolic illnesses.
* Because of the functional immaturity of the reproductive hormonal physiology as well as a variety of congenital steroidogenic and other metabolic abnormalities, adolescence poses a larger diagnostic difficulty. Similar important differentials exist in the postmenopausal age group, such as androgen-producing ovarian and adrenal cancers.

Introduction:

Polycystic ovarian syndrome (PCOS) is one of the endocrine conditions that affects women most frequently in the world (1). In women of reproductive age, it is characterised by hyperandrogenic anovulation. Stein and Leventhal, who discovered a link between amenorrhea and hyperandrogenism and infertility in 1935, were the first to describe PCOS (2).

This chapter discusses the definition and diagnostic criteria in adults, adolescents, and postmenopausal women. In addition, the pathophysiology and clinical presentation is described for detailed understanding.

Diagnosis of PCOS in Adults:

PCOS can be suspected in any woman of reproductive age who has irregular menstruation and hyperandrogenism symptoms (acne, hirsutism, male-pattern hair loss). Women who have gained weight suddenly or gradually and who satisfy the definitions of overweight or obesity should be tested for PCOS. Women who have polycystic ovaries on ultrasound but no other signs of PCOS, such as hyperandrogenism or menstrual problems, should avoid comprehensive testing. Despite this, having a high index of suspicion for PCOS is crucial since these women may have underlying cardiovascular disease risk factors such fatty liver, glucose intolerance, dyslipidemia, and obstructive sleep apnea that must be evaluated and treated.

CLINICO-PATHOLOGICAL FEATURES:

Menstrual dysfunction

Menstrual irregularities:

Women with PCOS may have irregular bleeding at intervals of more than 35 days or frequent bleeding at intervals of fewer than 21 days. (3). Sometimes, even while periods are falling at a regular interval, bleeding may be an-ovulatory (25-35 days). Thus, polymenorrhea, oligomenorrhea, or even amenorrhea can be used to describe menstrual disruption in PCOS; the latter two are strongly linked to anovulatory cycles.

Endometrial dysplasia and cancer:

In addition to the more common signs of oligomenorrhea or amenorrhea in women with PCOS, endometrial hyperplasia and endometrial cancer risk may rise from the unopposed stimulation of the endometrium from the estrogens linked to anovulation. Although a connection between PCOS and endometrial cancer was initially hypothesized in 1949 (4), the validity of the scientific data has been disputed for decades (5).

Ovarian dysfunction

Ovarian morphology and role of ultrasound:

On histology, the ovaries of women with PCOS are enlarged, with numerous peripheral tiny antral follicles and increased central stroma. The presence of 12 or more follicles measuring 2 to 9 mm in diameter and/or an enlarged ovarian volume greater than 10 ml (without a cyst or dominant follicle) in either ovary is a major diagnostic indicator for PCOS (6). Newer guidelines have proposed a minimum of 20 follicles per ovary, with no corpora lutea, dominant follicles, or cysts in the ovaries (3). If the patient has both oligomenorrhea and evidence of hyperandrogenism, and all causes other than PCOS have been ruled out, she meets the criteria for PCOS, and an ultrasound is frequently not necessary.

Anovulatory infertility:

Ovulation is irregular in women with PCOS, making conception more challenging. Most PCOS and oligo-ovulating women who want to get pregnant eventually use ovulation induction therapy.

Hyperandrogenism (Clinical evaluation):

Hyperandrogenism is PCOS's second symptom. Hirsutism, acne, and male-pattern hair loss are examples of clinical symptoms of hyperandrogenism. Extreme manifestations include masculinization, hoarseness of voice, and clitoromegaly.

Hirsutism:

Hirsutism is the most typical clinical symptom of hyperandrogenemia. It is described as having an excessive amount of terminal (thick, pigmented) body hair in a male pattern, and the modified Ferriman-Gallwey scoring system, which includes nine androgen-sensitive body regions, is frequently used to diagnose it (See Figure 1) (7).

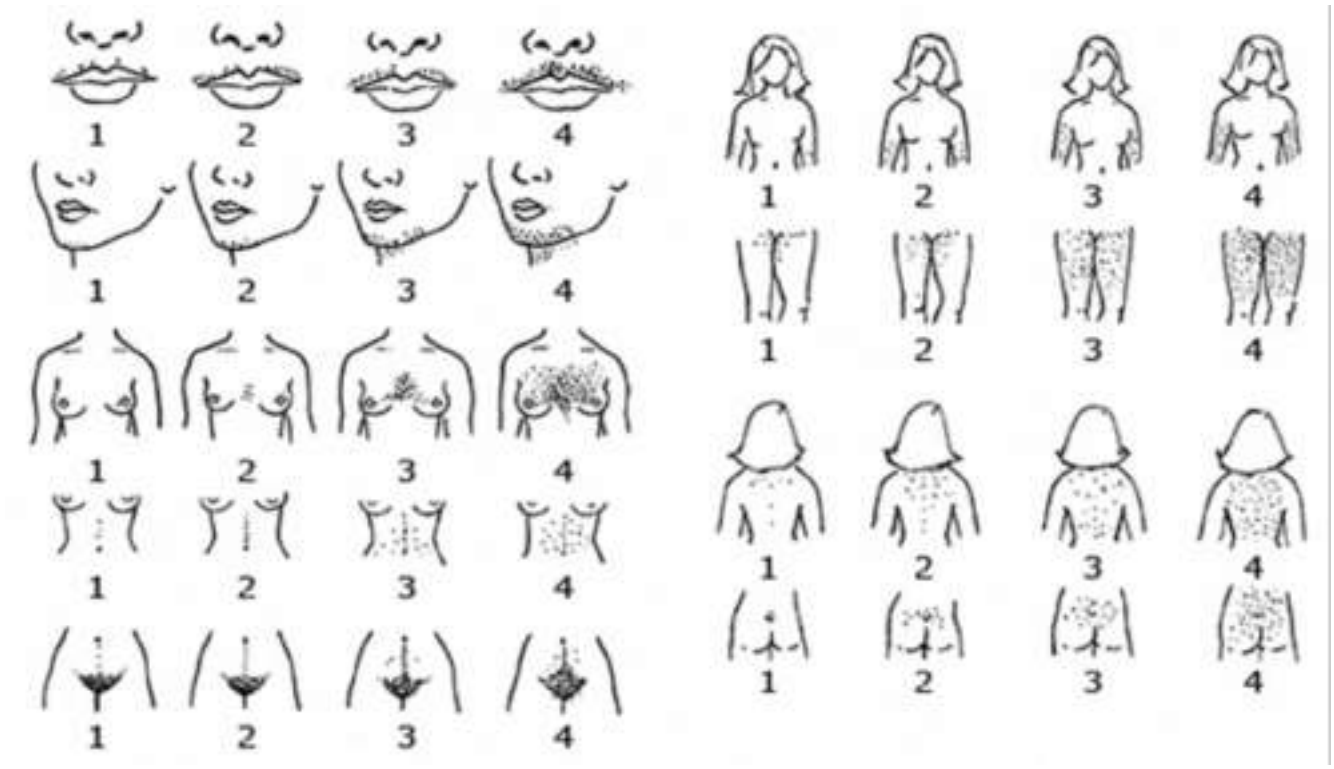

FIGURE: MODIFIED FERRIMAN-GALLWEY HIRSUTISM SCORING SYSTEM.

Each of the 9 body areas that is most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. The normal score is lower in Asian populations and higher in Mediterranean populations.

Acne

PCOS may be indicated in women with acne vulgaris. There is evidence that acne vulgaris has a hormonal and metabolic influence in women with PCOS. Greater levels of total testosterone, free testosterone, dehydroepiandrosterone sulphate, and cortisol were linked to more severe acne in PCOS women.

Virilization

A rare symptom of hyperandrogenism is virilization. The clinical manifestations of virilization include androgenic alopecia, clitoromegaly, voice deepening, increased muscle mass, and decreased breast size. Women who have virilization are almost always amenorrheic. Alopecia typically appears as male-pattern baldness with bitemporal recession in virilization. Any woman who experiences symptoms of virilization should always be evaluated for an androgen-secreting tumor.

Biochemical testing in PCOS
Essential hormonal testing to be performed:

1. **Serum Total Testosterone:** In clinically hyperandrogenic women, serum total testosterone concentration is regarded to give the most accurate overall indication of androgen production. Using liquid chromatography-tandem mass spectrometry (LC-MS/MS), the upper limit of normal for serum testosterone in women is 45 to 60 ng/dL (1.6 to 2.1 nmol/L); women with serum testosterone levels higher than 150 ng/dL need to be evaluated for the most serious causes of hyperandrogenism (ovarian and adrenal androgen-secreting tumors).

2. **Serum free testosterone:** Serum free testosterone may be a more sensitive test for the presence of hyperandrogenic disorders, as current direct assays are inconclusive. Equilibrium dialysis should be utilized if free testosterone is requested, although it is not always available (8).

3. **Sex hormone-binding globulin (SHBG):** SHBG measurements are another option for determining free testosterone levels indirectly. Although less accurate, a laboratory that calculates free testosterone levels from total testosterone and SHBG levels can provide a close estimate by using a formula (Free Androgen Index: Total Testosterone x 100 / SHBG) with results that agree with equilibrium dialysis results **(9).**

4. **Role of the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) ratio:** An elevated LH-to-FSH ratio is not a criterion for PCOS diagnosis **(10).** Many clinicians used to measure LH and FSH and use an elevated LH: FSH ratio (=2) as evidence for PCOS diagnosis **(11).** However, the LH: FSH ratio can be misleading. For example, if there has been a recent ovulation, LH will be reduced and the ratio will be =2 **(11).**

5. **Serum prolactin levels:** Prolactin levels in some hyperandrogenic women may be mildly elevated, but the significance is unknown (12). Prolactin levels above 40 mg/dL should prompt further investigation for other causes.

6. **Function of Anti-Müllerian Hormone (AMH):** Because serum anti-mullerian hormone (AMH) is produced by small preantral and early antral follicles, serum concentrations reflect the size of the primordial follicle pool (ovarian reserve). As the primordial follicle pool shrink with age, adult women's AMH levels gradually decrease until they are undetectable at menopause. Despite emerging evidence of AMH's role as a surrogate marker for PCOS diagnosis, an elevated AMH is not currently considered a criterion for PCOS diagnosis (13).

Tests in women on pharmacotherapy:

Some women may already be receiving pharmacologic therapy, typically estrogen-progestin oral contraceptives. In this instance, measuring serum androgens is worthless because oral contraceptives suppress serum gonadotropins and ovarian androgens, particularly testosterone. Similarly, androgen measurements should be avoided in women who are taking metformin or spironolactone because the interpretation of the results is complicated by the effects of these medications on androgen levels (14). According to recommendations, women should stop their medications at least four to six weeks before measuring serum androgens (15).

Tests is women with features of other endocrine disorders:

Women with other endocrine disorders, such as Cushing's syndrome, can occasionally present with symptoms similar to PCOS (oligomenorrhea, hirsutism, and obesity). Similarly, women with Acromegaly may present with oligomenorrhea as well as hirsutism, which may necessitate the measurement of serum insulin-like growth factor-1 (IGF-1) **(16).**

Diagnostic Criteria:
Rotterdam Criteria:

Most expert groups diagnose PCOS using Rotterdam criteria (3, 8, 15). The diagnosis must meet any two out of the following three requirements:

1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries (by ultrasound)
4. Many women with irregular menstruation and hyperandrogenic symptoms can be diagnosed based solely on their medical history and physical exam.

Clinicians and patients are confused when many classification systems are used. According to a summary report from the NIH Evidence-based Methodology Workshop on PCOS in December 2012, the Rotterdam criteria should be used for the time being because they are the most inclusive (See Table 1) (17).

TABLE 1. PROPOSED DIAGNOSTIC CRITERIA FOR POLYCYSTIC OVARY SYNDROME

NIH Consensus Criteria 1990 (All Required)	Rotterdam Criteria 2003 (Two Out of Three Required)	AES Definition 2008 (All Required)
Menstrual irregularity due to oligo- or anovulation	Oligo- or anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction oligo/anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

Diagnosis of PCOS in Postmenopausal women
Clinical Presentation:

The most common symptoms of hyperandrogenism in postmenopausal women are hirsutism and alopecia, while clitoromegaly, lowering of the voice, increased muscle strength, and an anabolic appearance are associated with higher androgen levels**.** Endometrial hyperplasia or endometrial cancer can also occur in some women.

Diagnostic criteria:

According to the 2013 Endocrine Society Clinical Practice Guidelines for the Diagnosis and Treatment of Polycystic Ovary Syndrome, the Rotterdam criteria should be used to diagnose PCOS in adult premenopausal women (see above) **(18).**

Diagnosis in Adolescents
Clinical Presentation:

Clinical PCOS characteristics usually start in adolescence, and adolescent hyperandrogenemia may be a harbinger to adult PCOS.

Hirsutism:

Normative data are scarce, however it appears that sexual hair growth matures throughout puberty and reaches maturity two years after menarche, at around 15 years of age (see figure 1) (19). Because idiopathic hirsutism accounts for half of all cases of mild hirsutism, adolescent PCOS guidelines (20) consider persistent testosterone elevation, stronger evidence of hyperandrogenism.

Acne:

A typical but variable cutaneous symptom of adolescent hyperandrogenemia is excessive acne vulgaris. The quantity of lesions present can be used to gauge the severity of acne. While adolescent girls frequently experience comedonal acne, moderate (more than 10 facial lesions) or severe inflammatory acne throughout the peri-menarcheal years is a sign of hyperandrogenemia (20).

Diagnostic criteria in Adolescents:

Recommendations for the diagnosis of adolescent PCOS have been issued by three worldwide expert conferences (3, 20). These papers concur on the following key requirements: clinical and/or biochemical evidence of testosterone excess (hyperandrogenism), and otherwise unexplained chronic evidence of ovulatory dysfunction (as evidenced by a menstrual irregularity based on chronologic and gynecologic age-appropriate norms).

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Chapter 2

Challenges in Diagnosing PCOS

Prof. Tasnim Ahsan

SUMMARY: This chapter focusses on the diagnostic challenges of Poly Cystic Ovarian Syndrome (PCOS) faced by clinicians. The establishment of this diagnosis though straightforward in most cases, can be difficult in some. No single diagnostic test establishes the diagnosis of PCOS. Polycystic appearance of the ovary on ultrasound is not a prerequisite for establishing the diagnosis therefore it should be undertaken meticulously in accordance with the Rotterdam diagnostic criteria and classified into the various phenotypes, for better assessment of cardio-metabolic risks in the future. All other causes of similar presentation should be excluded by appropriate hormone estimations.

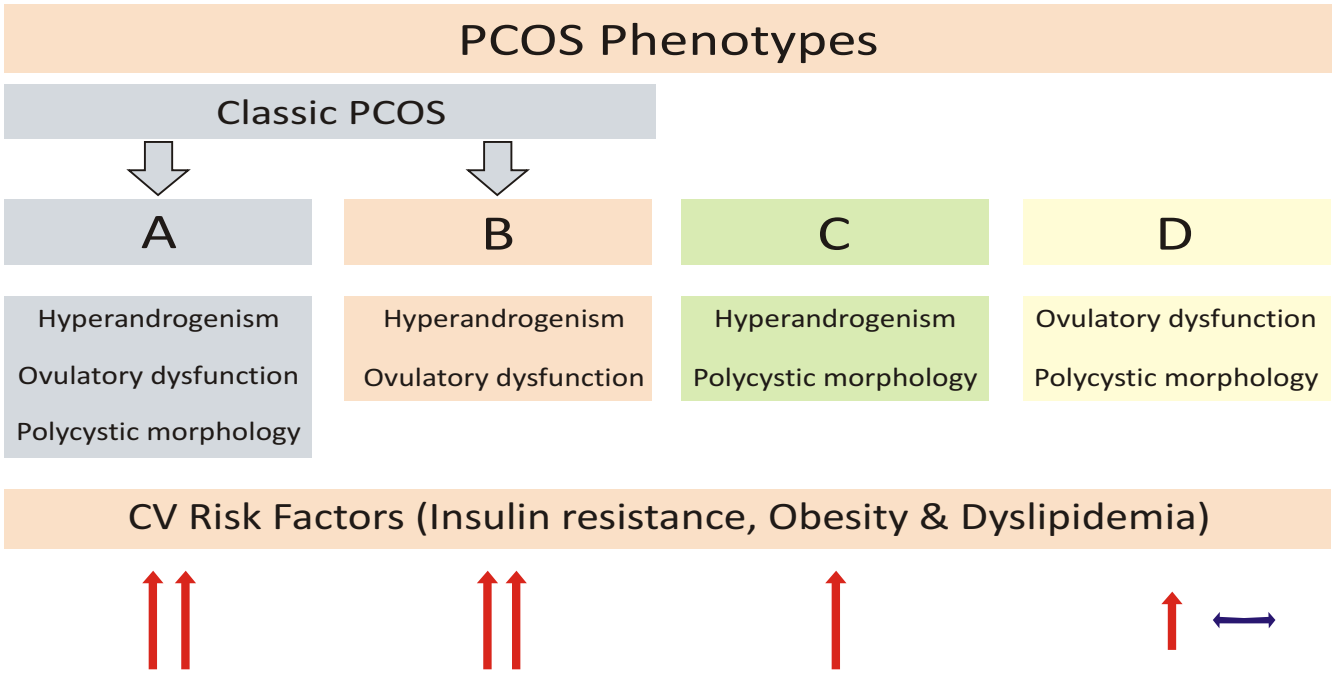
Introduction:

There is still a lack of clarity in understanding the underpinnings of the Polycystic Ovary Syndrome (PCOS). Even though the commonest phenotype of PCOS, i.e 'Stein Leventhal Syndrome' was first described over eight decades ago in 1935[1], the establishment of this diagnosis though straightforward in most cases, can be difficult in some. The challenge of this diagnostic label starts with the misnomer of this label itself, i.e 'Polycystic Ovary'; the characteristic ultrasound/ gross/histological appearance of the ovaries is due to multiple follicles, rather than cysts in the ovary. Moreover, polycystic appearance of the ovary is not a prerequisite for establishing the diagnosis. There is also no focus on the considerable metabolic impact of this disease in association with obesity, which finds no mention in the diagnostic criteria either. PCOS clusters in families, and both female and male relatives can show stigmata of the syndrome, including metabolic abnormalities. A number of candidate genes have been identified, but their role in contributing to PCOS is largely unknown.[2]

No single diagnostic test establishes the diagnosis of PCOS. Expert consensus rather than scientific evidence forms the basis for PCOS diagnostic criteria. Ever since the consensus reached in 2003, the Rotterdam criteria have been used extensively to classify PCOS for diagnostic and research purposes. According to the Rotterdam Criteria PCOS can be diagnosed when a patient presents with any combination of two of the following three criteria, with the exclusion of other diseases with a similar presentation[3]:

1. Clinical or biochemical hyperandrogenism
2. Oligo-anovulation/ irregular menstrual cycles
3. Polycystic ovaries (PCO)

PCOS thus defined provides for the possibility of four different phenotypes:[4]



Clearly it is not difficult to understand that these different phenotypic presentations are likely to behave differently as time passes, especially in terms of subfertility, progression of hyperandrogenism (acne, hirsutism and androgenic alopecia--scalp hair loss), obesity and its metabolic consequences. Abnormal gonadotropin secretion resulting from decreased hypothalamic feedback to circulating sex steroids, which are also abnormal, with both hyperandrogenism, as well as oestrogen excess. These changes are particularly pronounced in obese patients with PCOS, and are a result of altered ovarian morphological and functional changes. There is also increased peripheral synthesis of oestrogen in the excessive adipose tissue, which adds to the complexity of this disorder. The metabolic disorder of insulin resistance is further driven by obesity. In addition to its effect on other tissues, the raised insulin level also has LH like action on the ovary, thus adding to the ovarian dysfunction.

Oligo-amenorrhea

Menstrual irregularity is the most common cause for these patients to seek medical attention. The menstrual pattern of patients with PCOS is typically one of oligomenorrhea and less often amenorrhea. Primary amenorrhea is rare in PCOS, and should initiate investigations to assess the hypothalamus-pituitary-gonadal axis. Irregular menses may evolve over time with weight gain, although most cases present around menarche or shortly thereafter in teenage years. Irregular cycles are normal in the first-year post menarche, as part of the pubertal transition.

Irregular menstrual cycles in PCOS are defined as[5]:

* 1 to < 3 years post menarche: < 21 or > 45 days
* > 3 years post menarche to perimenopause: < 21 or > 35 days or < 8 cycles per year
* > 1 year post menarche > 90 days for any one cycle
* Primary amenorrhea by age 15 or > 3 years post thelarche (breast development)

Whenever irregular menstrual cycles are present, a diagnosis of PCOS should be considered.

Tests should be carried out to exclude other causes of oligomenorrhoea/amenorrhea. These tests include human chorionic gonadotropin (hCG-not available in Pakistan), prolactin, thyroid stimulating hormone (TSH), and follicle stimulating hormone (FSH). Estimating Luteinizing hormone (LH) does not add any diagnostic benefit as the LH: FSH ratio is not used as a diagnostic criterion. Cortisol assessment may be warranted when there are clinical signs of Cushing's syndrome. Serum Anti-mullerian hormone (AMH) is usually in the upper limit of normal or markedly elevated in women with PCOS, but international standardized diagnostic criteria are not available yet.[6]

Hyperandrogenism/hyperandrogenemia

Clinical hyperandrogenism is reflected by acne, growth of terminal (coarse) hair in the androgen-dependent areas (male pattern), and scalp hair loss of androgenic distribution. Hirsutism should be differentiated from hypertrichosis, which is prominent vellus hair, due to diffuse increase in the pilosebaceous unit, not driven by androgens, but by genetic factors. Racial factors are also significant in the initial density of the pilosebaceous unit, and their responsiveness to androgens.[7] The severity of hirsutism can be graded by the modified Ferryman Gallwey score, but the scoring has different racial significance, in accordance with hairiness of skin in different races.[8] Baseline scoring is helpful in the follow-up of patients to evaluate the effectiveness of treatment.

Clinical hyperandrogenism may or may not be associated with an elevation of total testosterone or free testosterone. Calculation of free androgen index (FAI) from total testosterone and SHBG levels may also be used to assess androgen effect. According to the Monash guidelines there was insufficient evidence to make definitive recommendations on the optimal hormone and method to measure biochemical diagnosis of hyperandrogenism in PCOS, although data indicates that, as a single measure, free testosterone measurements are the most optimal test to detect biochemical hyperandrogenism, followed by total testosterone, dehydroepiandrosterone sulfate (DHEAS), and androstenedione, not prioritizing one over the other. DHEAS may be mildly elevated in PCOS, but has no bearing on its management. However, in severe hirsutism when an androgen producing tumor is suspected, significantly elevated levels are seen in adrenal androgen producing tumors.

Measuring serum 17-hydroxyprogesterone is recommended in the early follicular phase or randomly in amenorrhoeic women, in all women with suspected PCOS, as non-classical CAH may have a very similar presentation.

Presentation with virilization and/or recent onset and rapidly progressive hirsutism, should merit evaluation for an androgen secreting ovarian or adrenal tumor.

Polycystic Ovaries

According to the Rotterdam criteria of 2004 Polycystic Ovarian morphology was defined as a per abdominal ultrasound of 12 or more follicles in each ovary measuring 29 mm in diameter and/or an increased ovarian volume of 10 mL in at least one ovary [3]. With the new generation of ultrasound machines, and much improved resolution of images (transducer frequency of ≥ 8 MHz), a higher follicle number cutoff is recommended for labeling the ovaries polycystic (20 - 25 follicles per ovary).[5,9] When per abdominal ultrasound is used, it is preferable to use the ovarian volume cutoff of ≥10 mL to diagnose polycystic ovaries. Moreover, multifollicular ovaries can be a normal stage of development in adolescence and early adulthood. Epidemiological studies reveal the prevalence of polycystic ovary morphology to be three to four times that of PCOS, indicating that this morphology is common in normal women.[10]

In summary, establishment of the lifelong label of PCOS, should be undertaken meticulously in accordance with the Rotterdam diagnostic criteria and classified into the various phenotypes, for better assessment of cardio-metabolic risks in the future. All other causes of similar presentation should be excluded by appropriate hormone estimations. If the patient is already taking an estrogen/progestogen pill, anti-androgens or metformin, these drugs should be withdrawn for 6 to 8 weeks before measurement of hormones.

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Chapter 3

PCOS and Reproductive Disorders

Dr. Aisha Sheikh

Case:

A 28-years old woman present with the complaint of failure to conceive. She is married for two years and is actively trying for conception for last 14 months. She was diagnosed as PCOS 8 years ago when she developed oligomenorrhea, hirsutism and weight gain. She tried actively for weight reduction at that time, took metformin for few years and her menstrual cycle regularized. She received laser treatment for her facial hirsutism. Following her marriage, she had been less adherent to lifestyle management and has noticed a 15 kg weight gain since her marriage, she again noticed oligomenorrhea for last 6 months. Her last menstrual period was two months ago. She is quite worried about her future prospects of fertility. She is taking folic acid 5 mg once daily. She did not have any significant past medical and surgical history. She has a family history of obesity, Type 2 Diabetes and Hypertension. On examination, her Body mass index (BMI) is 29 kg/m2, her blood pressure is 134/85 mmHg. There is acanthosis nigricans and few skin tags over the nape of her neck. There are few end-terminal hair over lower abdomen and sacral region. There are no stigmata of Cushing's syndrome and rest of her examination is unremarkable.

Infertility and its management

Polycystic Ovary Syndrome (PCOS) is associated with anovulatory infertility. (1) 70% to 80% of women with PCOS are at risk of infertility is and some three quarter of women with PCOS aiming to conceive might need infertility treatment.(2) The increased social pressure owing to infertility or delay in conception leads to increased mental stress, anxiety and depression in these women which can further impair self-care goals needed to achieve weight loss through life style modification. (3)

Infertility in PCOS should be managed by specialists with training and expertise in managing this condition.

Evaluation of infertility in PCOS:

Evaluation of infertility (or subfertility) is recommended after 12 months without pregnancy in couples having regular sexual intercourse (2 or 3 times/week). (2)The evaluation can start early if the woman's age is above 35 years or she has a known condition that leads to subfertility.

Considering that the woman was already diagnosed as PCOS based upon Rotterdam's criteria, other causes of subfertility in the couple needs to be explored. Data suggests that 10% of couples has a severe male factor infertility where the woman had PCOS, similarly 5% can have a co-existent tubal factor infertility. In women who are having oligomenorrhea/amenorrhea exclude pregnancy be getting beta-hCG before starting work-up and further management.

Evaluation of male: Semen analysis should be done in the male partner and appropriate referral given if there are abnormalities in semen parameters.

Evaluation of female: In the female evaluation should include:

I. History and physical exam
   * anatomical dysfunctions (endometriosis, pelvic inflammatory diseases) or
   * iatrogenic causes (surgery, chemotherapy, radiations should be explored)
   * The patient's personal medical and surgical as well as family history, followed by a complete physical and gynecological examination is necessary when exploring infertility.

Ii. Diagnostic tests:

a) Anti-Mullerian hormone (AMH) AMH is produced by granulosa cells of early follicles and helps to assess the ovarian reserve. (2)The level of AMH remains stable throughout the menstrual cycle so can be estimated at any time of the cycle. Due to the higher numbers of preantral and antral follicles in women with PCOS, the level of AMH is expected to be 2 to 3 times higher than non-PCOS women.(4)

b) Thyroid dysfunction and hyperprolactinemia should be ruled out as well.

c) Transvaginal ultrasonography (TVS) To evaluate the antral follicle count, endometrium thickness and diagnose uterine abnormalities (polyps, myomas and congenital malformation).(2)

iii. Advanced investigations Hysteroscopy, laparoscopy, tubal patency tests Based upon woman's suggestive history (age >35 years, failure to achieve pregnancy despite achieving ovulation on ovulation induction therapy, a suggestive history or when advancing to second line treatments)

Treatment:
Non-pharmacological measures

Weight reduction through life-style changes:
Lifestyle changes are the first line of treatment for women with PCOS. (5)Weight loss is recommended in overweight and obese women. A 5% to 10% weight loss in overweight and obese women may be sufficient to restore regular menstruation and ovulation and they can conceive spontaneously. (6) In rest of the women, this weight loss also augments the effect of ovulation-induction. (2)

Smoking cessation is another important intervention in women aiming for achieving fertility.

Anti-obesity medications:

Anti-obesity medications can be considered making sure that adequate contraception is used to avoid an unplanned pregnancy since all the approved anti-obesity medications are unsafe during pregnancy. (6)

Specific treatments to improve fertility:
First line therapeutic option ovulation induction

Ovulation induction is based on the principles of either lowering estrogen levels by
* inhibiting the final step of estrogen synthesis (Aromatase inhibitors letrozole) or
* blocking estrogen receptors at the level of hypothalamus (anti-estrogen clomiphene citrate).

Both of these agents release the Hypothalamus-pituitary axis from estrogen negative feedback. Letrozole additionally blocks the conversion of testosterone to estradiol and androstenedione to estrone in ovary. With the resultant accumulation of androgens inside the ovary, promoting the follicular FSH receptor, IGF-1 and IGF-1 receptor expression, which in turn stimulates follicular growth. Normal central feedback mechanisms remain intact in letrozole ovarian induction protocol.(10) Clomiphene citrate administration induces gonadotropin release by binding to the estrogen receptors (ERs) in the hypothalamus, thereby blocking the negative feedback effect of estradiol. Because letrozole does not inhibit negative feedback of estrogen to Hypothalamus-Pituitary-Ovarian axis, it usually induces single follicle development and avoids multiple pregnancies. (9)The other advantage is that letrozole does not affect endometrial estrogen receptors, and therefore does not exert any deleterious effect on endometrial thickness and cervical mucus and thus favors implantation of embryo. (11) Currently; Letrozole is considered first line treatment for ovulation induction. (5)These drugs are given from day 3 to 7 of menstrual cycle, starting with lower dose (Letrozole 2.5 mg daily or clomiphene citrate 50 mg daily), getting TVS around day 12 to observe the follicular size. If ovulation doesn't occur with lower dose, then doses are gradually built up in subsequent cycles to maximum doses (Letrozole 7.5 mg daily or clomiphene citrate 150 mg daily) and follicular size is observed. Ovulation induction is followed by timed intercourse or Intrauterine insemination.(9)

Metformin:

Recent systematic review demonstrated that in infertile, anovulatory PCOS women, metformin treatment resulted in higher ovulation, pregnancy and live birth rates than placebo. (12) However, the quality of the data was low to moderate. (13)Other studies have not shown similar outcomes with metformin alone. Although, isolated metformin treatment for anovulatory PCOS women can be used to improve ovulation but it might not be the most efficacious first-line therapeutic approach and thus women should be counseled that there are more effective ovulation induction agents. (6)In women with Clomiphene citrate resistance, adding metformin can improve ovulation and pregnancy rates.(5)

Second line therapeutic options:
Gonadotrophin therapy:

Gonadotrophin therapy can be used as second line pharmacological agents in women with PCOS who have failed first line ovulation induction therapy (no ovulation despite three cycles of ovulation induction treatment or failure to achieve clinical pregnancy within six months despite successful ovulation on ovulation induction therapy) provided there are no other infertility factors.(14)

Addition of metformin to Gonadotrophins in clomiphene citrate-resistant women with only anovulatory infertility may further improve ovulation, clinical pregnancy and live birth rates.(15) On the other hand it reduced the risk of ovarian hyperstimulation syndrome (OHSS). (14)

Gonadotrophin therapy in women with PCOS utilizes a low-dose step-up regimen to prevent (OHSS) and multiple pregnancies. (16)The high number of antral follicles in women with PCOS predispose them to develop OHSS and thus close monitoring is required.
To avoid the risk of multiple pregnancy, Gonadotrophin induced ovulation should only be triggered when there are fewer than three mature follicles and should be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.(9)

Laparoscopic ovarian drilling:

Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors. (2, 8)

Third line therapeutic options through assisted reproductive techniques (ART):
In vitro fertilization IVF/ Intracytoplasmic sperm injection ICSI

When other therapies have failed, woman with PCOS who have anovulatory infertility could be offered IVF ± ICSI as third line treatment option. (8)The use of IVF/ICSI is effective in such women as elective single embryo transfer is used thus minimizing the risk of multiple pregnancies. Cost of IVF/ICSI is prohibitive and there is a higher risk of OHSS. Women should be apprised of this higher OHSS risk and options to reduce the risk of OHSS should be explained.(9)

Unproven therapies:

Vitamin D:
Vitamin D deficiency/insufficiency is quite prevalent in general population and in particular among women of reproductive age group. Data suggests that low vitamin D levels are associated with IR. (7) Vitamin D deficiency reduce the success rates of infertility treatment. On the basis of limited research evidence, vitamin D supplementation may be recommended as a potential therapeutic adjunct for the ovulatory dysfunction and metabolic disorders observed in women with PCOS.(17)

Melatonin or inositol:
Data on the therapeutic efficacy of melatonin and inositol on endocrine and metabolic abnormalities are limited and inconclusive.(7, 18)

Polycystic Ovary Syndrome and complications in pregnancy
PCOS is characterized by hyperandrogenism (HA) and insulin resistance (IR). The insulin resistance is unique and is seen in both lean and obese women with PCOS, though obesity further aggravates the IR in the later group. In addition, a chronic low-grade inflammation is the hallmark of PCOS.(19) All these factors lead to various complications in pregnancy in women with PCOS.(20)

Early pregnancy loss/spontaneous miscarriages:

Women with PCOS are at 3-fold higher risk of spontaneous miscarriages compared to women without PCOS. HA and IR leading to hyperinsulinemia which is further enhanced in pregnancy have shown to contribute to early pregnancy loss owing to increased levels of plasminogen activator inhibitor-1 which is a a powerful inhibitor of fibrinolysis. (21)The unfavorable endometrial environment leads to reduced chances of successful implantation of the embryo.(4) Obesity and multiple pregnancy with assisted reproductive treatments are independent factors that contribute to higher miscarriages.

Gestational Diabetes Mellitus (GDM):

40% to 50% of pregnancies in women with PCOS can be complicated by GDM which is higher compared to women without PCOS. (22) Higher risk of GDM is particularly observed in normal or overweight women with PCOS. In contrast, the risk of GDM is similar in women with or without PCOS if the BMI is above 30kg/m^2.

Hypertensive disorders of pregnancy:

Women with PCOS are at three to four-fold higher risk of developing Pregnancy induced hypertension (PIH - 10% to 30% risk) and Preeclampsia (8% to 15% risk). Others have reported as much as 25% greater risk of preeclampsia. (22)

Small for gestational age (SGA) or intrauterine growth restriction (IUGR):

HA, IR, Hyperinsulinemia and GDM through a complex interplay lead to almost a two-fold higher risk of fetal growth compromise in the form of SGA or IUGR. The risk is increased in obese women with PCOS.

Preterm Birth:

Multiple pregnancy, hyperglycemia in pregnancy, hypertensive disorders in pregnancy and fetal growth compromise can lead to delivery plans before term that will further enhance the risk of fetal prematurity, respiratory distress syndrome and neonatal intensive care admission.(22)

Prevention and monitoring for complication in pregnancy:

Preconception control of maternal BMI through at least a 5% to 10% weight loss is crucial in reducing the risk of complications during pregnancy. Lifestyle modification though a healthy, nutritionally balanced diet and regular exercise are the key to achieve weight loss. (23) This requires behavior modification towards healthier life style choices and is a process that will eventually ensure adherence to such behaviors during pregnancy as well. Screening for glucose abnormalities and hypertension should be done in all women with PCOS in the preconception period and be stabilized if an abnormality is found. The role of metformin to reduce IR and hyperinsulinemia and thus reducing the risk of early pregnancy loss is variably proven in research and can be considered at dose of 1500 mg per day or more. (6, 15) Smoking including second-hand smoking should be discouraged. Any mental health issues should be identified and optimized in the preconception period.(9)

Close maternal monitoring during pregnancy is required for timely identification of hyperglycemic and hypertensive disorders in pregnancy and adequate intervention if needed. Continued Adherence to healthy lifestyle should be encouraged during pregnancy and the gestational weight gain of the woman must be according to The Institute of Medicine recommend BMI-specific gestational weight gain goal. (9) Metformin treatment can be continued till 16 weeks of gestation with the intention of prevention of spontaneous miscarriage. (15) Low dose aspirin therapy can be considered in high-risk PCOS women to reduce the risk of preeclampsia.

Close fetal monitoring during pregnancy is required to identify any abnormalities of growth so that timely intervention can be undertaken. Multidisciplinary care is offered to such pregnancies wherever needed to improve the pregnancy outcomes.

Continued care should be provided to these women and their children in the post-partum period to ensure that breast feeding is established and continued for two years. If the woman had developed GDM or PIH, they should be screened at regular intervals for any residual or evolving glucose abnormalities/chronic hypertension. (9) Women should be encouraged to adhere to healthier life style after delivery as well, and aim towards weight reduction once the baby is progressed to weaning.

In conclusion, PCOS affects a woman's health across lifespan. An adequate weight control ensures spontaneous conception and enhances the fertility treatment success in those who require fertility treatments. PCOS is associated with a myriad of complications during pregnancy, adequate weight and metabolic control in the preconception period, proper maternal and fetal monitoring during pregnancy and timely intervention can ensure improved pregnancy outcomes. The healthier lifestyle behaviors should continue after delivery as well to ensure reduction of risk of chronic complications associated with PCOS.

Back to the case:
This lady has PCOS and is having obesity. She needs proper counseling about importance of weight management. A 10% weight loss will remarkably improver her response to fertility treatments and might conceive spontaneously.

The couple, however needs certain tests. To begin with get a beta-hCG tested on the woman to rule out pregnancy, if that is negative, offer further investigations. Get her husband's semen analysis to rule out male factor infertility. The woman should get her TSH, Prolactin and AMH level tested. She needs a metabolic work-up in the form of oral glucose tolerance test, fasting insulin level, lipid profile and liver function tests. If an abnormality is found in lipid profile and LFTs, do not treat it with statins since she is planning for pregnancy, counsel her that weight reduction will further improve these parameters. A 25OHD should be tested as well and vitamin D replaced to optimum level if a deficiency is found. Get her TVS to evaluate the antral follicle count, endometrium thickness and diagnose uterine abnormalities. Tubal patency tests can be deferred at this stage since there is no suggestive history that makes an indication for this test.

Following the tests put her on metformin at least 1500 mg daily dose (start with low dose and gradually build up). Give her progesterone for withdrawal bleeding. Follow her up with lab report and counsel further, monitor for weight changes, encourage dietary control and exercise, involve clinical nutritionist and if needed a physiotherapist in her care. If she is too much stressed, anxious that is hampering her quality of life and inter-personal relationship then seek expert help from clinical psychologist. Once she has lost at least 10% of her weight which can take about 4-6 months, she can go ahead with ovulation induction treatment with letrozole. Seek expert help to administer ovulation induction and further monitoring.

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Chapter 4

PCOS and Endometrial Problems

Dr. Amena Moazzam Baig

Key Points

1) Progesterone resistance reduces endometrial receptiveness and causes hyperplasia
2) Insulin resistance plays causative role in endometrial dysfunction in PCOs
3) Unopposed action of estrogen in absence of progesterone leads to hyperplasia and endometrial cancer
4) Women with PCOs are at 2-7% increased risk of developing Endometrial cancer

Case Scenario:

Mrs. XX, a 35 years old lady is referred to endocrine clinic for assessment of her complaints of missed periods along with weight gain for the past 6years. Her onset of puberty was at 10 years and menarche at age of 11years.She has also been unable to conceive for past 4 years.

She conceived her first child using clomiphene 8years back and ever since complains of gradual weight gain of 15 kg and delayed menstrual cycle with heavy flow. She had one failed attempt of IVF 3years back. She also gives history of acne and excessive terminal hair involving the face and upper arms area. She does give family history of obesity and diabetes mellitus, however no history of thyroid illness and steroid excess. She has been taking Oral contraceptive pills on off as prescribed by her gynecologist.

On examination, her weight is 71 kg, height 155cm (BMI=29). Blood pressure of 130/85mmhg. Acanthosis Nigricans is visible on nape of neck and arm pits. Terminal hair on chin, upper arms and front of chest (Ferriman Gallway score =12). Pustular acne on forehead and upper back and mild frontal recession of hairline. There was no evidence of virilization, goiter, and steroid excess or delayed reflexes.

Laboratory tests:

Total testosterone = 3 mmol/l (0.5-2.4nnmol/l)
TSH= 2miu/L (0.6-4.5miu/l)
Prolactin=12 ng/ml (10-24ng/ml)
LH=7mIU/L, FSH=5mIU/l (0.9-12mIU/l)
USG pelvis= Endometrial thickness of 12 mm with normal ovaries
Give your assessment and management plan

Introduction:

Menstrual cycle and ovulation: Menstruation is a dynamic cyclic process with sloughing of the uterine lining in response to estrogen and progesterone hormones and their interaction. The median duration of cycle is 28 days +/- 5 days. Progesterone is a steroid hormone produced mainly by the ovaries under the influence of luteinizing hormone during normal menstrual cycle and human chorionic gonadotropic hormone during pregnancy (1). It has been noted that progesterone hormone is required for the implantation, decidualization and maintenance of pregnancy.(2)

Polycystic ovarian syndrome is one of the most common hormonal disorders seen in female of reproductive age group. It is responsible for both reproductive and metabolic abnormalities during life time of the women (3) and is characterized by hyper-androgen, olgo/anovulation, inability to conceive and increased abortion rate.

Following are some of the changes seen in the endometrium:

1) **Progesterone resistance leading to hyperplasia**: Progesterone resistance is the most important change seen in PCOs. Progesterone resistance refers to the decreased responsiveness of target tissues to bioavailable progesterone (4) leading to the decline of estrogen's antagonistic ability, the aggravation of inflammation, and obstruction of endometrial remodeling. It is one of the major factor which leads to the decline in endometrial receptivity and subsequently increase the risk of endometrial atypical hyperplasia and cancer (5). Androgen receptors and steroid receptor co-activators are over-expressed in the endometrium of women with PCOS. In addition, biomarkers of endometrial receptivity to embryonic implantationsuch as á$_v$â$_3$-integrin and glycodelinare decreased, and epithelial expression of estrogen receptor á (ERá) abnormally persists in the window of implantation in endometrium in women with PCOS.

2) **Insulin resistance**: In addition, the endometrium is also a target for insulin, the receptor for which is cyclically regulated in normo-ovulatory women. In vitro, insulin inhibits the normal process of endometrial stromal differentiation (decidualization). In addition, insulin-like growth factors (IGFs) and their binding proteins are regulated in and act on endometrial cellular constituents, and hyperinsulinemia down-regulates hepatic IGFBP-1, resulting in elevated free IGF-I in the circulation.

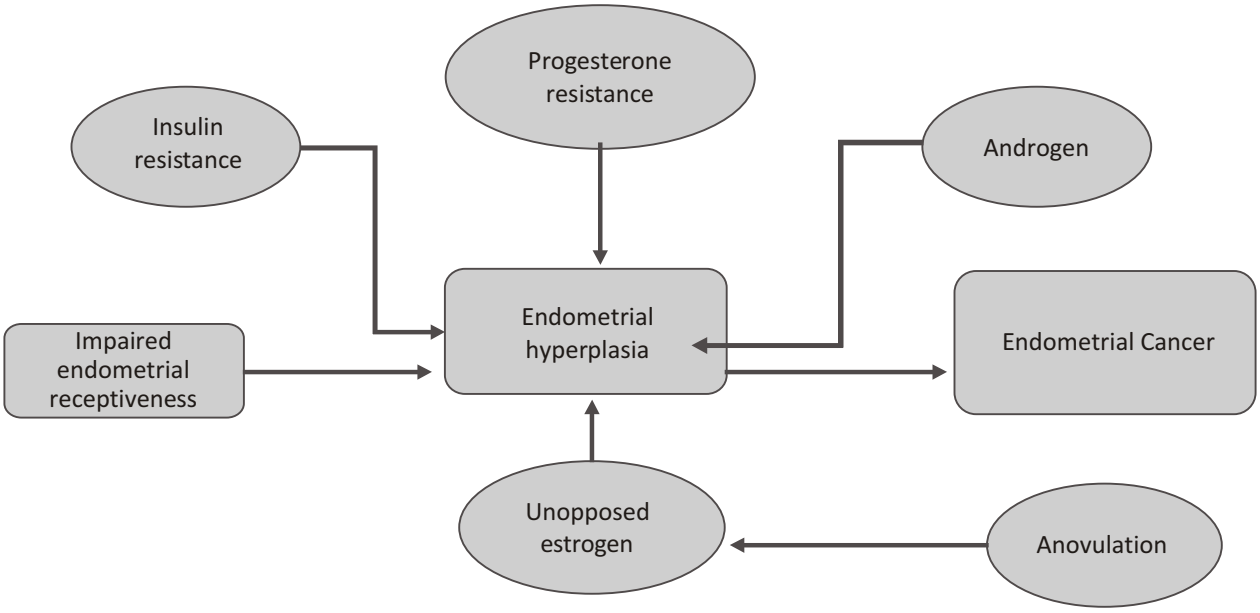

Figure No1: Pathology of endometrial hyperplasia and cancer

3) **Androgens:** Raised levels of dehydroepiandrosterone (DHEA) and androstenedione produced by the ovarian follicles and adrenal cortex lead to hirsutism and acne. In addition, it impairs the growth and differentiation of the endometrial cells and decidualization of endometrium and interferes with implantation. This leads to decrease levels of progesterone and reduced receptiveness of endometrium (6)
4) **Chronic inflammation**: PCOs is a pro-inflammatory state, these raised levels of inflammatory markers lead to proliferation of endometrial cells and raised level of estrogen and carcinogenic metabolites.

Thus, elevated estrogen (without the opposing effects of progesterone in the absence of ovulation), hyperinsulinemia, elevated free IGF-I, androgens, and obesity all likely contribute to endometrial dysfunction, infertility, increased miscarriage rate, endometrial hyperplasia, and endometrial cancer common in women with PCOS.

Common Presentation:

PCOs patients usually complain of menstrual abnormalities like oligo- menorrhea or menorrhagia, inability to conceive / anovulation and increased rate of abortion. Gestational hypertension, edema and Preeclampsia due to progesterone resistance is also seen in these women.

Important points in history to rule out differentials:

1) History of virilization to rule out adrenal hyperplasia
2) Family history of infertility and early menopause
3) Long term use of OCP and their side effects
4) Drug history /past medical history of relevant disease like diabetes mellitus, hypertension and obesity

Differential Diagnosis:

* **Pregnancy**: It is important to rule out pregnancy in amenorrhea patient
* **Menopause:** Premature ovarian failure needs to be ruled out along with menopause.
* **Secondary causes of anovulation**: CAH, Hypothyroidism, hyperprolactinemia, Cushing syndrome

Investigation: Proper history and examination followed by investigations.

Table No.1: Laboratory work up:

Sr. #	Tests	Inference
1	Beta Hcg	To rule out pregnancy
2	LH. FSH, Estradiol	To ensure functionality of Hypothalamic Pituitary Ovarian axis
3	AMH	Quantity and quality of eggs /growing follicles
4	S Testosterone/DHEA	Androgen levels
5	Prolactin	To rule out secondary cause like prolactinoma
6	TSH	To rule out hypothyroidism
7	17-Oh progesterone	To rule out congenital adrenal hyperplasia (virilizing form)
8	Hysterosalpingography	Patency of tubes
9	Ultrasound pelvis	Ovarian size, endometrial thickness and growing follicles

Management Plan: (7)

1) **Multidisciplinary approach:** involving the endocrinologist, gynecologist, psychologist and dietician.
2) **Pharmacological treatment**

A-Used for non-fertility indication:

* **COCP (Combined oral contraceptive pill): is** first line treatment. Lowest effective oestrogen dose should be used
* **COCP +life style modification+ metformin :** Should be considered for women with PCOs for management of metabolic features where COCP and life style do not achieve it**.**
* **COCP +anti androgen:** Antiandrogen can be used with contraceptive to avoid male fetal virilization.
* **Life style modification +metformin:** Should be used in adults with insulin resistance, hormonal and metabolic problems

B-Used for fertility

Tubal patency should be ensured.

* **Ovulation induction:** Agents such a letrazole, metformin and clomiphene can be used.

Gonadotrophins: Can be used as second line treatment who have failed fertility with first line.

* **In-vitro Fertilization (IVF)**: This technique along with intra cytoplasmic sperm injection can be used as third line treatment.

3) **Psychosocial counselling to rule out depression**
4) **Life style modification to treat obesity**

Endometrial Cancer in PCOs

Patient with polycystic ovary syndrome have a 2.7-fold increased risk for developing endometrial cancer. The increased malignancy risk due to prolonged exposure of the endometrium to unopposed estrogen that results from anovulation. In addition, secretory endometrium of some women with PCOS who undergo ovulation induction or receive exogenous progestin exhibits progesterone resistance and thus cell proliferation. Endometrial surveillance includes transvaginal ultrasound and/or endometrial biopsy to assess thickened endometrium, prolonged amenorrhea, unopposed estrogen exposure or abnormal vaginal bleeding. Management for abnormal vaginal bleeding or endometrial hyperplasia includes estrogen-progestin oral contraceptives, cyclic or continuous progestins or a levonorgestrel-releasing (Mirena) intrauterine device. Lifestyle modification with caloric restriction and exercise is appropriate to treat obesity as a concomitant risk factor for developing endometrial disease. (8)

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Chapter 5

Dermatological Manifestations of PCOS

Dr. Musarrat Riaz
Dr. Saima Askari

Summary:

Women with PCOS should be evaluated for dermatological manifestations including hirsutism, acne, alopecia and acanthoses nigricans. Women with high hirsutism score should be tested for elevated androgen levels. pharmacological treatment should be considered to treat hirsutism instead of cosmetic procedures. Oral contraceptives work in the majority of women with hirsutism. An antiandrogen should be added if no result after six months Antiandrogens should not be used as monotherapy. Among cosmetic procedure, photo epilation is ideal for women with dark hair and electrolysis for light-colored hair.

Case:

A 25 years old female presented to your clinic with the complaint of excessive hair growth on face for last 2 years. She is also complaining of weight gain and menstrual cycle irregularities. Her mother is very concerned because her marriage is expected after 6 months. On examination obese female with a BMI of 30 kg/m2, hirsutism score 14, acanthosis nigricans present.

How will you approach further?

Introduction:

Polycystic ovary syndrome (PCOS) is the most common endocrine cause of hirsutism, acne, and pattern alopecia. It is a heterogeneous syndrome of hyperandrogenic anovulation that is typically due to intrinsic ovarian dysfunction. The condition is often complicated by insulin-resistant hyperinsulinemia leading to increased risks of diabetes mellitus and metabolic syndrome with associated complications (1). Evaluation for hyperandrogenemia is suggested in women with moderate or severe hirsutism or menstrual irregularity, acanthosis nigricans, or intractable obesity. An endocrinologic work-up is necessary to rule out other hyperandrogenic disorders that require specific therapy (e.g., virilizing tumors, non-classic congenital adrenal hyperplasia, hyperprolactinemia, and Cushing's syndrome). Ultrasonography helps in the differential diagnosis and may demonstrate the polycystic ovaries. (Although not mandatory for diagnosis of PCOS). Management of PCOS is determined by symptomatology. For those women not desiring pregnancy, the most common therapies are oral contraceptive pills, antiandrogens (contraindicated in the absence of adequate contraception), and insulin-lowering treatments (which have little effect on hirsutism) (2).

Pathogenesis:

PCOS is an ovarian dysfunction attributed to dysregulated hypothalamic-pituitary-gonadal axis and decrease insulin sensitivity. There is excessive production of androgens from ovarian theca cells in response to high luteinizing hormone (LH) along with decrease sensitivity to insulin which leads to hyperinsulinemia with resulting hyperglycemia, high androgens production, and decrease sex-hormone-binding globulin levels (SHBG). A higher insulin level directly stimulates the production of androgen by binding to the ovary's insulin-like growth factor I (IGF-1) receptor. The levels of IGF-I and IGF-II rise, and IGF-I stimulates the action of 5-alpha reductase, which intensifies the hirsute response and causes alopecia and acne. Whereas IGF-II promotes LH-stimulated androgen production from ovarian theca cells (1,2)

Androgens, including testosterone, dihydrotestosterone, and their prohormones dehydroepiandrosterone sulfate and androstenedione, are the key factors in the growth and development of sexual hair. Androgens act on sex-specific areas of the body, converting small, straight, fair vellus hairs to larger, curlier, and darker terminal hairs. In addition to hirsutism, hyperandrogenemia can manifest as acne, menstrual dysfunction, or alopecia, or could be asymptomatic. The severity of hirsutism is variable at a given level of androgen excess, suggesting that hirsutism is also related to the sensitivity of hair follicles to androgens.

Cutaneous manifestations:

The common cutaneous manifestations of PCOS are hirsutism, acne, alopecia, and /or acanthosis nigricans.

Hirsutism:

The most distressing and dermatological consultation seeking symptom of PCOS is hirsutism which is defined as excessive male pattern terminal hair growth in females at androgen-dependent areas. Individuals variation is seen in hair growth because of difference in enzyme activity named as 5-alpha reductase that convert testosterone into its more active form dihydrotestosterone (DHT). Increase activity of 5-alpha reductase in PCOS per se along with triggering from hyperandrogenism, hyperinsulinemia may result in conversion of vellus hair into thicker and darker terminal hairs especially on androgen-sensitive sites. Moreover, there is alteration of anagen phase of the hair cycle. In some areas, this phase gets prolonged, while anagen phase shortening is seen in the scalp (3).

Acne:

Although acne is one of the cutaneous symptoms of PCOS, it must be distinguished from acne vulgaris, which is more frequently encountered. PCOS should be taken into account for women who exhibit concomitant symptoms of hyperandrogenism, insulin resistance, menstrual abnormalities, and failure to respond to standard medication. In comparison to hirsutism, the prevalence of acne alone (excluding hirsutism) is quite low. Androgens enhance sebum production, which leads to aberrant follicular epithelial cell desquamation and the development of comedones. Further colonization by Propionibacterium acnes resulting in inflammation of follicles and promote formation of papules, pustules, nodules, cysts, and scarring (2,3).

Alopecia:

Alopecia is characterized by thinning or progressive hair loss. PCOS typically causes vertex thinning while maintaining the frontal hairline, but rarely, it can cause central scalp hair loss akin to androgenic alopecia. Because of hyperandrogenism reduced levels of the cytochrome p 450 enzyme, increased levels of androgen receptors along with increased 5-alpha reductase enzyme activity and brief anagen phases may ultimately lead to shrinkage of terminal hairs with eventual conversion to vellus hairs.

Acanthosis nigricans:

The appearance of brown velvety, verrucous hyperpigmentation of skin, which is typically seen on the back of the neck and intertriginous areas like the armpits and groins, beneath the breast, and inside the thighs is feature of acanthosis nigricans (AN), a surrogate marker of insulin resistance. However, only a small no of women with PCOS have reported AN. Keratinocytes and fibroblasts multiply as a result of high serum insulin binding to IGF-1 receptors. Papillomatosis, hyperkeratosis, and acanthosis with or without basal layer hyperpigmentation are some of the histological characteristics(3).

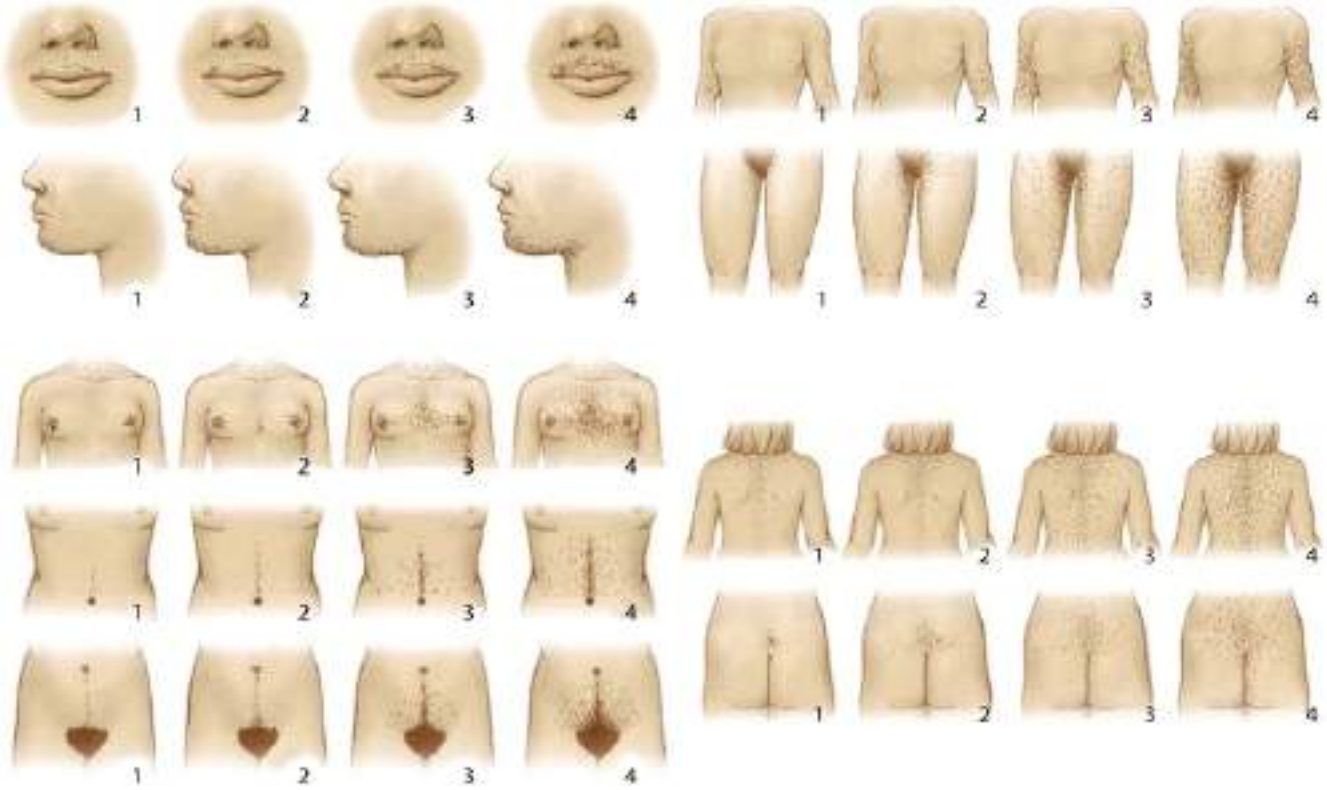
Evaluation for dermatologic manifestations of PCOS:

* A comprehensive history and physical examination should be completed for symptoms and signs of clinical hyperandrogenism, including acne, alopecia and hirsutism and, in adolescents, severe acne and hirsutism
* The medical history should include a medication and supplement review.
* The patient should be asked if the excess hair growth began at puberty or after, and if its onset was rapid.
* A menstrual and reproductive history should also be obtained, as well as the hair patterns of family members (if possible) because idiopathic hirsutism is often familial.
* Patients should be asked if they have noticed changes in their voice, abdomen, breasts, skin, or muscle mass.
* It is also important to ask what hair removal measures have already been tried.
* Health professionals should be aware of the potential negative psychosocial impact of clinical hyperandrogenism. Reported unwanted excess hair growth and/or alopecia should be considered important, regardless of apparent clinical severity.
* Standardized visual scales are preferred when assessing hirsutism, such as the modified Ferriman Gallwey score (mFG) with a level = 4 - 6 indicating hirsutism, depending on ethnicity, acknowledging that self-treatment is common and can limit clinical assessment.
* The Ludwig visual score is preferred for assessing the degree and distribution of alopecia
* There are no universally accepted visual assessments for evaluating acne.
* 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.
* As ethnic variation in vellus hair density is notable, over-estimation of hirsutism may occur if vellus hair is confused with terminal hair; only terminal hairs need to be considered in pathological hirsutism, with terminal hairs clinically growing > 5mm in length if untreated, generally being pigmented.

Physical examination:

* Should begin with determination of the distribution and degree of hair growth using a scoring method such as the Ferriman-Gallwey scale (Figure 1).
* The patient should be evaluated for signs of virilization, including clitoromegaly, deep voice, balding, or loss of typical female body contours.
* An abdominal and bimanual examination should be performed to identify palpable tumors.
* A skin examination should check for acne, striae, or acanthosis nigricans.
* The patient's breasts should be examined for galactorrhea.
* Physicians should look for other typical signs of endocrinopathies, such as Cushing syndrome or thyroid dysfunction.

Figure 1 Modified Ferriman-Gallwey scale



If possible, androgenic medications should be stopped. Any patient with rapid onset of hirsutism, obvious signs of virilization, or a palpable abdominal or pelvic mass should undergo a thorough workup for a possible androgen-secreting tumor. In contrast, patients with mild hirsutism and normal menses do not require laboratory workup and can safely be started on empiric therapy. If the condition does not respond to therapy or progresses, further testing is warranted.

Investigations:

* In patients with moderate or severe hirsutism or a history of possible PCOS, an early morning testosterone level should be obtained. A total testosterone level greater than 200 ng per dL (6.94 nmol per L) is indicative of an androgen-secreting tumor. Plasma free testosterone is 50 percent more sensitive than total testosterone, but because this testing is expensive and not widely available, it should be considered only if total testosterone levels are moderately elevated.
* Routine testing of other androgens, such as dehydroepiandrosterone sulfate, is not recommended, because mild elevations are common and have limited predictive value in the setting of normal testosterone levels.
* Further workup should include thyroid function tests, and prolactin and 17-hydroxyprogesterone levels.
* A urine free cortisol level, dexamethasone suppression test, or midnight cortisol level can be included if Cushing syndrome is suspected.
* If the 17-hydroxyprogesterone level is greater than 200 ng per dL (6.1 nmol per L), a corticotropin stimulation test should be performed to evaluate for adrenal hyperplasia.
* A patient with idiopathic hirsutism or a mild to moderately elevated testosterone level and an anovulatory history suggestive of PCOS should be treated appropriately and monitored for improvement.

Available treatment options:

Combined oral contraceptive pills:

Estrogen used in oral contraceptive pills (OCPs) inhibits LH, increase SHBG, and reduces ovarian androgen production. These actions lower free testosterone, which improve PCOS' cutaneous manifestations like acne and hirsutism. As testosterone derivatives, the progestins used in OCP are regarded as having varying degrees of androgenic characteristics. While CPA (cyproterone acetate) and drosperinone are androgenic receptor antagonists, more recent progestins like norethindrone, desogestrel, and norgestimate show some androgenic activity. Due to its ability to inhibit 5-alpha reductase, CPA is more effective. Drosperinone is an aldosterone antagonist that also has some antiandrogenic and antimineralocorticoid properties that work to block the effects of oestrogen on the rennin-angiotensin-aldosterone pathway.

OCPs significantly decrease PCOS's cutaneous symptoms however; OCPs should be used for at least 6 to 9 months before any hirsutism improvement is shown (3,4).

Antiandrogens:

Antiandrogens mainly act by inhibiting 5-alpha reductase, which reduces androgen synthesis, or by competitively inhibiting androgen-binding receptors. In sexually active women, OCPs should be added to all antiandrogens due to the possibility of feminization of the male fetus if pregnancy occurs (5,6).

Spironolactone:

It is the most powerful antiandrogen that has proven results on hirsutism, even more so than OCPs. It has been discovered to work well for alopecia and acne. Aldosterone antagonist spirolactone has 5-alpha reductase inhibitor and androgen receptor effects. The dose is 25100 mg/day, which is normally well tolerated, but some women may have symptoms of tiredness, postural hypotension, and dizziness. So, begin with a low dose (25 mg) and gradually raise it over the course of a week. Because of a dose-related menstrual irregularity, it is administered along with OCP.

Flutamide:

The nonsteroidal anti androgen flutamide inhibits androgens by competitively inhibiting receptors, lowering androgen production and raising inactivation. The dose is typically between 250 and 750 mg per day. It works well for hair loss, acne, and hirsutism; however, hepatotoxicity is the main concern.

Finasteride:

Finasteride prevents the conversion of testosterone into the more active metabolite DHT by acting as a strong competitive inhibitor of the type 2 isoenzyme of 5-alpha reductase. It is used along with OCPS and has been found to be more beneficial to patients who use OCPs alone. When estrogens are contraindicated, these anti androgens are the preferred treatment for hirsutism. In these circumstances, a finasteride and spironolactone combination has also been used and proven to be successful.

Insulin sensitizers:

Metformin would be beneficial in reducing insulin levels, and by this change, decreases ovarian testosterone levels by competitive inhibition of the ovarian insulin receptors. This drug is helpful in hirsutism management in women with PCOS (4).

Eflornithine hydrochloride:

Eflornithine is an FDA approved drug by for the treatment of hirsutism. It is an irreversible inhibitor of l-ornithine decarboxylase, an enzyme needed for hair growth. It helps in slowing and miniaturizing the hair follicle making them less coarse. Continued twice-daily use for at least 4-8 weeks is necessary before effectiveness may be observed. It can be combined with laser treatments for enhanced effects (5,6).

Cosmetic/Local therapy:

Available options are medical therapy or physical method for removing hairs either by waxing, threading, bleaching, plucking, or shaving. Electrolysis and photo epilation are hair follicles destruction with energy sources.

Permanent method of hair removal:

The techniques for permanent destruction of hair follicles are electro epilation and laser photo thermolysis. In electrolysis, there is threat of post-inflammatory pigmentation and scarring, whereas laser is costly but less hurting and faster. Laser therapy selectively destroys the hair follicle without damaging adjacent tissues by its photothermal and photochemical effect. Along with destruction of hair follicle, it also induces the miniaturization of terminal coarse hairs into vellus hairs (7). According to light source, laser may be classified into three categories:

1. Red light systems (694nm ruby),
2. infrared light systems (1064nm neodymium: yttriumaluminumgarnet), and
3. intense pulsed light sources (5901200 nm).

Multiple sittings at regular intervals are required for laser therapy and it has been observed that 6575% hair reduction is possible at 3 months after one to two sittings whereas >75% hair reduction in 91% of cases at 8 months after four sittings with diode laser in women with hirsutism. The laser hair removal is more effective for women of fair skin with dark hairs. Various studies have shown significant reduction in hair growth in PCOS women following laser therapy.

How to manage dermatologic manifestations of PCOS:

Lifestyle modification:

Life-style modification is the first step of PCOS management including dietary modifications, increasing physical activity, and weight loss if overweight/obese. It has been proved that only 5% loss of total body weight decreases the testosterone levels, insulin resistance and cardiovascular disease risk as well.

Medical therapy:

The therapeutic objective is to inhibit ovarian androgen synthesis and reduce their bioavailable forms by increasing SHBG levels.

Combined medical and local therapy

This approach is recommended in all women with PCOs having cutaneous manifestation because systemic therapy would correct the underlying metabolic and endocrinal abnormalities along with reducing the circulating androgen levels, whereas the local therapy will give the symptomatic and quick relief to the patient.

Hirsutism:

Cosmetic therapy combined with OCPs is advocated in women with hirsutism, but the response to treatment is typically expected after at least 69 months of continuous therapy because of long hair growth cycle of around 6 months. If sub-optimal response is achieved after 6 months of OCPs usage only, antiandrogen can be added.

Acne:

OCPs have been also found very effective for acne in PCOs and especially in cases of deep-seated nodules and relapsing acne on isotretinoin.

Alopecia:

Topical minoxidil is recommended as first-line treatment for alopecia. OCPs and antiandrogens are usually recommended; however, very limited data is available regarding exact efficacy in alopecia (8).

Acanthosis nigricans:

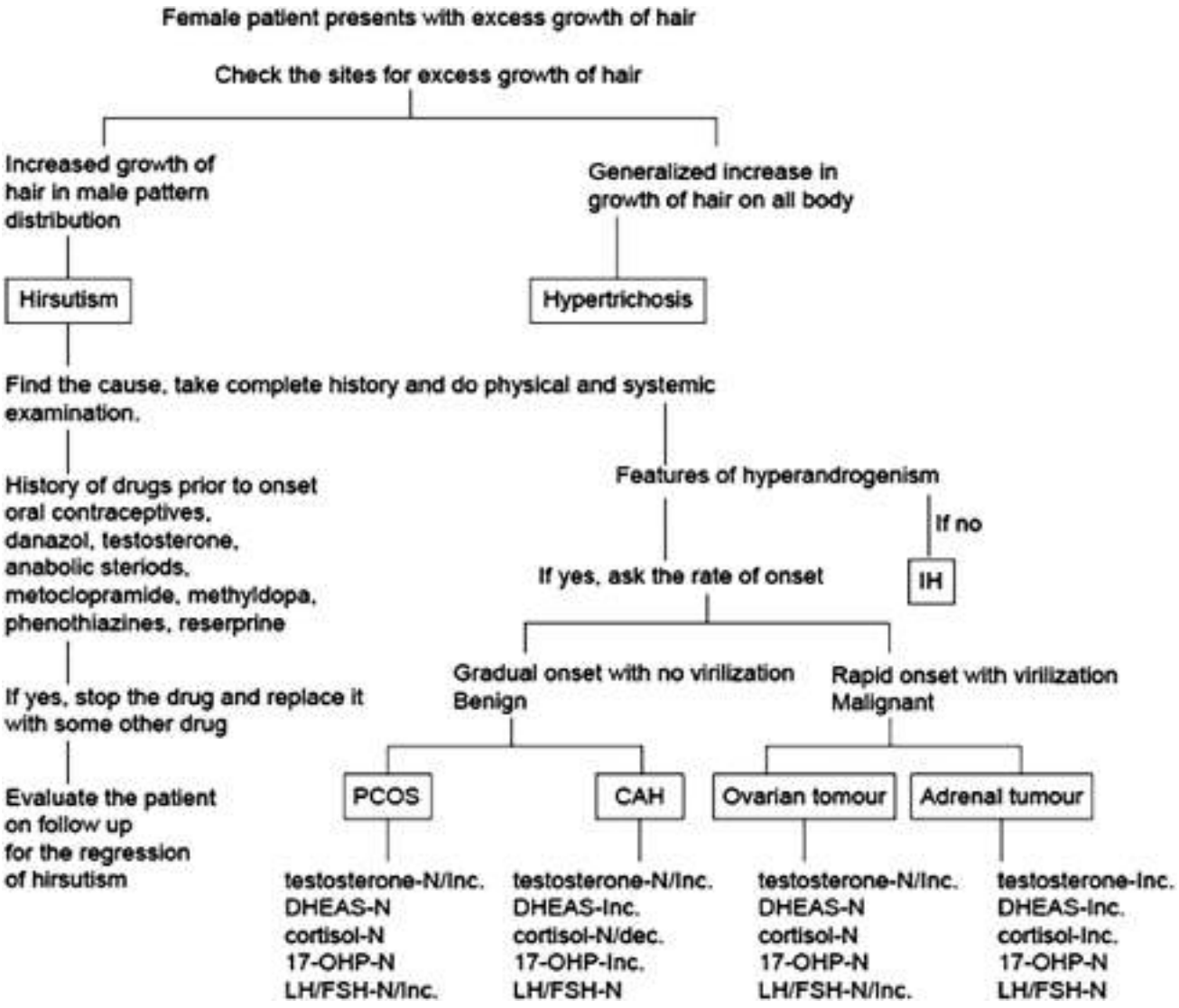
Topical medications that have been found effective in some cases of acanthosis nigricans include keratolytic (eg, topical tretinoin 0.05%, ammonium lactate 12% cream, or a combination of the 2) and triple-combination depigmenting cream (tretinoin 0.05%, hydroquinone 4%, fluocinolone acetonide 0.01%) nightly with daily sunscreen. Calcipotriol, podophyllin, urea, adapalene, and salicylic acid also have been reported, but variable results preclude their generalized recommendation.

Oral agents that have shown a few benefits including etretinate, isotretinoin, metformin and dietary fish oils.

Psychological support:

Women with PCOS are more at risk to develop psychological and behavioral issues because of androgenic effects which threaten their female identity, esthetically disfigurement, overweight/ obesity, and associated reduced fertility. They are more prone to substance abuse and smoking as well. Therefore, it is crucial to discuss psychosocial issues and provide adequate psychological support and timely refer to psychologist if needed.

Figure 2 provides a suggested approach to evaluating hirsutism.



Summary of management options are listed in the following table:

Lifestyle Modifications	Pharmacological therapy			Cosmetic/Local Therapy	Psychosocial Support
* Dietary Modifications * Exercise * Weight Management	* Hormonal pills containing Estrogen plus Progestins a) progestins with low androgenic activity. Eg: Norethindrone, Desogestrel, norgestimate b) Antiandrogenic progestins. Eg:Cyproterone acetate, Drospirenone	Antiandrogens Spironolactone Flutamide Finasteride	Insulin Sensitizer Metformin	* Medical local therapy * Eflornithine hydrochloride * Waxing * Bleaching * Threading * Laser	

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Chapter 6

Metabolic Consequences of PCOS

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Professor Nadia Ather

Summary

The metabolic irregularities associated with PCOS include increased risk of developing diabetes mellitus (type 2 and gestational), dyslipidemia, non-alcoholic fatty liver disease and hypertension. Insulin resistance is associated with a five-fold higher risk for T2DM and two-fold higher risk for CVD. Dyslipidemia and NAFLD are more prevalent in women with PCOS. Assessment for metabolic parameters including body mass index (BMI), waist circumference, blood pressure, serum lipid and glucose profile determinations are recommended for all women with PCOS. Oral glucose tolerance test should be done in women with PCOS who are obese, with advanced age, having personal history of gestational diabetes or family history of type 2 diabetes mellitus. Lifestyle modifications along with metformin are mainstay of treatment.

Introduction:

Polycystic ovarian syndrome (PCOS) is one of the most frequently found endocrine disorders in females throughout their child bearing age, concomitant with a wide range of cardiometabolic repercussions. The estimated prevalence is about 10%. The main pathology revolves around insulin resistance, generalized inflammation, obesity and hyperandrogenism.

The metabolic syndrome associated with PCOS include

* Increased risk of developing diabetes mellitus (type 2 and gestational),
* Dyslipidemia,
* Non-alcoholic fatty liver disease and
* Hypertension.

These factors are interdependent and progressive. The outcome of this ally of metabolic irregularities, in the form of increased cardiovascular disease morbidity and mortality late in life, still remains unanswered. So far researchhas shown a possibility of increased risk of cardiovascular eventsspecially related to coronary artery disease.

Insulin Resistance (IR) and Type 2 Diabetes mellitus:

Insulin resistance is the leading factor in the development of metabolic irregularities in patients with PCOS. The prevalence of insulin resistance in nonobese PCOS individuals is approximately 30% which reaches to 70% in obese females. with. It is also observed that women with PCOS are at increased risk of glucose intolerance, when compared with age- and weight-matched women without PCOS. Other risk factors which increase the insulin resistance in women with PCOS are high testosterone and low sex hormone-binding globulin (SHBG) concentrations. It has been shown that the hyperandrogenic and anovulatory phenotype is the most insulin resistant, regardless of BMI or central adiposity.

A defect in glucose-stimulated insulin secretion in PCOS, which contributes to insulin resistance, results in the development of type 2 DM in these women. Increased basal insulin secretion and decreased hepatic insulin clearance result in hyperinsulinemia, which in turn increases androgen production. Androgens alter insulin action (to some extent) in target tissues and increase visceral adiposity in women with PCOS. The prevalence of impaired glucose tolerance (IGT) and type 2diabetes mellitus (T2DM) in PCOS patients is 2335% and 410%, respectively; while in thin and lean women with PCOS the respective prevalence is 1015% and 12%. This prevalence of type 2 diabetes in women diagnosed with PCOS is 7 times higher than controls (15% to 2% respectively). It is also observed that the insulin resistance combined with abdominal obesity is thought to account for the higher prevalence of type 2 diabetes in PCOS. Furthermore, the risk of developing type 2 diabetes is also noted to be increased in non-obese

women with PCOS. Hence PCOS is an independent risk factor for type 2 diabetes in middle age. PCOS is also related to a higher risk of developing gestational diabetes mellitus (GDM).

The prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and T2DM in this age group of women with PCOS was 3%, 15.2% and 1.5%, respectively. Although the frequency of IGT was equal between obese and non-obese PCOS adolescents.

Dyslipidemia:

Lipid abnormalities are highly prevalent (70%) in women with PCOS. Lipid abnormalities that were found in these patients were increased levels of low-density lipoprotein cholesterol (LDL-C) and very-low density lipoprotein cholesterol (VLDL-C), with high serum triglyceride (Tg).

In PCOS, smaller and dense LDL particles predominate; resulting in a more atherogenic lipid profile.This is further worsened by obesity and insulin resistance.Insulin resistance augments the hepatic secretion of VLDL (the major source of Tg), decreases the elimination of VLDL and chylomicrons from the circulation and increases the clearance of apolipoprotein A. Lipoprotein-a (Lpa) and ApoB (the major apolipoprotein of atherogenic lipoproteins and indicator of small and dense LDL particles) may also be elevated in PCOS women, which are considered independent risk factors for CVD. It is also seen that these are elevated in approximately one third of PCOS women with normal plasma lipid profile. This type of atherogenic dyslipidemia is more pronounced in obese females with PCOS.

Abdominal Obesity-Metabolic Syndrome (MetS):

It is composed of a group of metabolic irregularities, including abdominal obesity, hyperglycemia, hypertension and dyslipidemia, with insulin resistance playing a pivotal role in its pathogenesis. It is associated with a five-fold higher risk for T2DM and two-fold higher risk for CVD.One of the most significant contributors of metabolic syndrome in females with PCOS is the body's distribution of adipose tissue, rather than increased BMI. It is the abdominal obesity which acts as an independent risk factor for CVD.Waist-to-height ratio (WHtR) is more strongly associated with T2DM and metabolic syndrome than the raised BMI, thus it is superior to BMI in predicting incidents of CVD, CVD mortality and all-cause mortality. Androgenic obesity, may, cause insulin resistance, glucose intolerance, diabetes mellitus, and high androgen production. It is seen that central fat deposition increases low-grade inflammation and insulin resistance, independent of age and BMI. Adipose hypertrophy, associated with hyperandrogenemia and reduced catecholamine induced lipolysis, has been reported in various studies, which in turn leads to insulin resistance.

The prevalence of MetS is higher in women with PCOS compared with the general population (ranging from 33% to 47% in most studies, increasing to 53% in ages 30 39 years).

Adipokines disbalance:

Anumber of cytokines secreted by adipose tissues called “adipokines” are responsible for a relationship between adiposity, insulin resistance, systemic inflammation and concomitant increased risk of atherosclerosis. The most important are adiponectin and leptin. Adiponectin has insulin sensitizing and anti-inflammatory characteristics. Low circulating adiponectin levels are usually found in obesity and MetS. Lower adiponectin levels were found in females with PCOS regardless of their parameters.

Leptin, on the other hand, has a dual regulatory role, both central and peripheral. It increases satiety, controls appetite and energy expenditure. High leptin concentrations are associated with systemic inflammation, insulin resistance and high risk of atherosclerosis. Higher leptin levels were found in PCOS women when compared with their healthy counterparts in a meta-analysis. In non-obese PCOS patients, leptin levels were moderately higher when compared with non-obese controls. Leptin may also contribute to hyperandrogenism by promoting steroidogenesis and inhibiting neuropeptide Y, which leads to high gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH) levels.

Non-Alcoholic Fatty Liver Disease (NAFLD):

NAFLD includes a broad spectrum of pathology ranging from simple steatosis, to non-alcoholic steatohepatitis (NASH). Steatosis occurs due to lipid accumulation in the liver parenchyma while NASH is advanced stage, resulting in inflammation and fibrosis. This condition is associated with increased risk of CVD. Increased prevalence of NAFLD, which may result in fibrosis, has been seen in PCOS women (2762%).High androgen levels and other metabolic irregularities in women with PCOS lead to an increase in liver enzymes. Other risk factors for NAFLD development in these patients include: Insulin resistance, obesity, particularly visceral adiposity, and increased triglyceride.High Osteopontin (OPN),a glycoprotein,is associated with bioactive androgen levels and liver fat content irrespective of obesity in PCOS women.This glycoprotein may predict the chances of developing NAFLD in women with PCOS.

Hypertension:

Regarding hypertension there seems to be a direct relationship between insulin plasma levels and blood pressure. The prevalence of hypertension (mainly systolic) in PCOS premenopausal women is about 925.7%, which is relatively higher than those without PCOS. The incidence of preeclampsia in obese women with PCOS, compared to the general pregnant population, is 4 times higher.There are studies showing the development of hypertension in postmenopausal women who had PCOS during their reproductive ages confers a higher risk for developing hypertension after menopause.The loss of physiological nocturnal drop in both systolic (51%)and diastolic pressures(23%)has been reported in PCOS women. Androgens seem to play a major role in the pathogenesis of hypertension through activation of renin-angiotensin system.Beside this, obesity and insulin resistance may also play their part.

Cardiovascular Disease Risk in PCOS:

There is an increased cardiometabolic risk profile in women with PCOS as suggested by previously mentioned studies. These women are seen to have more extensive coronary artery disease confirmed by angiography. The carotid artery intima-media thickness was found to be increased by 0.072 mm in PCOS women. Also, the odds for carotid artery calcification (CAC) in PCOS women was 2.7, reported in another study. Women with PCOS have a larger left atrial size, higher left ventricular index, and lower left ventricular ejection fraction when compared to those without PCOS. It is postulated that higher incidence of cardiovascular events is caused by insulin resistance, which has a direct atherogenic action and also its adverse effects on the lipoprotein profile. Although, it is reported by most prospective studies in general population that hyperinsulinemia is independently associated with the presence of atherosclerosis and coronary heart diseases. However, whether this risk may lead to potential cardiovascular events or not, remain unanswered due to lack of well designed, high quality longitudinal studies.

Evaluation for metabolic irregularities in women with PCOS:

* Body mass index, waist circumference, serum lipid, glucose profile and blood pressure determinations are recommended for all women with PCOS.
* Oral glucose tolerance test should be done in those women with PCOS who are obese, with advanced age, having personal history of gestational diabetes or family history of type 2 diabetes mellitus.
* Assessment of serum insulin concentrations should not be performed routinely.
* The use of hemoglobinA1c (HbA1c), as a screening test is not supported by either the Endocrine Societyand ESHRE/ASRM, except for the cases of inability or unwillingness of the patient to complete an OGTT.
* Screening is suggested to be done every three to five years if patient remains asymptomatic.

Management of the metabolic irregularities in women with PCOS:

Lifestyle modifications:
The initial therapy for PCOS is weight loss. Weight loss can also restore menstrual regularity and fertility. Lifestyle modifications might improve insulin resistance, hyperandrogenism and is recommended for primary CVD prevention.

The Endocrine Society clinical practice guidelines suggest the use of exercise along with diet modification as the first-line treatment to manage obesity in women with PCOS.

Insulin-sensitizing agents are essential to correct the underlying metabolic abnormalities. Metformin is the treatment of choice in adolescents with PCOS. The guidelines particularly recommend metformin in those patients with PCOS with failed lifestyle modification and who have impaired glucose tolerance or type 2 diabetes. However, a study conducted by Naderpoor, et al. showed that metformin treatment considerably improves body mass index (BMI), serum lipids, and glucose homeostasis.

A combination of lifestyle and metformin is more beneficial than lifestyle alone in reducing BMI and adipose tissue levels. It also regulates the menstrual cycle in women with PCOS.

Pioglitazone significantly improves endocrine and metabolic irregularities in women with PCOS, and it can be used as a beneficial alternative to metformin in women who are unable to take or tolerate metformin, particularly who are not obese.

Hormonal contraceptive, namely, Drospirenone (the progestogen source of HCs) appears to be significantly beneficial for long-term cardiovascular and metabolic abnormalities. It improves hyperandrogenism, lipid profiles, highly sensitive C-reactive protein (hsCRP) levels and insulin resistance.

Inositol
Recently, the use of inositol, for managing the metabolic irregularities of PCOS has shown some benefit, although conclusive evidence is still not available. Treatment with two inositol isomers, myo-inositol and d-chiro-inositol, could be proposed as a favorable therapeutic approach for the treatment of patients with PCOS.Inositols improve insulin resistance, serum androgen levels and many features of metabolic syndrome, ultimately reducing cardiovascular risk.

Statins

The Endocrine Society clinical practice guidelines disapprove statins for the time being, for all patients with PCOS, and demands further studies to explore their effects in these patients. Patients with atherogenic dyslipidemia may be treated by metformin, although it is not effective against LDL-cholesterol. Depending on the cardiovascular disease risk, fenofibrate, nicotinic acid or omega-3-fatty acids may be added to statins if needed.

Anti-hypertensive medications

For BP,140 mmHg systolic or 90 mmHg diastolic, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) are generally preferred.

Bariatric surgery is recommended in morbidly obese (BMI 40 kg/m^2) women with PCOS or obese women with metabolic comorbidities. (BMI 35 kg/m^2).

One of the studies has proved that thisprocedure resulted in decreased BMI, glycosylated hemoglobin (HbA1c), total cholesterol, LDL-C and triglyceride levels.

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Chapter 7

PCOS and Mental Health

Dr. Nazish Imran
Dr. Zainab Pervaiz

SUMMARY:

This chapter focusses on the psychological impact of Poly Cystic Ovarian Syndrome (PCOS). PCOS is known to be associated with various mental health issues including Depression, Anxiety, Eating Disorders, and others. Routine screening should be done to identify these mental health issues. The diagnosis involves taking detailed history, Mental State Examination and various diagnostic tools such as GAD-7 and PHQ-9. Management of symptoms requires a comprehensive approach including lifestyle modifications, treatment of the PCOS symptoms, Cognitive Behavioral Therapy (CBT) and the use of psychotropic medication.

CASE SCENERIO:

A young female patient presented to the psychiatric OPD after a referral from her gynaecologist. The patient reported suffering from low mood for the past two years. The symptoms started when she was diagnosed with PCOS based on her menstrual irregularities and other clinical findings. The patient had acne marks all over her face and said that "it shatters my self confidence." She had stopped attending most social gatherings because somebody would always make comments on her acne marks and weight. On further assessment she started crying and reported that she feels tired all the time, wakes up several times at night and fears that she won't be able to have children in the future. During Mental State Exam patient had morbid obesity, restlessness, and an ill-looking appearance. Her mood was noted to be low and irritable. Rest of the Mental Status Examination was unremarkable. GAD-7 and PHQ-9 were administered, and the patient was found be suffering from moderate Depression. An extensive management plan including lifestyle modifications for weight loss and CBT was advised to the patient.

INTRODUCTION:

Polycystic Ovarian Syndrome (PCOS) has long been identified as the most common disorder causing metabolic and hormonal disturbances in women. However, the mental health implications of PCOS have only recently gained importance. Different studies have identified an increased risk of various mental health conditions including Mood Disorders, Anxiety, Psychosis, eating disorders and issues related to negative body image and self-esteem in women suffering from PCOS.[1]

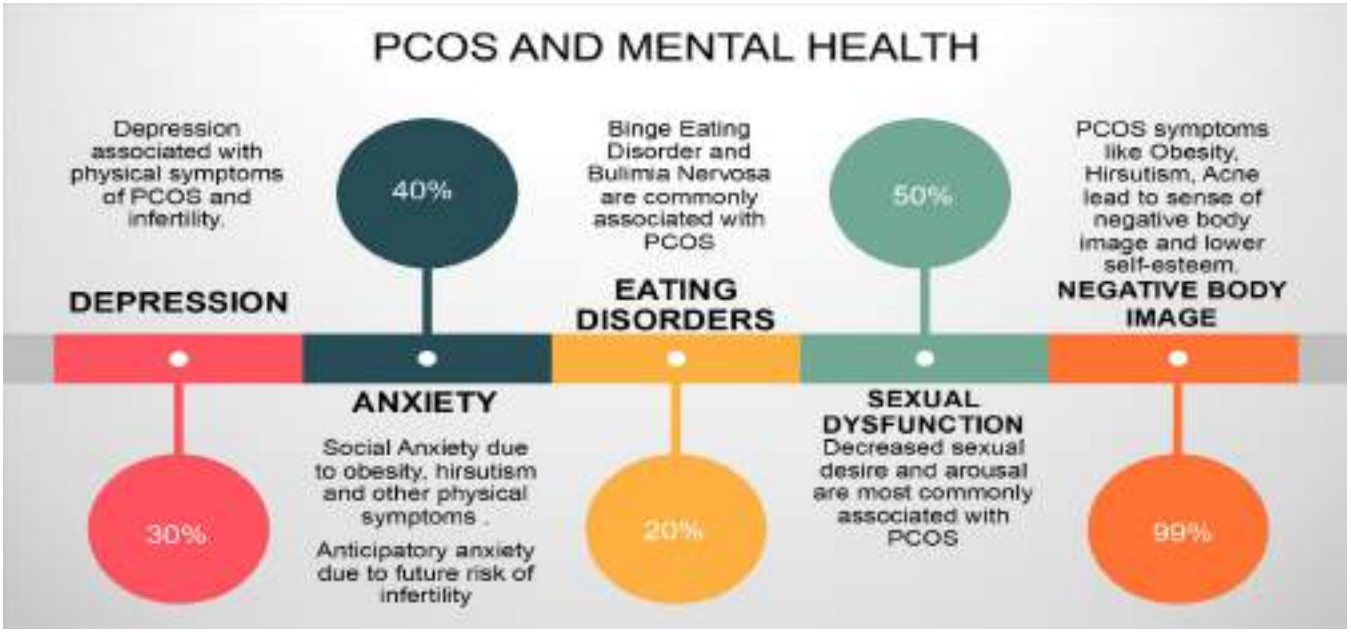

Figure 1: PCOS & Mental Health

Depression and Anxiety disorders have been identified as the most common psychological association of PCOS. The risk has been estimated as up-to 30% for depression and up-to 40% for anxiety and related disorders.[3] Different risk factors have been identified including infertility, obesity, androgen excess and the physical symptoms of PCOS including hirsutism, acne, and menstrual irregularities. These physical symptoms of PCOS can also lead to dissatisfaction with body image and lower self-esteem in women suffering from PCOS as compared with women without PCOS. These issues with perceived body image and self-esteem cause significant emotional distress and serve as a risk factor for depression and disordered eating patterns.

Several studies have reported an increased incidence of eating disorders including Bulimia Nervosa and Binge Eating Disorder in women suffering from PCOS. The risk for eating disorders has been linked to insulin resistance and excess androgen levels that can lead to issues with impulse control. Women with PCOS are also at a risk of developing Bipolar Affective Disorder[4] and Psychosis, and this vulnerability has been attributed to inflammatory mechanisms and abnormal variations in the levels of Estrogen in PCOS.[2] Similarly the physical manifestations of PCOS like obesity can also lead to sleep related issues and sexual dysfunction.[5] Apart from the physical symptoms, Polycystic Ovarian Syndrome also carries a significant risk of Infertility that adds to the psychological burden of the disease and negatively impacts the health-related quality of life. PCOS is also associated with an increased risk of developing Post-Partum Depression. Lastly, maternal hyper-androgenism due to PCOS has been linked to an increased risk of certain childhood mental health disorders including Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD). This risk is particularly higher in the female offspring born to mothers with hyper-androgenism.[6] Hence, high prevalence of depression, anxiety and other mental health issues in women suffering from PCOS signifies the need of routine screening for these issues at initial presentation.

COMMON PRESENTING SYMPTOMS AND IMPORTANT POINTS IN HISTORY: [3]

The most commonly reported symptoms of depression in PCOS include fatigue, sleep and appetite disturbance, and diminished interest in daily activities. Other symptoms of Depression as defined by DSM-V include low mood, hopelessness, lack of concentration, lower self-esteem and suicidal ideation.

People with PCOS are more likely to suffer from generalized anxiety disorder, social phobias and even panic attacks. These symptoms might be related to the physical symptoms of PCOS and infertility. Some of the symptoms of anxiety in PCOS include excessive worry, nervousness and restlessness, fatigue, and lack of self-confidence. Social Phobias in PCOS are usually seen as fear of being criticized publicly for the various physical symptoms like obesity, hirsutism etc.

Disordered eating behaviors most commonly present as Binge eating disorder and Bulimia Nervosa. Binge eating disorder is characterized by episodes of excessive eating in a limited amount of time with associated feelings of distress. Bulimia Nervosa is characterized by episodes of excessive eating followed by compulsive behaviors like self-induced vomiting, use of purgatives and fasting for stress relief.

The most common sleep disorders identified in PCOS are hypersomnia and obstructive sleep apnea. Sexual dysfunction usually presents in the form of decreased sexual satisfaction in such women.[5]

Bipolar Affective Disorder is characterized by episodes of Depression and Mania. Mania is defined by mood elation, grandiosity, agitation, and risky behaviors. Psychosis presents with history of odd behavior, disturbance in thought leading to false beliefs (delusions) and disordered perception (hallucinations).

MENTAL STATE EXAMINATION:

Assessment of mental state is the psychiatric version of relevant physical examination done in other specialties. Mental state examination includes comments on general physical appearance and assessment of speech, mood and affect, thoughts and perceptions and cognitive abilities. This examination enables the doctor to differentiate between different psychiatric disorders and helps in making a diagnosis.

Below are the relevant findings that might be present in a patient suffering from PCOS and co-morbid psychiatric symptoms:

* GENERAL PHYSICAL APPEARANCE: Unkempt appearance points towards depression, disheveled appearance and poor eye contact may indicate Psychosis while provocative dressing points towards Mania. A person with anxiety may appear to be restless and agitated. A person with eating disorder might be obese or severely malnourished at presentation.

* SPEECH: Paucity of speech may indicate Depression and Psychosis; loud and fast speech may indicate Mania.

* MOOD: Low mood point towards depression and elated mood points towards Mania. A patient with eating disorder may also describe having low and irritable mood.
* DISTURBANCE OF THOUGHT AND PERCEPTION: Disturbance in thoughts which are known as delusions and disturbance in perception known as hallucinations are usually seen in Psychosis. A person suffering from Mania can have Delusions of Grandiosity and a person suffering from depression can also have some form of thought disturbance.
* COGNITION: Cognitive disturbance is usually seen in organic disorders and might be seen in patients suffering from Psychosis whereby patient might not be able to identify himself, others, and surroundings.

ASSESSMENT OF DEPRESSION AND ANXIETY IN WOMEN WITH PCOS:

The high prevalence of depression and anxiety symptoms in PCOS justifies the inclusion of psychological screening in all patients at diagnosis, as well as at follow up, after initiation of treatment, however this holistic approach often remain neglected. Assessment of psychological symptoms and quality of life can be performed by clinical interview as well as using appropriate validated tools. The choice for use of questionnaires to assess depression and anxiety depends on specialists involved and often includes Hospital Anxiety and Depression Scale (HADS questionnaire), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7).

PHQ-9 has been found to be a valid and reliable tool to screen, rate and monitor outcomes of depressive illness in Pakistan. [7] Nine items assess the frequency of depressive symptoms over the past two weeks on a 4-point Likert-scale ranging from 0 (not at all) to 3 (nearly everyday). The score range of the PHQ-9 is 0-27 points, and higher scores indicated more severe depressive symptomatology.

The 7-item Generalized Anxiety Disorder (GAD-7) scale is also validated in Urdu language in Pakistan and is a brief measure to assess the frequency of anxiety symptoms over the past two weeks on a 4-point Likert-scale ranging from 0 (never) to 3 (nearly every day). [8] The total score of GAD-7 ranged from 0 to 21, with increasing scores indicating more severe functional impairments because of anxiety.

DIFFERENTIAL DIAGNOSIS:

People with depression experience a range of symptoms including persistent depressed mood or loss of interest and pleasure for at least 2 weeks. They have considerable difficulty with daily functioning in personal, family, social, educational, occupational, or other areas. Anxiety core symptoms include worry on most days for more than six months, and difficulty controlling these feelings of anxiety and worry. It is important to remember that many people with depression also suffer from anxiety symptoms and medically unexplained somatic symptoms.

MANAGEMENT OF PSYCHOLOGICAL SYMPTOMS OF PCOS:

The worrisome high prevalence of psychological problems in PCOS needs to be addressed as part of comprehensive management of the disorder. Apart from psychoeducation on PCOS, because of poor understanding of the disease and its link with mental health, there are various approaches in managing the psychological aspects of PCOS.

TREATING THE SYMPTOMS OF PCOS:

Evidence suggests that addressing symptoms of PCOS like obesity, infertility, hirsutism etc. improves the mental distress related to PCOS and improves the symptoms of depression and anxiety.

LIFESTYLE MODIFICATION:

Lifestyle modifications are considered the cornerstone of management of PCOS and also helps in improving mood symptoms. Weight loss is one of the biggest health concerns of women with PCOS. Three component lifestyle interventions including diet, exercise and CBT is noted to lead to weight loss, better mood, and improve self-esteem in women diagnosed with PCOS. [8] Another study recommended using 5 A's model for counselling in lifestyle modification for mental health promotion in PCOS. It includes ask, advise, assess, assist, and arrange. Ask/ assess include body mass index calculation as well as understanding patient's lifestyle with respect to exercise and nutritional behaviours. In **advice**, psychoeducation is provided about course of illness and link of nutrition and physical activity is explained alongside information about calories balancing. **Agree** stage involves identification of behavioural goals and making practical plan to implement it. In **Assist** barriers to implementation of lifestyle modification plan and possible solutions including social support available are discussed. In **arrange** step, progress status of dietary behaviours and physical activity is monitored using method preferred by the patient. [9]

COGNITIVE BEHAVIORAL THERAPY(CBT):

CBT is a type of psychotherapy based on the concept that negative thoughts and feelings contribute towards depression and anxiety, Thus CBT focuses on changing the dysfunctional thoughts that lead to negative mood states. It is considered first line treatment for depression and anxiety. Various studies have shown CBT to improve the psychological aspects of PCOS. [8] [10]

USE OF PSYCHOTROPIC MEDICATIONS:

Antidepressants:

Antidepressants are also used for treating depression and anxiety however, it is advisable to first focus on PCOS treatment as well as lifestyle modifications and CBT before antidepressants. Some antidepressants can cause weight gain and potentially impact blood glucose, thus limiting their use as first line treatment for depression and anxiety in women with PCOS. Mood stabilizers such as Sodium Valproate increase the risk of PCOS should be used with caution.

Antipsychotic medication:

Antipsychotic medication should be used in PCOS with caution since the metabolic side effects of these drugs can worsen the symptoms of PCOS. Such drugs should be preferred which are least likely to disrupt the metabolic profile of the patient.

Thus, to conclude, PCOS status may have significant negative impact and consequences on the psychological well-being and quality of life. High prevalence of depression and anxiety in patients with PCOS implies regular screening for psychological symptoms in the initial evaluation as well as follow-up of women with PCOS. Management of symptoms requires a comprehensive holistic approach by engaging patients and families.

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Chapter 8

Dietary Management in PCOS

Dr. Tehmina Rashid

Summary:
Lifestyle change is the first line of treatment for the management of women with PCOS. Nutritional counseling along with Regular physical activity, maintaining appropriate body weight for PCOS patients has been one of the treatment methods for many years.

Life Style interventions (preferably multicomponent diets, exercise, and behavioral strategies) should be recommended for all patients with PCOS and obesity because these changes not only lead to weight loss but also help in improving insulin resistance.

Weight loss:
Achievable goals such as 5% - 10% weight loss in those with excess weight yields significant clinical improvements and are considered successful weight reduction within six months. Ongoing assessment and monitoring are important during weight loss and maintenance in all women with PCOS (1)

Calories advise:
Strict calorie restriction does not give the expected results, several studies have assessed the effects of calorie restriction with the modification in macronutrient composition or dietary pattern that shows there is no ideal macronutrient distribution and dietary pattern for PCOS, little variation in weight loss is due to compliance to dietary advice and body's response to different macronutrients. Negative energy balance with a calorie deficit of 300 1000k calories shows success in full weight and fat loss and improves menstrual cycle and fertility (1,2001,500 kcal /day) could be prescribed for women, also considering individual energy requirements, body weight, and physical activity level. Food choices must be healthy and balance should be taken. (3,)(4).

Carbohydrate intake:
There is no optimum amount of carbohydrate intake for women with PCOS; any range of carbohydrate can be taken depending upon an individual's dietary assessment, metabolic goals, dietary habits, and preferences. Carbohydrate choices should base on high fiber choices, including fruits, vegetables, whole grain cereals, lentils, beans, and pulses refined carbohydrates and high fructose sources should be discouraged.

Low Glycemic Index:
Low glycemic index diet decreases insulin resistance, fasting insulin, total and low-density lipoprotein (LDL), triglycerides, waist circumference, and total testosterone compared with a high glycemic index diet. low glycemic index diet includes non-starchy (such as bean sprouts, brussels sprouts, broccoli, cabbage, cauliflower, celery, cucumber, eggplant, mushrooms, onions, peppers, salad greens, spinach, tomato, turnips, zucchini, melons, berries like strawberries, raspberries, blackberries and blueberries, citrus fruits like oranges, tangerines, grapefruit and lemons, peaches, plums, apricots, cherries, and pears), low-fat dairy products, legumes, and whole grains. (5)

GLYCEMIC INDEX DIET CHART: (6)

HIGH GLYCEMIC INDEX	MEDIUM GLYCEMIC INDEX	LOW GLYCEMIC INDEX
White Bread	Sweet Corn	Barley
White Rice	Spaghetti	Orange
Cornflakes	Banana	Dates
Instant Oats Porridge	Mango	Peaches
Rice Porridge		Carrots
Watermelon		Non-starchy Vegetables
Potato Boiled		Milk
Glucose		Chickpeas
		Kidney Beans
		Lentils

Fat consumption:

Saturated fat ingestion stimulates increasing inflammation, therefore, eliminating saturated fat from these is imperative, fish oil offers many benefits helps in reduction in triglycerides levels, improving the fatty liver, and decreasing inflammation, it also helpful in lowering testosterone and regulate the menstrual cycle in both overweight and lean women. (7)

Are ketogenic and intermittent fasting helpful?

At present, there is a lack of research on this topic, and there is no consensus on the best diet for PCOS, future research is needed to see the long-term dietary treatment of PCOS as there is insufficient data is available to support the efficacy, safety and health benefits of these diets. So it is best to follow the healthy eating principles in PCOS. (8) Therefore, a general conclusion is that by following the main principles of a healthy diet, the physiological homeostasis can be managed, as well as faster recovery from disease achieved.

Women with PCOS are sometimes treated with metformin, which normalizes glycemia and improves insulin resistance, but its chronic intake is additionally associated with deficiencies in thiamine and cobalamin. Therefore, it is a good idea to supplement with thiamine, which, by activating transketolase, contributing to the inhibition of mechanisms damaging blood vessels thus reducing the risk of cardiovascular diseases.

Vitamin D levels should also be evaluated in women with PCOS, as it increases insulin synthesis and release, increases insulin receptor expression, and increases insulin response to glucose transport.

Physical activity levels recommendations:

In adults, 150 minutes of moderate-intensity/ week is required or 75 minutes or more of vigorous exercise per week for adults between the ages of 18 64 years includes strength-building activities not two consecutive days per week.

In adolescents, moderate-to-vigorous physical activity, including strength training, for at least 60 minutes per day is required. (1) It is also necessary to minimize screen time and sitting time as well.

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Commonly Asked Questions About PCOS

1. What are the symptoms of PCOS?

Symptoms of PCOS vary, some will experience mild while others severe symptoms.

Symptoms may include:

* Irregular or no periods
* Oily skin
* Acne
* Unwanted facial or body hair (hirsutism)
* Thinning hair or hair loss from the scalp (alopecia)
* Difficulty becoming pregnant
* irregular ovulation, or no ovulation at all
* Depression or mood changes
* Weight problems being overweight, rapid weight gain or difficulty losing weight

2. Will PCOS affect my fertility and chances of getting pregnant?

The hormonal imbalance that PCOS causes interferes with ovulation, and therefore can affect fertility. PCOS can also affect how regular cycles are, meaning there may be fewer cycles in a year and it is harder for a woman to detect her fertile phase.

PCOS is a treatable condition, so there is a chance that you will be able to get pregnant.

3. Do I need to have IVF?

In most cases, the answer is no, especially if PCOS is your only condition.

Of course, a full personal assessment of the couple is needed, but most patients are able to conceive naturally after a diagnosis of polycystic ovaries.

4. Are there any lifestyle changes I can make?

Symptoms can be improved through dietary and lifestyle changes, including:

* Eating a balanced diet
* Adding more lean protein, fruit and vegetables to your diet
* Avoiding excess caffeine and alcohol
* Do regular exercise
* Get plenty of good quality sleep
* Avoid unnecessary stress

5. How is PCOS treated?

Once a diagnosis is made on the basis of history, physical examination and/or blood tests, your health care professional may prescribe certain medications along with lifestyle modifications.

6. Does the diagnosis of PCOS is made by ultrasound examination?

While ultrasound examination may help in diagnosis of PCOS and excluding other causes, the diagnosis is solely not dependent on ultrasound.

7. Will having PCOS affect the outcome of my IVF?

Normally we have the same good results with PCOS patients that we have with all patients. The only additional risk for PCOS patients is an increased risk of hyperstimulation as a result of the IVF process.

8- Am I more prone to develop diabetes and hypertension due to PCOS?

Women with PCOS are at increased risk of developing diabetes, hypertension as well as other cardiovascular problems, if not managed properly.

9. **Metformin is an anti-diabetic. Do I need to take it even if I am not diabetic?**

Metformin is used for many conditions resulting from insulin resistance; hence it is not used only for the treatment of diabetes.

The End

PCOS

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ISBN 978-627-7643-00-3