Mogs for Women
Our speciality is you

The Mumbai Obstetric & Gynecological Society

MOGS MEDIA

Vol 5 | PCOS

Dr Rishma Dhillon Pai
President MOGS

Dr Anahita Chauhan
Secretary MOGS

Dr Rajendra Sankpal
Treasurer MOGS

Dr Pratik Tambe
Editor

Dr Atul Ganatra
Co Editor

Dr Rohan Palshetkar
Co Editor

www.mogsonline.org

President's Message

Dear Colleagues,

It gives me great pleasure to bring to you the fifth edition of '**MOGS MEDIA**' . This is a series of focussed newsletters where we bring to you an important subject discussed in detail with all the latest updates which are relevant to you in your daily practice. This issue is on the important and common problem of **PCOS.** The editor Dr Pratik Tambe and all the contributors have made a lot of effort to bring you the latest information on the subject and we are thankful to them .

I am sure you enjoyed the unique 'Conflict to Clarity' conference with many International and national experts sharing their experiences. Also the wonderful devotional songs by our chief guest, Padmashri Anup Jalota ji. It was the first time free papers by our postgraduates and seniors were presented on a digital platform and this received an overwhelming response. I am sure you have benefitted from the many focussed webinars we have been doing. I hope the '**Pearls of Wisdom**' videos which you are receiving regularly are adding to your knowledge. Our digital PG training programme - The **Dr NA Purandare** practical training event which has hundreds of young doctors tuning in, is helping young doctors get ready for exams and clinical practice.

MOGS V Care & Share programme was started by us to support our frontline workers and the women whose health we look after. PPE, N95 masks, face shields, fetal dopplers etc have been donated by us to all major and many peripheral municipal and government hospitals. We reached out to our resident doctors by giving immunity boosters etc in August and again in September, we have distributed care packages to all doctors in government and municipal hospitals. We lent our support to breast feeding mothers in breast feeding week, by giving hundreds of new mothers in municipal hospitals protein supplements, masks, sanitizers etc and again in September we gave them care packages. We need your help and support for this ongoing programme. You can donate by online payment on our website or by bank transfer.

We have many different academic and fun activities planned this year Do visit our website for updates. www.mogsonline.org and download our **upgraded app.**

Thank you once again for all your support over the years and we look forward to a wonderful year at MOGS.

Stay safe, stay healthy.

Best Wishes

Dr Rishma Dhillon Pai

President MOGS.

Mogs for Women

Our speciality is you

Online payment gateway on MOGS website

http://mogsonline.org/vcareshare/

MOGS V Care & Share

MOGS extends a helping hand to our frontline healthcare workers and patients.
Support our efforts - contribute generously - if not now, when?

NEFT Details of MOGS			
Name as per Bank Account	**The Mumbai Obstetric & Gynecological Society**	RTGS/NEFT/IFSC Code	**BARB0JACOBC**
Bank Account No	**24480100012858**	Gstcertificate	**27AAATT4562C1ZL**
Bank Name	**BANK OF BARODA**	Pan card	**AAATT4562C**
Bank Branch	**JACOB CIRCLE BRANCH, Mumbai 400 011**	SAC CODE	**998599**
MICR Code	**400012092**		

Editors' message

Dear MOGS members,

The MOGS Media series of newsletters have been one of the highlights of the MOGS year so far. The newsletter is themed on areas of practical interest with individual topics having relevance in day-to-day practice for practising obstetricians and gynaecologists. The previous four issues on Preterm Birth, Anaemia and Nutrition in Pregnancy, Optimising IUI Results and Endometriosis were well received and widely appreciated by readers throughout the country.

It is with great pride that we bring you the fifth issue on "PCOS"which addresses the commonly encountered manifestations of the most common endocrinological condition we see in clinical practice. A wide variety of clinical evidence and recent guidelines and publications are addressed in the articles in this volume.

We thank the MOGS President Dr Rishma Dhillon Pai and the office bearers for giving us the opportunity to be part of such an innovative, important and immensely practical initiative. We hope you enjoy reading the articles and find them useful. We would welcome any comments or suggestions regarding the same and encourage you to reach out to us with feedback.

Wishing you, your families and staff good health and safety in these difficult times!

Dr Pratik Tambe
Editor

Dr Atul Ganatra
Co Editor

Dr Rohan Palshetkar
Co Editor

Dr Pratik Tambe
Dr Atul Ganatra
Dr Rohan Palshetkar
(Editors)

MOGS MEDIA

Vol 5 | PCOS

Mogs for Women
Our speciality is you

TABLE OF CONTENTS

REVISED DIAGNOSTIC CRITERIA

Dr Gaurav S Desai MS FCPS
Pelvic Surgeon and Fertility Specialist
Assistant Professor, Seth GS Medical College & KEM Hospital Mumbai
Managing Council member, MOGS

Q. According to 2018 ESHRE guidelines what are irregular cycles?

A. Irregular cycles are considered normal in the first year post menarche. Cycles are said to be abnormal and irregular if they are less than 21 days or more than 45 days between 1 and 3 years after menarche. In women more than 3 years after menarche till perimenopause cycles lasting for less than 21 days or more than 35 days (or less than 8 cycles annually) are said to irregular. More than a year after menarche any one cycle lasting over 90 days is irregular. Primary amenorrhea by 15 years of age or more than three years after breast development is considered abnormal.

Q. Are there any points to consider in the diagnosis of women with PCOS and irregular cycles?

A. For adolescents with PCOS timely diagnosis is key and should be discussed with the patient. For adolescents who have features of PCOS but do not meet diagnostic criteria (those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence) reassessment is advised at or before full reproductive maturity, 8 years post menarche.

Q. Which tests are useful to assess hyperandrogenism in PCOS?

A. Free testosterone, free androgen index or calculated bio available testosterone should be used. Liquid chromatography–mass spectrometry (LCMS)/mass spectrometry and extraction/chromatography immunoassays should be used. Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated.

Q. How does one assess biochemical hyperandrogenism in PCOS in women on hormonal contraception?

A. Reliable assessment is not possible in women on hormonal contraception, due to effects on sex hormone-binding globulin and altered gonadotrophin-dependent androgen production. In this situation drug withdrawal for three months or longer before measurement is recommended, and contraception management with a non-hormonal alternative is advised during this time.

Assessment of biochemical hyperandrogenism is most useful in establishing the diagnosis of PCOS and/or phenotype where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent. Marked increase in androgen levels should raise suspicion of other causes including androgen secreting neoplasms.

Q. According to the criteria how does one diagnose clinical hyperandrogenism?

A. Detailed history and physical examination are important. Note any alopecia, hirsutism and acne. Standardised visual scales: Modified Ferriman Gallwey score (mFG) ≥ 4 - 6 indicating hirsutism. The Ludwig visual score is preferred for assessing the degree and distribution of alopecia.

Q. When should ultrasound be used?

A. Ultrasound should not be used in young women less than 8 years after menarche (false positive due to multicystic ovaries). Transvaginal ultrasound (with a frequency bandwidth that includes 8MHz) for sexually active women is ideal.

Q. What are the ultrasound criteria for PCO morphology?

A. Threshold for PCO should be on either ovary, a follicle number per ovary of > 20 and/or an ovarian volume ≥ 10ml, ensuring no corpora lutea, cysts or dominant follicles are present. An ovarian volume ≥ 10ml on either ovary is also acceptable. Ultrasound is not necessary in women with irregular periods and hyperandrogenism but is recommended.

Q. What should the USG report include?

A. Ultrasound report should include: last menstrual period, transducer bandwidth frequency, approach/route assessed, total follicle number per ovary measuring 2-9mm, three dimensions and volume of each ovary, endometrial thickness and appearance: 3-layer endometrial assessment may be useful to screen for endometrial pathology, other ovarian and uterine pathology, as well as ovarian cysts, corpus luteum, dominant follicles ≥ 10mm.

Q. What is the place of AMH in PCOS diagnosis?

A. As of today serum AMH should not be used in the diagnosis of PCOS. With better standardisation this is a possibility.

Q. What are the ethnic variations clinicians should consider when diagnosing PCOS?

A. PCO phenotype is mild in Caucasians. Body mass index (BMI) is higher in Caucasian women. Hirsutism is more severe in Middle Eastern, Hispanic and Mediterranean women. There is increased central adiposity, insulin resistance, diabetes, metabolic risks and acanthosis nigricans in South East Asians and Indigenous Australians.

Q. What should one look for when considering PCOS in menopausal women?

A. PCOS in elderly women should be suspected when they have a past diagnosis of PCOS, a long-term history of irregular menstrual cycles and hyperandrogenism and/or PCOM. Recent onset androgenic clinical features require ruling out androgen-secreting tumours and ovarian hyperthecosis.

References

1. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, Piltonen T, Norman RJ; International PCOS Network. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome.FertilSteril. 2018 Aug; 110(3): 364-379.

2. Costello MF, Misso ML, Balen A, Boyle J, Devoto L, Garad RM, Hart R, Johnson L, Jordan C, Legro RS, Norman RJ, Mocanu E, Qiao J, Rodgers RJ, Rombauts L, Tassone EC, Thangaratinam S, Vanky E, Teede HJ; International PCOS Network. Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: assessment and treatment of infertility. Hum Reprod Open. 2019 Jan 4;2019(1):hoy021.

COUNSELLING IN ADOLESCENT PCOS

Dr Shrutika Thakkar MS DNB
Fellowship in Reproductive Medicine
Director Medansh Hospital, Youth Council member - MOGS

The art of medicine is to amuse the patient while nature cures the disease - Voltaire

Introduction

PCOS has been an enigma with a complex mish-mash of reproductive, metabolic and psychological features that we gynaecologists have not yet unravelled. The pathology probably originates in intrauterine life through developmental programming. The manifestations of the disease appear in adolescence and may change to metabolic disease as age advances hence correct diagnosis and management at an early age are very crucial.

Diagnosis of PCOS during adolescence is both controversial and challenging due to the overlap of normal pubertal physiological changes (irregular menstrual cycles, acne and polycystic ovarian morphology on pelvic ultrasound) with adult PCOS diagnostic criteria.

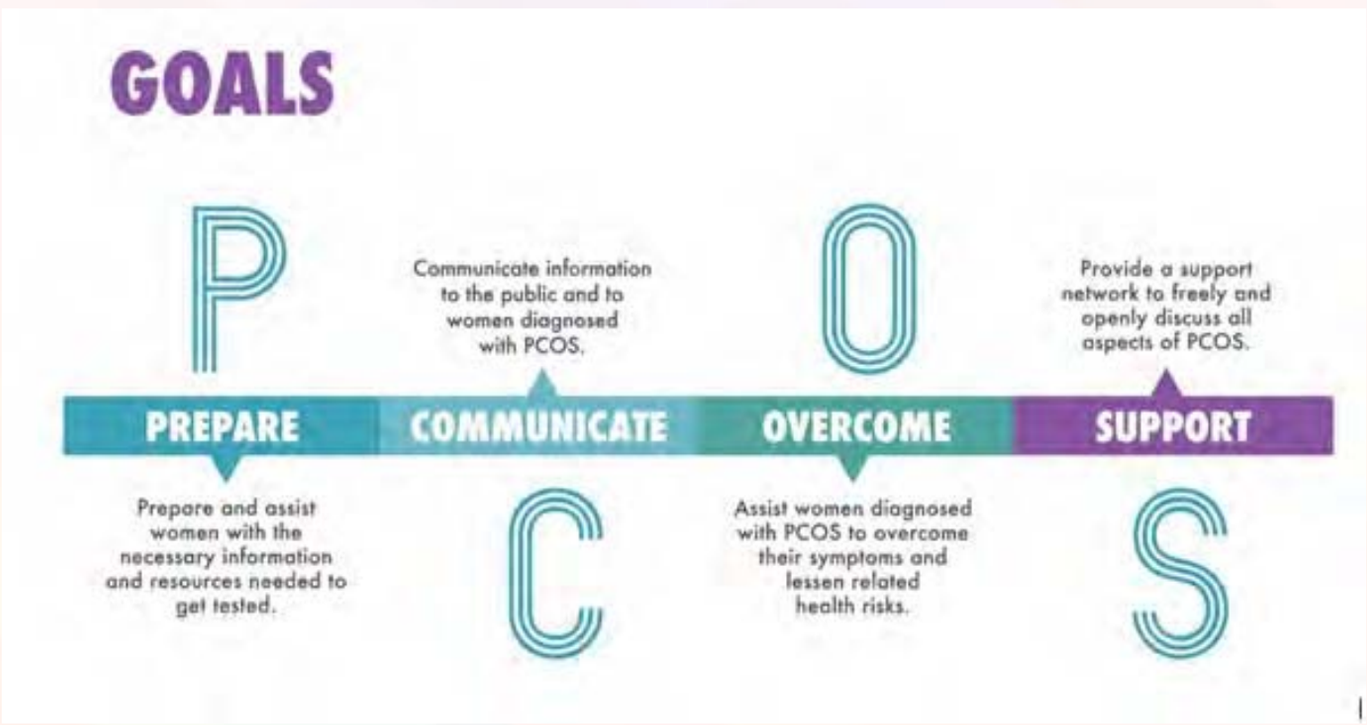

Fig 1 Goals in PCOS counselling

Counselling in PCOS is based on 4 important goals:

- P= Prepare women with correct testing
- C= Communicate information about the disease
- O= Overcome the symptoms and lessen health risks
- S=Support system for all aspects of the disease

While counselling an adolescent girl and her family regarding PCOS there are two pertinent concerns that the clinician must address:

1. The first concern involves control of irregular menstrual cycles
2. The second issue involves the avoidance of the associated long term sequelae due to

a. Hyperandrogenism and cosmetic concerns

b. Obesity, insulin resistance, glucose intolerance and risk of type 2 diabetes

c. Emotional well being especially depression – anxiety, eating disorders Future fertility

Irregular menstrual cycles

As per the 2018 International evidence-based guideline for the assessment and management of polycystic ovary syndrome in adolescents, both oligo-anovulation and hyperandrogenism are required for diagnosis, with ultrasound not recommended for diagnosis. As depicted in Table 1, the guidelines have laid out stringent criteria for defining what constitutes as irregular menses in adolescents.

The guidelines state specifically for the first one year post menarche irregular menstrual cycles are normal. This is a huge positive comment for anxious mothers who drag their daughters to the gynaecologist's clinics soon after menarche worried that the period irregularity could mean PCOS has set in. The guidelines specifies further that one must not be in a hurry to label an adolescent girl who doesn't meet the diagnostic criteria to have PCOS; rather it is advisable to wait for 8 years post menarche and till then call the patient as 'increased risk'.

1		Screening, diagnostic assessment, risk assessment and life-stage	
1.1		Irregular cycles and ovulatory dysfunction	
1.1.1	CCR	Irregular menstrual cycles are defined as: • normal in the first year post menarche as part of the pubertal transition • > 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) When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.	❖❖❖❖
1.1.2	CCR	In an adolescent with irregular menstrual cycles, the value and optimal timing of assessment and diagnosis of PCOS should be discussed with the patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors.	❖❖❖❖
1.1.3	CPP	For adolescents who have features of PCOS but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with PCOS features before combined oral contraceptive pill (COCP) commencement, those with persisting features and those with significant weight gain in adolescence.	
1.1.4	CPP	Ovulatory dysfunction can still occur with regular cycles and if anovulation needs to be confirmed serum progesterone levels can be measured.	

Table 1 2018 International evidence-based guideline for the assessment and management of polycystic ovary syndrome recommendations

Hyperandrogenism

Clinical hyperandrogenism in adolescents may manifest as severe acne and hirsutism; for young girls this may be result in a poor body image. Reported unwanted excess hair growth should be considered important, regardless of apparent clinical severity. Symptoms such as hirsutism, acne, acanthosis nigricans, alopecia are painful, uncomfortable, and unpredictable for many PCOS patients because these symptoms are culturally defined as unfeminine and undesirable. Inquiry regarding self-treatment should be made and recorded in the examination. Offering professional help involving a multi-disciplinary team of dermatologists, cosmetologists and psychologists is the best approach in such cases.

Often the solution is such cases is cosmetic therapy such as laser treatment. It has been shown that women with hirsutism had enhanced self-esteem after effective hair removal. If cosmetic therapy is not effective or un affordable for patients who are concerned with hirsutism, medical therapy with anti-androgens may be helpful in managing hyperandrogenism.

Obesity, type 2 diabetes, glucose intolerance and insulin resistance

Lifestyle interventions are the best approach for dealing with PCOS associated obesity, type 2 diabetes, glucose intolerance and insulin resistance in order to prevent a future progression to metabolic syndrome in later life. Counselling must include questions directed towards identifying patients' unsafe weight loss strategies and eating patterns and encouraging them to use an appropriate plan for weight loss of 5% to 10%. It also involves advising patients to have regular physical exercise. As proven in a prior study, yoga significantly increases HQOL of PCOS patients compared to traditional physical exercises and is highly recommended.

The key principles of intervention and counselling are:

- Involve a dietician and give the patient a concrete diet plan with a goal of losing around 0.5-1 kg/ week
- Plate method of eating
- Educate about glycaemic index of food items
- Positively motivate for weight loss as dropouts are a major problem
- Empathise with patient and say diets are difficult to maintain but necessary
- Offer bariatric surgery in extreme cases

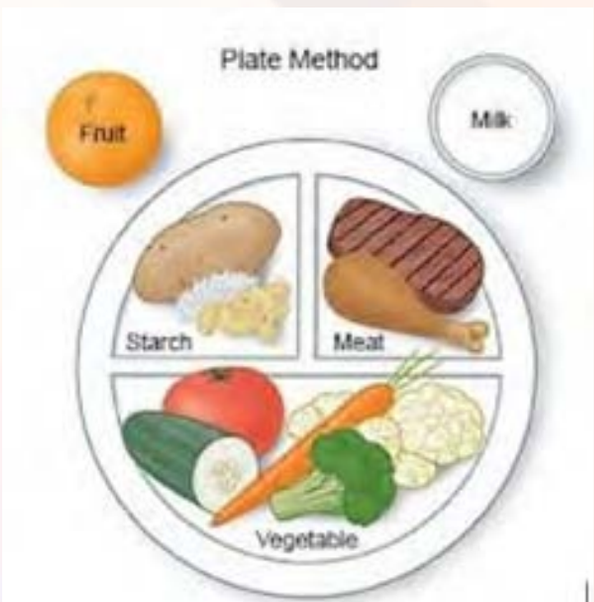

Fig 2 Dietician recommended proportions

Emotional wellbeing

For young girls, body image has the elements of femininity and attractiveness that can be a symbol of social acceptance amongst peers. The various symptoms of PCOS can result in feelings of stigmatised and mood disorders such as depression, limited sense of well-being, and dissatisfaction with life. Another factor that affects the body image of females with PCOS is their weight. This could be rooted in cultural preferences that consider android fat pattern as unattractive. Additionally, one of the consequences of body dissatisfaction are eating disorders. This is because self-esteem, as an important element for a female's social function and interpersonal relationships, is exclusively based on their body image.

The first consensus recommendation of the 2018 guidelines was that 'Health professionals should be aware that in PCOS, there is a likely increased prevalence in adolescence of moderate to severe anxiety and depressive symptoms' and; the second consensus recommendation was that 'Anxiety and depressive symptoms should be routinely screened in all adolescents and women with PCOS at diagnosis'. If the screening results are positive, help of a qualified team of psychiatrists, psychologists and counsellors.

Future fertility

An important concern amongst the young PCOS girls as well as their mothers is the future fertility and impact on reproductive capability of the girls when they become adults. A lot of myths persist that women with PCOS cannot get pregnant, and one must mention to the anxious patient that the reality is that it is highly treatable and nearly every woman with PCOS should be able to get pregnant.

Conclusions

Adolescent PCOS needs to be approached with a multi-pronged focus. Treatment options need to be tailored to the clinical presentation as shown in Fig 3. Counselling and offering positive motivation should encompass at least half if not more, of the time spent in consultation with patient and her family.

One of the most crucial and effective treatments for PCOS is lifestyle interventions. Even minor lifestyle interventions are important for the improvement of symptoms, decrease of weight, and improvement of fertility in patients with PCOS. The other important factor for PCOS patients that prompts intervention and improves self-efficacy is psychological well-being. Both these factors should be the pillars of counselling in an adolescent.

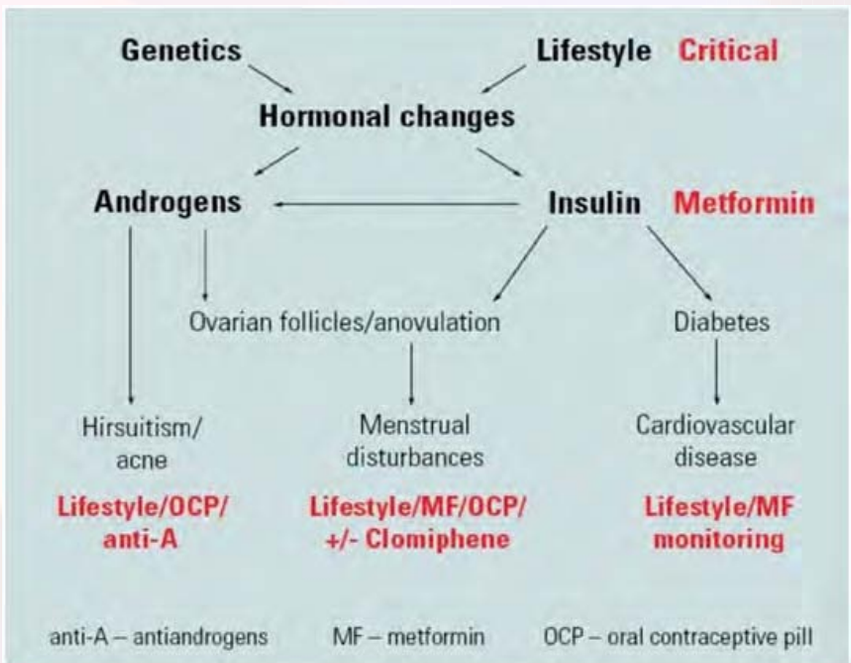

Fig 3 Summary of targeted approach to therapy in polycystic ovarian syndrome

References

1. Teede, Helena J, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Human Reproduction 33.9 2018: 1602-1618.
2. Peña, AS, Witchel, SF, Hoeger, KM, et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Medicine, 2020;18, 1-16
3. Azizi, M, Elyasi, F.Psychosomatic aspects of polycystic ovarian syndrome: a review. Iran J Psychiatry Behav Sci 2017:11(2), e6595.
4. Teede H, Zoungas S, Deeks A, Farrell E, Moran L, Vollenhoven B: Check: independent learning program for GPs. Polycystic ovary syndrome. Edited by: Royal Australian College of General Practitioners. 2008, South Melbourne, Victoria: Royal Australian College of General Practitioners, Unit 432

MANAGING HYPERANDROGENISM

Dr Pratik Tambe MD FICOG
Chairperson, AMOGS Endocrinology Committee (2020-22)
Governing Council member, ICOG (2021-22)
Chairperson, FOGSI Endocrinology Committee (2017-19)
Managing Council member, MOGS and ISAR

Background

Hyperandrogenaemia refers to excessive circulating levels of male hormones (testosterone, dihydrotestosterone, androstenedione and DHEAS) and hyperandrogenism refers to the consequent effects of excessive male hormones, viz. acne, hirsutism and alopecia. However, the issue may not be so straightforward or clear cut as normal peripheral blood levels may be associated with excessive androgen induced features and high levels of male hormones may not have consequent skin changes.

The levels of sex hormone binding globulin, diurnal variation in the binding proteins and hormonal levels, changes in adrenal corticosteroids all obfuscate the evaluation and prevent a clear picture from emerging and negate the usage of such assays in monitoring response to therapy. This article focuses on the clinical issues surrounding hyperandrogenism, its assessment and evidence based medical management for the same.

Evaluation

Hyperandrogenism is a key component of the diagnostic criteria for polycystic ovary syndrome. It is part of the (two of three) recommendations by the Rotterdam criteria from 2003 and is also clarified by the Androgen Excess Society guideline in 2006. The most recent ESHRE / ASRM / CREPCOS Consensus Guideline published in 2018 reiterates and cements the position of hyperandrogenemia and hyperandrogenism as one of the most important components of PCOS from a diagnostic and therapeutic perspective.[1,2,3]

Biochemical assays

For the purpose of biochemical evaluation, calculated free testosterone, free androgen index or bio available testosterone should be used in the diagnosis of PCOS. This is a strong evidence-based recommendation which was reached after examination of literature showing that androgen levels in adolescents reach adult levels around the time of menarche.[4]

There were two conditional evidence-based recommendations derived from studies in adult women that reported the diagnostic accuracy of different hormone markers to detect PCOS. High quality assays, such as liquid chromatography–mass spectrometry (LCMS) and extraction/chromatography immunoassays, should be used for the most accurate assessment of total or free testosterone in PCOS.

Androstenedione and dehydroepiandrosterone sulfate (DHEAS) provide limited additional information in the diagnosis of PCOS and should be evaluated if total or free testosterone are not elevated.

Androstenedione and DHEAS are more useful in excluding other causes of hyperandrogenism. Androstenedione is elevated in non-classical adrenal hyperplasia. DHEAS is a predominantly adrenal androgen and mild elevations can be seen in PCOS, whereas significant elevations and/or virilisation is seen in androgen-secreting adrenal tumours.[5,6]

Functional hyperandrogenism in PCOS

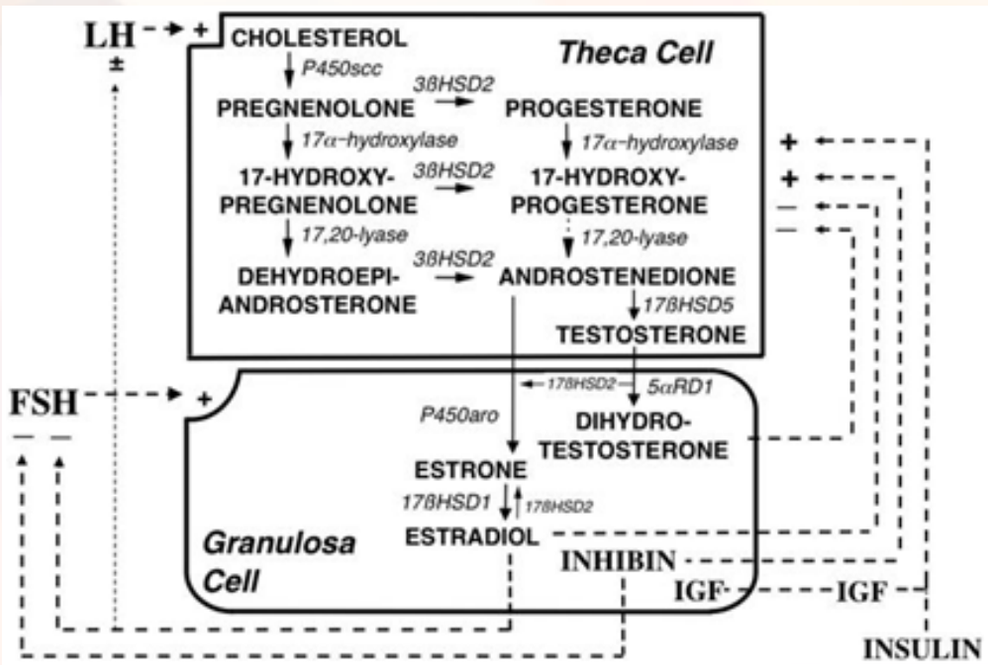

Fig 1 Steroid biosynthetic pathways in the antral follicle of the ovary aka the 2 cell 2 gonadotropin model of ovarian steroidogenesis[7]

Androgen and androgen precursors normally are produced by the ovaries and adrenal cortices in about equal amounts in response to LH and ACTH, respectively. About half of testosterone arises from peripheral metabolism of secreted precursors in liver, skin and fat.

The ovarian androgenic response to LH appears to be normally modulated by intra ovarian mechanisms so as to optimise androgen and estrogen formation and to promote follicular maturation, because although androgens are essential substrates for estradiol formation while in excess, they hinder ovulation. There is desensitisation of the theca cells to LH, minimising the androgenic response to high LH levels commencing with desensitisation at the level of the LH receptor. Excess insulin is an extra ovarian modulator that has the potential to override normal intraovarian down-regulatory mechanisms that control ovarian androgen production.

The common denominator of the great majority (87%) of PCOS patients is functional ovarian hyperandrogenism (FOH). Two-thirds of PCOS cases have 17-OHP hyper responsiveness to GnRH agonist or hCG stimulation (functionally typical FOH). Two-thirds of the remainder have FOH detectable by DAST (dexamethasone androgen suppression test), in which testosterone remains elevated after suppression of adrenal androgen production.[7]

Clinical hyperandrogenism

When evaluating a woman with hirsutism, the Ferriman–Gallwey (FG) score is a simple and commonly used method to quantify hair growth. This method evaluates nine androgen sensitive sites and grades them from 0 to 4. Scores above eight are considered abnormal in Caucasian and African American females. Scores between 8 and 15 are usually considered to be mild hirsutism, whereas scores greater than 25 indicate severe hirsutism.[8]

Some limitations of this scoring system include: (a) the variation in hair growth between different ethnic groups; (b) failure to account for regional hirsutism; and (c) the fact that many women may have treated their excessive hair growth with cosmetic measures such as chemical depilatories, electrolysis, laser therapy, etc.

Evaluation of physical signs of insulin resistance such as acanthosis nigricans and Cushing's syndrome (i.e., thinning of the skin, rounding of the face, dorsal fat pad, abdominal striae, or easy bruising) is required. Male pattern baldness, increase in muscle mass, acne, and deepening of the voice are signs of virilization. Abdominal and pelvic exams should be performed to look for masses and to evaluate clitoral size.[9]

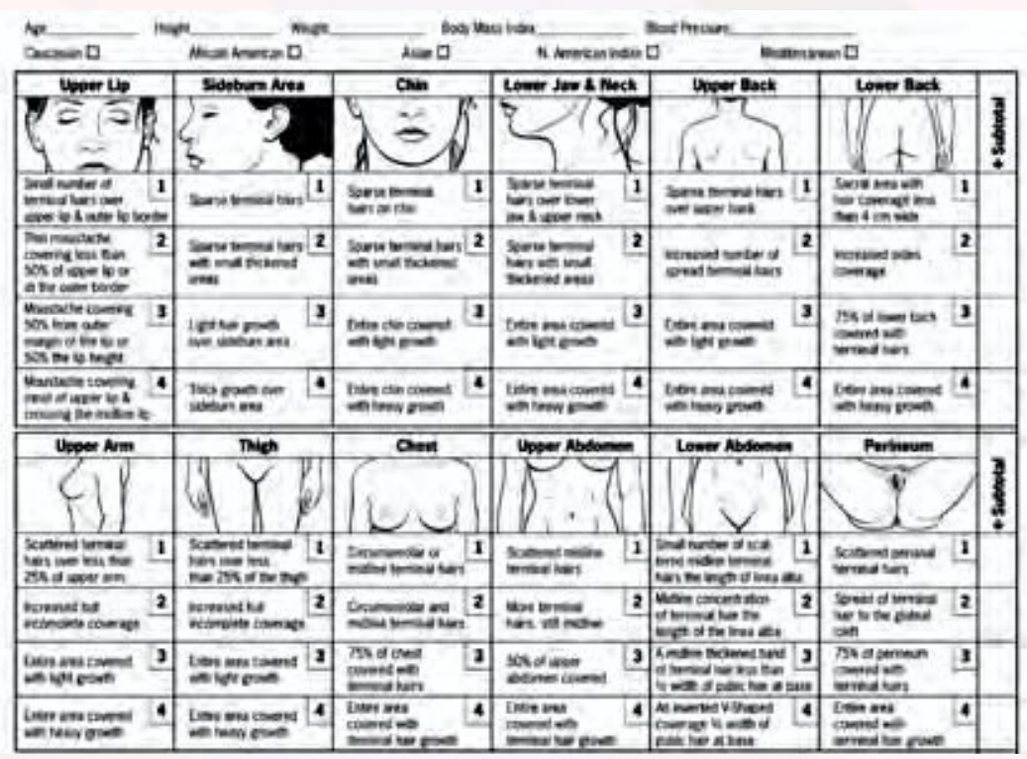

Fig 2 Ferrimen Gallwey score for assessment of hirsutism

Anxiety, depression and body image issues

Healthcare professionals should be aware that there is a high prevalence of moderate to severe anxiety and depressive symptoms in adults and a likely increased prevalence in adolescents, especially those suffering from hyperandrogenism. Healthcare professionals should be aware that features of PCOS can impact on body image.

Anxiety and depressive symptoms should be routinely screened in all women with PCOS. If the screen for these symptoms and/or other aspects of emotional wellbeing is positive, further assessment and/or referral for assessment and treatment should be completed by suitably qualified health professionals. Comprehensive health behavioural or cognitive behavioural interventions could be considered to increase support, engagement, retention, adherence and maintenance of healthy lifestyle and improve health outcomes in women with PCOS.[3]

Approaches to treatment

While PCOS accounts for 70-80% of cases of hirsutism seen in clinical practice, one must always ensure that it is a diagnosis of exclusion by attempting to identify and exclude the other causes for the same. These include adrenal hyperplasia, androgen secreting tumours, acromegaly, Cushing syndrome, hyperprolactinaemia, thyroid dysfunction, drug induced and idiopathic causes. Common drugs implicated in the causation of hirsutism include carbamazepine, clonazepam, corticosteroids, fluoxetine, paroxetine and tacrolimus.[10]

Lifestyle interventions

Multi component lifestyle interventions including diet, less sedentary behaviour, exercise and behavioural strategies should be recommended in all those with PCOS and excess weight to achieve reductions in weight, central adiposity and insulin resistance. This is extensively covered in another article in this volume.

Combined oral contraceptive pills (COCP)

The COCP alone should be recommended in adult women with PCOS for management of hyperandrogenism and/or irregular menstrual cycles. The COCP alone should be considered in adolescents with a clear PCOS diagnosis or could be considered in those deemed 'at risk' but not yet diagnosed with PCOS in both groups for the management of clinical hyperandrogenism and/or irregular menstrual cycles.

These recommendations are based on studies including two RCTs and a meta-analysis which evaluated the effect of metformin versus the COCP, showing improvements in menstrual irregularities and acne. Although the COCP is relatively safe, there are absolute medical contraindications to consider according to World Health Organisation Guidelines such as history of migraine with aura, deep vein thrombosis, pulmonary embolism, known thrombogenic mutations, multiple risk factors for cardiovascular disease, breast cancer, neuropathy, severe cirrhosis, malignant liver tumours, smoking and obesity.[3,11,12]

Specific types or doses of progestins, oestrogens or combinations of COCP cannot currently be recommended due to insufficient data among women and adolescents with PCOS. Various COCP preparations have similar efficacy in treating hirsutism. A practice point included states that COCPs with 35 µg of ethinylestradiol and cyproterone acetate should not be used as first-line therapy due to the absence of evidence of greater efficacy and the presence of higher risks, including deep venous thrombosis.

All COCPs are associated with an increased risk of deep venous thrombosis, but the risk is higher with COCPs containing 30–35 µg of ethinylestradiol and gestodene, desogestrel, cyproterone acetate or drospirenone when compared to the COCP containing 30 µg of ethinylestradiol with levonorgestrel, norethisterone (norethindrone) or norgestimate. Lower-risk COCP preparations should be recommended as first-line therapy.

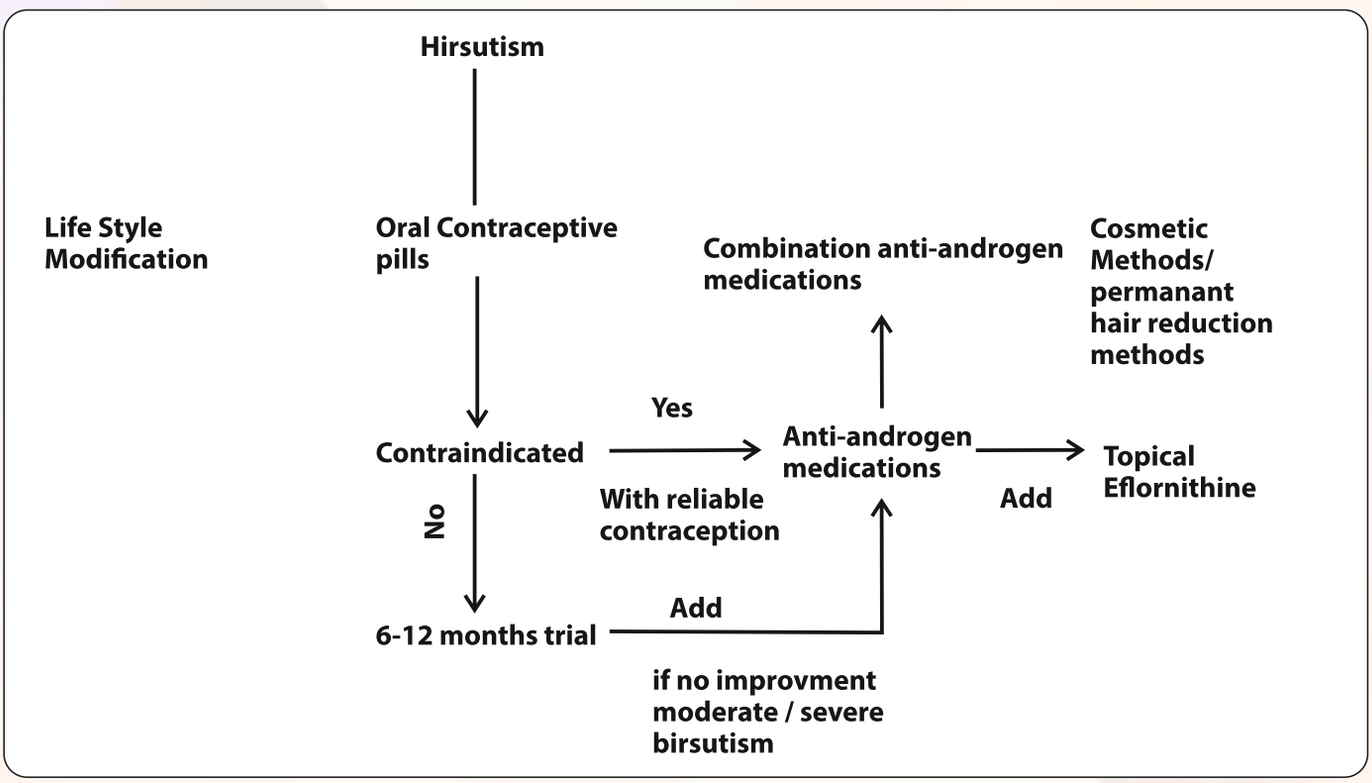

Fig 2 Algorithm for management of hirsutism in PCOS

Insulin sensitisers

Metformin

Metformin in addition to lifestyle, could be recommended in adult women with PCOS, for the treatment of weight, hormonal and metabolic outcomes. Metformin in addition to lifestyle interventions could be considered in adolescents with a clear diagnosis or with symptoms of PCOS before a diagnosis is made.

This evidence-based recommendation is based on a meta-analysis evaluating the effect of metformin versus placebo which included 20 RCTs and highlighted the beneficial effects of metformin on BMI, waist-to-hip ratio and triglycerides.

Metformin doses used in the trials were 1500–1700mg per day. Side effects included mild to moderate gastrointestinal side effects that were self-limiting (nausea, vomiting, diarrhoea, abdominal pain and non-specified gastrointestinal disturbances).[13]

Myoinositol

A systematic review of 11 RCTs on the role of myoinositol and d-chiroinositol in the treatment of PCOS concluded that these agents reduce insulin levels, improved hormonal parameters, reduced body weight, decreased circulating leptin levels, increased HDL concentrations and improved the metabolic profile in PCOS women. Inositol phosphoglycans are thus second messengers in the insulin signalling pathway and further studies and robust evidence regarding these new insulin sensitisers is awaited before a wider recommendation regarding their routine use can be made.[14]

Combined COCP and metformin

In combination with the COCP, metformin should be considered in women with PCOS for management of metabolic features where COCP and lifestyle changes do not achieve desired goals. In combination with the COCP, metformin could be considered in adolescents with PCOS and BMI ≥ 25 kg/m^2 where COCP and lifestyle changes do not achieve desired goals. Although the combination of metformin and the COCP offers additional benefits, these do not surpass the impact of the COCP plus lifestyle interventions and hence the combination is only indicated when the COCP and lifestyle interventions have failed to meet the treatment goals.

Combined COCP and anti-androgens

In combination with the COCP, anti-androgens should only be considered in PCOS to treat hirsutism, after 6 months or more of COCP and cosmetic therapy have failed to adequately improve symptoms. They may also be considered for treatment of androgen-related alopecia in PCOS. Where COCPs are contraindicated or poorly tolerated, anti-androgens should be considered to treat hirsutism. This group of drugs are not safe in the first trimester of pregnancy and hence their use in patients at risk of conception needs to be counselled and effective contraception must be practiced simultaneously.[3]

Anti-androgens

Cyproterone is a 17-hydroxyprogesterone acetate derivative with strong progestogenic effects. It competes with DHT for the androgen receptor and decreases serum LH and ovarian androgen production. It is used at a low dose of 2 mg as the progestin part of combination oral contraceptives, or at a higher dose of 12.5 to 100 mg per day as mono therapy.

Spironolactone is an aldosterone antagonist related structurally to progestins. It competes with dihydrotestosterone (DHT) for binding androgen receptors. Spironolactone also has an inhibitory effect on 5-alpha reductase and at doses higher than 200 mg per day inhibits action of various enzymes involved in androgen biosynthesis. Starting dose is usually 50 mg twice daily, which is then increased to 100 mg twice daily if needed. The main side effects include hyperkalemia, irregular menses, and teratogenicity.

Finasteride is a type-2, 5-alpha reductase inhibitor. Only a partial inhibitory effect is anticipated with finasteride as it does not affect type-1, 5-alpha reductase inhibitors. Usual dose for hirsutism is 5 mg per day, although some data suggest that a higher dose of 7.5 mg per day might be more effective. The main side effect is the feminisation of a male fetus because DHT is involved in the development of male external genitalia.

Flutamide is a non steroidal antiandrogen. It blocks androgen receptors, preventing the binding of DHT. Usual dose is 250 to 750 mg per day, which is equal in efficacy to spironolactone 100 mg/day or finasteride 5 mg/day. Flutamide is associated with hepatotoxicity, which may be dose dependent. It is not recommended as first line therapy and the lowest effective dose should be used with careful monitoring of liver function.[9]

A Cochrane meta-analysis in 2015 including 157 studies comprising 10,550 women evaluated the available interventions for hirsutism excluding laser and photoepilation alone. The combinations of ethinyl estradiol + cyproterone acetate and ethinyl estradiol + desogestrel showed an improvement in Ferrimen Gallwey scores by -1.84. Flutamide 250 mg twice daily was better than placebo (mean difference MD -7.60). Spironolactone 100 mg daily was more effective than placebo (MD -7.69). It showed similar results when compared to finasteride 5 mg and flutamide 250 mg twice daily. The quality of evidence was moderate to low quality.[15]

In a study published in 2018 on 200 women over a mean followup of 34.2 months, 85.1%, 82.7%, and 79.3% of patients reported improvement in hirsutism, menstrual dysfunction and acne, respectively. The modified Ferriman–Gallwey (mFG) hirsutism score improved by 59.9%. COCP + spironolactone formed the main subgroup of 138 women treated.[16]

Medication)	*Dosage*	*Adverse effects*	*Comments*	*FDA pregnancy category*
Oral contraceptives (various)	One tablet daily	Gastrointestinal upset, headache	Recommended first-line agents; formulations containing norgestimate, desogestrel, or drospirenone are preferred	x
Metformin (Glucophage)	5OO to 1,000 mg twice daily	Gastrointestinal upset	Useful for treating polycystic ovary syndrome, but no data to support primary use for hirsutism	b
Spironolactone (Aldactone)	100 to 200 mg daily	Hyperkalemia, irregular menses	Risk of pseudohemaphroditism in male fetuses if used during pregnancy	d
Fina-steride (Propecia)	2.5 mg daily	Hepatotoxicity		x
Glucocorticoids (prednisone)	5 to 10 mg daily	Weight gain, bone density loss, adrenal suppression	Indicated in congenital adrenal hyperplasia	c
leuprolide (lupron)	3.75 to 7.5 mg intramuscularly monthly	Hot flashes, atrophic vaginitis, bone density loss	Consider adding back hormone therapy; expensive	x
Ketoconazole	400 mg daily	Dry skin, headache, hepatotoxicity	Typically used only after failure of other therapies	c
Eflornithine (Vaniqa)	Apply topically twice daily	Acne, erythema, burning	FDA approval is only for use for unwanted facial hair	c

Table 1 Commonly used drugs in medical management of hirsutism[10]

Topical treatments

Eflornithine hydrochloride 13.9% is a topical preparation that inhibits hair growth by irreversibly inhibiting ornithine decarboxylase. It does not remove hair, but rather slows hair growth. It can be used alone or in conjunction with other therapies.

Randomised control trials have reported a more significant hair growth reduction when comparing a combination of laser therapy with eflornithine versus laser therapy and placebo cream, especially early in the treatment course. The Endocrine Society guidelines suggest the addition of eflornithine to photoepilation therapy in women who desire a more rapid initial response.

Nonpharmacological approaches

Temporary methods such as shaving, plucking, or waxing are effective, safe, and inexpensive. They can be used alone or in combination with pharmacologic therapy. Permanent methodsinclude photoepilation (laser or intense pulsed light) or electrolysis. Women with hyperandrogenemia will experience hair regrowth and guidelines suggest concomitant use of pharmacological treatment to prevent recurrence.

Multidisciplinary care

Having a team approach and taking a second opinion from an endocrinologist, dermatologist, cosmetologist, dietician, counsellor and taking help from a personal trainer to reinforce the lifestyle modifications and exercise will help address some of the other issues that are central to the syndrome of PCOS.

Conclusions

The management of PCOS is multi-dimensional. While obesity, irregular cycles and fertility issues are some of the common issues encountered in clinical practice, a large group of patients presents with acne, hirsutism and hyperandrogenic issues which cannot be easily treated in a short time. Appropriate evaluation, ruling out other causes of hyperandrogenemia and a step care approach with periodic reassessment should form the cornerstone of management of this distressing condition.

References

1.Rotterdam ESHRE / ASRM - Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril2004a;81:19–25.

2. AzzizR, CarminaE, DewaillyD, Diamanti-KandarakisE, Escobar-MorrealeHF, FutterweitW, JanssenOE, LegroRS, NormanRJ, TaylorAEet al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab2006;91:4237–4245.

3. Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome [published correction appears in Hum Reprod. 2019 Feb 1;34(2):388]. Hum Reprod. 2018;33(9):1602-1618. doi:10.1093/humrep/dey256
4. AS Pena, SF Witchel, KM Hoeger, SE Oberfield et al. Adolescent polycystic ovary syndrome according to the international evidence-based guideline. BMC Med 2020 Mar 24. doi: 10.1186/s12916-020-01516-x
5. Stener-Victorin E, Holm G, Labrie F, Nilsson L, Janson PO, Ohlsson C. Are there any sensitive and specific sex steroid markers for polycystic ovary syndrome? J Clin Endocrinol Metab. 2010;95(2):810–819.
6. Salameh WA, Redor-Goldman MM, Clarke NJ, Mathur R, Azziz R, Reitz RE. Specificity and predictive value of circulating testosterone assessed by tandem mass spectrometry for the diagnosis of polycystic ovary syndrome by the National Institutes of Health 1990 criteria. Fertil Steril. 2014;101(4):1135–1141.e1132.
7. RL Rosenfield, DA Ehrmann. The pathogenesis of Polycystic Ovary Syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev 2016 Oct;37(5):467-520. doi: 10.1210/er.2015-1104
8. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961;21:1440–1447.
9. J MIhailidis, R Dermesropian, P Taxel, et al. Endocrine evaluation of hirsutism. Int J Womens Dermatol 2017 Mar;3(1 Suppl):S6-S10. doi: 10.1016/j.ijwd.2017.02.007
10. D Bode, DA Seehusen, D Baird. Hirsutism in women. Am Fam Physician.2012;85(4):373-380.
11. Al Khalifah RA, Florez ID, Dennis B, Thabane L, Bassilious E.Metformin or oral contraceptives for adolescents with polycystic ovarian syndrome: A meta-analysis.Pediatrics. 2016 May; 137(5):e20154089
12.El Maghraby HA, Nafee T, Guiziry D, Elnashar A. Randomized controlled trial of the effects of metformin versus combined oral contraceptives in adolescent PCOS women through a 24 month follow up period. Middle East Fertil Soc J. 2015;20(3):131–137.
13. Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials.J Clin Endocrinol Metab. 2008 Nov; 93(11):4299-306.
14. Unfer V, Nestler JE, Kamenov ZA, et al. Effects of inositols in women with PCOS: a systematic review of randomised controlled trials. Int J Endocrinol 2016; 2016:1849162.doi: 10.1155/2016/1849162
15. EJ van Zuuren, Z Fedorowicz, B Carter, N Pandis. Cochrane Database Syst Rev 2015 Apr; 2015(4):CD010334.doi: 10.1002/14651858.CD010334.pub2
16. U Ezhe, A Huang, M Landay, R Azziz. Long term response of hirsutism and other hyperandrogenic symptoms to combination therapy in polycystic ovary syndrome. Journ Wom Health 2018(7):892-902. doi: 10.1089/jwh.2017.6833

WEIGHT LOSS STRATEGIES

Dr Neelam Bhise MS (Obs Gyn)
Clinical Course in Assisted Reproduction, Singapore
Clinical Course in Assisted Reproduction, IRR, Kolkata
Director Acme Fertility, Chembur and Vashi
Youth Council member, MOGS

Introduction

Obesity in PCOS is underpinned by insulin resistance, hyperandrogenism and genetic factors.[1]

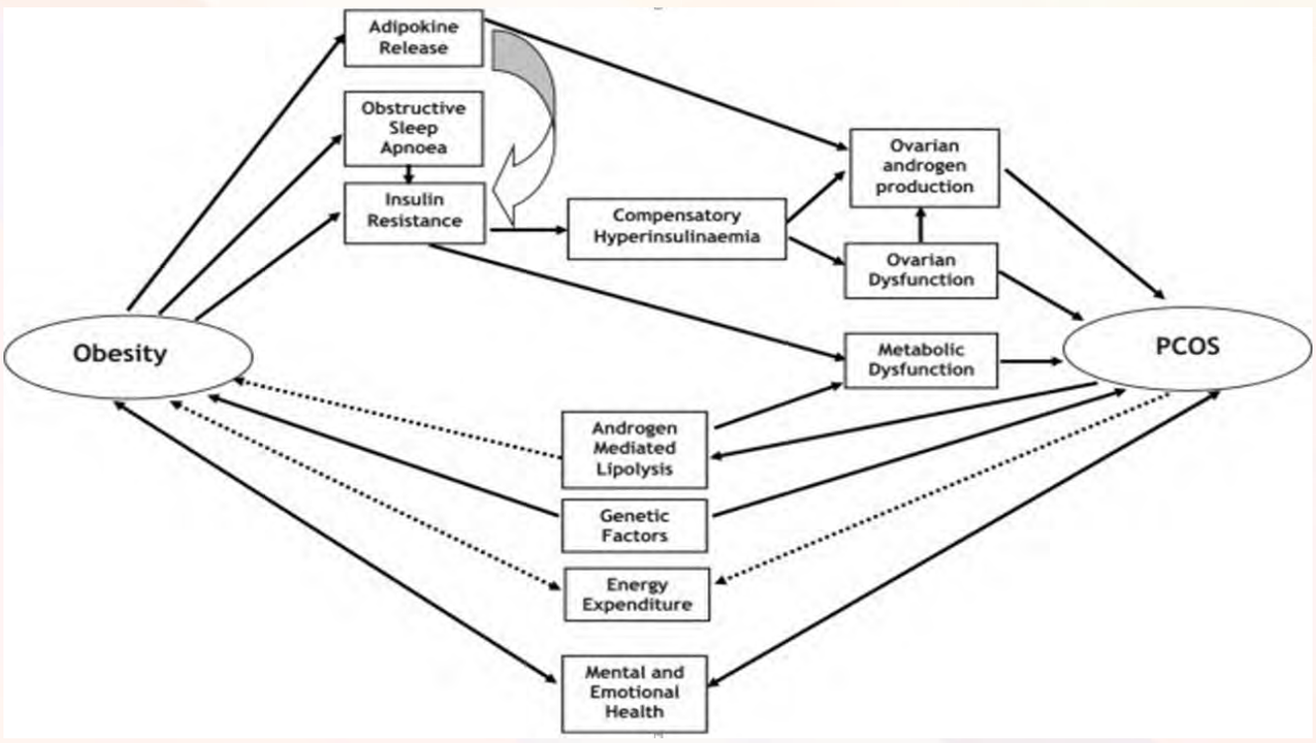

Fig 1 PCOS: obesity and its pathophysiology

	Caucasians	Asians
Normal	18.5-25	18.5-23.5
Overweight	25-30	23.5-27.5
Class 1 obesity	30-35	27.5-32.5
Class 2 obesity	35-40	32.5-37.5
Class 3 obesity	>40	>37.5

Table 1 BMI standards in clinical practice

Strategies for overweight and Class 1 obesity (BMI 23.5-32.5)

Various dietary plans like very-low-calorie diets, hypocaloric diet (less than 35% of fat and less than 45% CHO), hypocaloric diet + metformin, hypocaloric diet + anti-obesity drug (Orlistat) + moderate intensity aerobic training and intensified exercise training are critically discussed in systematic reviews. [2] Multi disciplinary approach with dietician, counsellor and exercise trainer as facilitators for weight loss helps the patient to achieve and maintain the weight consistently. Combination of pharmacological agents and lifestyle, exercise and diet give maximum impact in initial weight loss. Associated comorbidities like impaired glucose tolerance, thyroid and hyper cholesterolemia must be investigated and corrected in order to achieve the target of weight loss.

Pharmacological agents for weight loss treatment

Reduction of insulin resistance, reduction in abdominal obesity and androgen index remain the main targets of pharmacological interventions.

Orlistat works by inhibiting pancreatic lipase thereby reducing absorption of fats from diet. Studies support evidence of weight loss with 60 mg twice daily dose for 12 weeks. Studies in small groups showed both metformin and or list at showed a similar effect on weight loss and ovulation rates. Long term use has been associated with gastrointestinal distress.[3,4]

Atorvastatin /rosuvastatin It has long been hypothesised that statins would be beneficial in PCOS treatment because of their effect in reducing sex steroid production and improving dyslipidemia. However, statins have been shown to worsen insulin sensitivity. Although statins improve lipid profiles and reduce testosterone levels in women with PCOS, there is no evidence that statins improve resumption of menstrual regularity or spontaneous ovulation nor is there any improvement of acne or hirsutism.

Metformin Dose of 1500 mg/day effective as insulin sensitiser for weight loss and metabolic effect. Metformin is proved to be beneficial in documented insulin resistance. HOMA–IR more than 4.5 suggests insulin resistance.

$(\text{HOMA-IR}) = [\text{glucose (mg \%)} \times \text{insulin (mcu/mL)}]/405$

COCs The role of OC pills in weight loss is to reduce hyperandrogenism and endometrial cancer risk. Drosperinone150 mcg containing OC pills with or without spironolactone in dose of 100mg/day was found to be effective for symptoms of PCOS due to antiandrogenic effects of progestin component. However, metabolic disorders may be aggravated or even triggered by the use ofsome COCs. Medical eligibility criteria for hormonal contraceptive use in women with comorbidities should be checked.[7]

Class 2 and 3 obesity (BMI >32.5)

While bariatric surgery represents an excellent alternative strategy to lifestyle implementation for effective and long term weight loss, micronutrient deficiencies and malabsorption prevalence in post bariatric surgery pregnancies need special consideration. Role of the gynaecologist remains in counselling patients regarding possible pregnancy management challenges such as increased risk of birthdefects, PIH, GDM, growth restriction etc.

Novel therapies

Effective means of maintaining weightloss over the longer term remains a challenge. Appetite enhancement is a key driver of weight regain. Appetite suppressant effects of key gut peptides are promising and promote certain gut peptides such as peptidetyrosine tyrosine (PYY) as potential future therapies.[1]

References

1. Weight Management Interventions in Women with and without PCOS: A Systematic Review JosefinKataoka , Nutrients2017 Sep; 9(9): 996 Published online 2017.
2. Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. Thomas M Barber,Clin Med Insights Reprod Health. 2019; 13: 1179558119874042
3. Randomised, double-blind, clinical investigation to compare orlistat 60 milligram and a customized polyglucosamine, two treatmentmethods for the management of overweight and obesity, Manfred Stoll, BMC Obes. 2017; 4: 4. Published online 2017.
4. The effects of metformin or orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study,SedighehGhandi J Assist Reprod Genet. 2011 Jul; 28(7): 591–96. Published online 2011 Apr 12.
5. Anderson Sanches de Melo. Combined oral contraceptives plus spironolactone compared with metformin in women with polycysticovary syndrome: a one-year randomized clinical trial in European Journal of Endocrinology.

OVULATION INDUCTION PATHWAYS

Dr Nandita Palshetkar
MD, FCPS, FICOG, FRCOG
President AMOGS
Immediate Past President FOGSI
President Elect ISAR

Dr Rohan Palshetkar
MS OBGY, FRM
MD, FCPS, FICOG, FRCOG
2nd Joint Secretary AMOGS
Joint Treasurer MAGE
Managing Committee Member MOGS, MSR

Background

Anovulatory infertility is a common problem faced in infertility practice. The causes of anovulation have been classified by the World Health Organisation into 3 categories based on the gonadotropin profile:

WHO type 1 (hypogonadotropichypogonadism)(10%)

Caused by any lesion affecting the pituitary or hypothalamus and affecting gonadotropin production including idiopathic, weight-related amenorrhoea, Sheehan syndrome, extreme stress and strenuous exercise, Kallman's syndrome, craniopharyngiomas etc.

WHO type 2 (normogonadotropichypogonadism)

The commonest cause of an ovulation accounting for 85% of cases and is most commonly caused by polycystic ovarian syndrome. Hyperprolactinaemic amenorrhoea is another cause, where in addition to amenorrhoea and infertility, women may have galactorrhoea.

WHO type 3 (hypergonadotropichypogonadism) (5%)

This is usually an indication of ovarian failure.

Treatment strategies and goals

In an ovulatory women, the purpose of treatment in ovulation induction is the development of at least one follicle, whereas in other causes of infertility, ovarian stimulation is used to increase the number of follicles, known as super ovulation or controlled ovarian hyperstimulation. Induction of ovulation is possible in the first two types. However, in the third type, ovulation induction is usually unsuccessful due to follicular depletion and the only way to achieve a pregnancy may be through

Traditionally, the first-line treatment for an ovulatory and oligo-ovulatory women, though recent guidance has now advocated the use of aromatase inhibitors as the first line of therapy, especially in PCOS as per the new ESHRE/ASRM joint PCOS Guideline.

Background

Anovulatory infertility is a common problem faced in infertility practice. The causes of anovulation have been classified by the World Health Organisation into 3 categories based on the gonadotropin profile:

WHO type 1 (hypogonadotropichypogonadism)(10%)

Caused by any lesion affecting the pituitary or hypothalamus and affecting gonadotropin production including idiopathic, weight-related amenorrhoea, Sheehan syndrome, extreme stress and strenuous exercise, Kallman's syndrome, craniopharyngiomas etc.

WHO type 2 (normogonadotropichypogonadism)

The commonest cause of anovulation accounting for 85% of cases and is most commonly caused by polycystic ovarian syndrome. Hyperprolactinaemic amenorrhoea is another cause, where in addition to amenorrhoea and infertility, women may have galactorrhoea.

WHO type 3 (hypergonadotropichypogonadism) (5%)

This is usually an indication of ovarian failure.

Treatment strategies and goals

In an ovulatory women, the purpose of treatment in ovulation induction is the development of at least one follicle, whereas in other causes of infertility, ovarian stimulation is used to increase the number of follicles, known as super ovulation or controlled ovarian hyperstimulation. Induction of ovulation is possible in the first two types. However, in the third type, ovulation induction is usually unsuccessful due to follicular depletion and the only way to achieve a pregnancy may be through

Traditionally, the first-line treatment for an ovulatory and oligo-ovulatory women, though recent guidance has now advocated the use of aromatase inhibitors as the first line of therapy, especially in PCOS as per the new ESHRE/ASRM joint PCOS Guideline.

Aromatase inhibitors (AI)

Aromatase Inhibitors such anastrozole and letrozole have been used for ovulation inductions. They prevent aromatisation and this prevents androgens from being converted to estrogen. This causes a low estrogenic state. And therefore acts on HPO axis and pitutary. This causes compensatory increase in the pulsatile GnRH secretion and thereby causes follicular growth.1

Post letrozole supplementation, estrogen levels increase immediately, which causes an abrupt decrease in FSH levels. This ensures mono-follicular growth and the increase in estrogen helps in endometrial preparation and production of cervical mucus.

Therapy regimen and efficacy

Letrozole doses can be started from 2.5mg/day to 7.5mg/day. Anastrozole is given as 1mg daily. Both medications are started as per the CC protocol. Extended Regimens (10 days) and single dose regimens (20mg on Day 3), have also been used with studies suggesting positive results.[2,3]

Letrozole can be combined with planned relations or IUI. In anovulatory women, AI have shown almost a 60% ovulation rate with pregnancy rates varying from 12-40%. [4.5]

Indications

Letrozole is indicated in women who are resistant to CC or those women in which CC is contraindicated due undesirable side effects.10AI can also be implemented in cases where the endometrium is thin (<7mm) where CC was used as oral ovulogen. [6,7]

In a recent Cochrane review, PCOS patients seem to have better pregnancy as well as live birth rate when letrozole was used.27 This differs from a previous review, which did not detect a difference.[8]

Adjuvant regimens

These have traditionally been described in textbooks of reproductive endocrinology (especially glucocorticoids and bromocriptine) and are mentioned here for completeness; their utility is restricted in day-to-day practice.

Clomiphene and glucocorticoids

With normal and elevated levels of DHEA in CC resistant patients, addition of dexamethasone (0.5-2mg) or prednisolone (5mg) has shown increase in ovulation and pregnancy rates. The mechanism of action is not clearly known but there is a hypothesis that suggest the androgen suppression has direct effects on the oocyte and indirect effects on cytokines and intrafollicular growth factors.[5]

Clomiphene and human chorionic gonadotropin

hCG injection may benefit as surrogate LH surge to trigger ovulation in patients where CC is used especially in cases of unexplained infertility or co-existing male factor

Clomiphene and metformin

Metformin should be considered in combination with CC in patients who are CC resistant. Metformin is usually given in a dose of 1500-2000mg/day. The starting dose of 500mg/day should be given after which the dose should be increased to the require dose. A liver function test should always be carried out prior to starting metformin.

A meta-analysis has suggested that metformin may improve success in weight management. Otherwise, the role of metformin in ovulation induction is controversial. Interestingly, metformin may have a role as pretreatment before standard assisted reproduction techniques. A recent RCT demonstrated improved pregnancy rates after 3–9 months of metformin before assisted reproduction techniques.[9]

Exogenousgonadotropins

Gonadotropins were first obtained by purifying urine; nowadays many commercially available preparations are from highly purified urinary source medications or are the product of recombinant technology. The major boon of recombinant gonadotropins is that they provide a more consistent supply, there is barely any variation in the activity of the molecule and the biggest advantage is that there in antigenic urinary protein present. [10,11]

Indications

Clomiphene citrate resistant an ovulation

WHO group 2 patients who do not respond to oral ovulogens should be subjected to exogenous FSH and LH. Exogenous gonadotropins should be used as 2nd line of treatment for ovulation induction.[12]

Superovulation

Super ovulation is often the goal of using gonadotropins in this population attempting to optimise cycle fecundity.

Therapy regimen and efficacy

As a prerequisite, extensive counselling is essential. The couple must understand the expected expenditure and time that needs to be committed for monitoring the effects of the medicine. Serum estradiol levels as well as follicular number and growth must be monitored to prevent OHSS. The dose and duration of gonadotropins depends on age, BMI and ovarian reserve of the patients.

The 'step-up' protocol is aimed at crossing the FSH threshold and reduce the risk of complications. The drawback of this protocol is that increases the duration of the cycle and can result in multi follicular growth.

The 'step-down' protocol overcomes these problems by replicating the natural hormonal cycle. FSH is started at a higher dose so that the dominant follicle develops faster. Once the dominant follicle is established, the FSH levels can be reduced slowly to ensure mono follicular growth.[24]

It is important to monitor the patients, because the FSH window needs to be managed to ensure either mono or multi follicular growth. The cycle can be cancelled if there are more than 3 dominant follicles. The biggest concern of the step down protocol is starting the patient with a high initial dose of FSH whose threshold is low.

A low dose or chronic low dose step up regimen may be considered in the first cycle to gauge a response for an individual patient. Eventually the other cycles can be done depending on the response in the first cycle.

GnRH agonists and antagonists

Among the various GnRH agonist protocols, namely ultra short, short and long, the long GnRH agonist protocol has been used as the gold standard in IVF since its discovery in the 1980s. GnRH antagonists have recently offered an alternative approach in IVF treatment.

The long GnRH agonist protocol involves administration of 0.1 mg GnRH agonist (e.g., triptorelin/leuprolide) starting on preceding cycle-day 21 followed by administration of gonadotropin at 150-225 international units (IU) daily starting on cycle-day 2. The adjustment of dose is based on follicular development and administration of GnRH agonist and gonadotropin lasts until the hCG trigger injection, which is around 14 days post GnRH agonist regimen or when follicles reach 16 to 18 millimeters (mm) in size.

For the GnRH antagonist protocol, administration of gonadotropin is initiated after monitoring of patients' follicles sizes on cycle-day 2/3. Gonadotropin dosage varies according to the follicular response. Approximately after the 6th day of gonadotropin injection or when follicular size reaches more than or equal to 14 mm, subcutaneous administration of the GnRH antagonist (eg.Cetrorelix 0.25 mg/d) begins.

Insulin sensitisers

It has been found in recent studies that insulin sensitisers like myo-inositol improved the ovulation and pregnancy rate in insulin-resistant patients with PCOS when given alone or in combination with clomiphene citrate.[13]

This is further discussed extensively in the article reviewing the role of insulin sensitisers.

Cochrane meta-analysis

42 RCTs and 7,935 women were analysed in a Cochrane meta-analysis in 2018.Letrozole had higher live birth rates compared to clomiphene (with timed intercourse) (OR 1.68, 95% CI 1.42 to 1.99; 2,954 participants; 13 studies; I2 = 0%; number needed to treat for an additional beneficial outcome (NNTB) = 10).[14]

There is evidence for a higher pregnancy rate in favour of letrozole (OR 1.56, 95% CI 1.37 to 1.78; 4629 participants; 25 studies; I2 = 1%; NNTB = 10; moderate-quality evidence). There is little or no difference between treatment groups in the rate of miscarriage by pregnancy (20% with CC versus 19% with letrozole; OR 0.94, 95% CI 0.70 to 1.26; 1210 participants; 18 studies; I2 = 0%) and multiple pregnancy rate (1.7% with CC versus 1.3% with letrozole; OR 0.69, 95% CI 0.41 to 1.16; 3579 participants; 17 studies; I2 = 0%).

There is low-quality evidence that live birth rates are similar with letrozole or laparoscopic ovarian drilling (OR 1.38, 95% CI 0.95 to 2.02; 548 participants; 3 studies; I2 = 23%). There is low-quality evidence that pregnancy rates are similar (OR 1.28, 95% CI 0.94 to 1.74; 774 participants; 5 studies; I2 = 0%). There is insufficient evidence for a difference in miscarriage rate (OR 0.66, 95% CI 0.30 to 1.43; 240 participants; 5 studies; I2 = 0%), or multiple pregnancies (OR 3.00, 95% CI 0.12 to 74.90; 548 participants; 3 studies; I2 = 0%).

Additional comparisons were made for Letrozole versus placebo, Selective oestrogen receptor modulators (SERMS) followed by intrauterine insemination (IUI), follicle stimulating hormone (FSH), anastrozole, as well as dosage and administration protocols. There is insufficient evidence for a difference in either group of treatment due to a limited number of studies. Hence, the reviewers concluded that more research is necessary.[14]

Conclusions

Although clomiphene citrate as a treatment modality has existed for more than 50 years, an increased awareness of the effect of obesity and different PCOS phenotypes has emerged. Accordingly, ovulation induction in women suffering from oligo- and an ovulation seeking fertility treatment has to be individualised according to weight, treatment efficacy and patient compliance, with the aim of achieving mono follicular growth, mono-ovulation and subsequently the birth of a singleton baby.

References

1. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th edition. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. x, 1439.
2. Mitwally MF, Casper RF. Single-dose administration of an aromatase inhibitor for ovarian stimulation. FertilSteril 2005;83(1):229–31.
3. Atay V, Cam C, Muhcu M, et al. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. J Int Med Res 2006;34(1):73–6.
4. Badawy A, Mosbah A, Tharwat A, et al. Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol. FertilSteril 2009;92(1):236–9
5. Keay SD, Jenkins JM. Adjunctive use of dexamethasome in Clomid resistant patients. FertilSteril 2003;80(1):230–1 [author reply: 231].

6. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate. FertilSteril 2001; 75(2):305–9.
7. Begum MR, Ferdous J, Begum A, et al. Comparison of efficacy of aromatase inhibitor and clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. FertilSteril 2009;92(3):853–7. Hum Reprod Update.
8. 2012 May-Jun;18(3):301-12. doi: 10.1093/humupd/dms003. Epub 2012 Mar 19. Aromatase inhibitors for PCOS: a systematic review and meta-analysis
9. Morin-Papunen, L., Rantala, A.S., Unkila-Kallio, L., Tiitinen, A., Hippelainen, M., Perheentupa, A., Tinkanen, H., Bloigu, R.,Puukka, K., Ruokonen, A., Tapanainen, J.S., 2012. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebocontrolled randomized trial. J. Clin. Endocrinol. Metab. 97, 1492– 1500.
10. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th edition. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. x, 1439.
11. Lathi RB, Milki AA. Recombinant gonadotropins. CurrWomens Health Rep 2001;1(2):157–63.
12. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. FertilSteril 2008;89(3):505–22.
13. Gynecol Endocrinol. 2015 Feb;31(2):131-5. Ovulation induction with myo-inositol alone and in combination with clomiphene citrate in polycystic ovarian syndrome patients with insulin resistance. KamenovZ1, Kolarov G, Gateva A, Carlomagno G, Genazzani AD.
14. Franik S, Eltrop SM, Kremer JAM, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD010287.

ROLE OF INSULIN SENSITISERS

Dr Amiti Agrawal MS FRM FMIS MRM (UK)
Fertility Consultant and IVF Specialist
Director Sunshine Fertility and IVF Centre, Mumbai
Youth Council member, MOGS

Introduction

Polycystic ovary syndrome (PCOS) has a heterogeneous presentation, which includes hirsutism, often related to hypersecretion of ovarian androgens, anovulation or Ovulatory infertility, menstrual irregularity, and pregnancy complications. In 2003, a consensus workshop group held in Rotterdam by ESHRE and ASRM recommended atleast 2 of the following features are needed for diagnosis of PCOS: anovulation or oligo-ovulation, hyperandrogenism and polycystic ovaries on ultrasonography. PCOS is associated with metabolic derangements and treatment of this leads to resumption of ovulation. Insulin resistance plays an important role in the pathogenesis of PCOS in the subset of patients who have either increased BMI or hyper insulinemia and/or significant hyperandrogenism.[1,2,3]

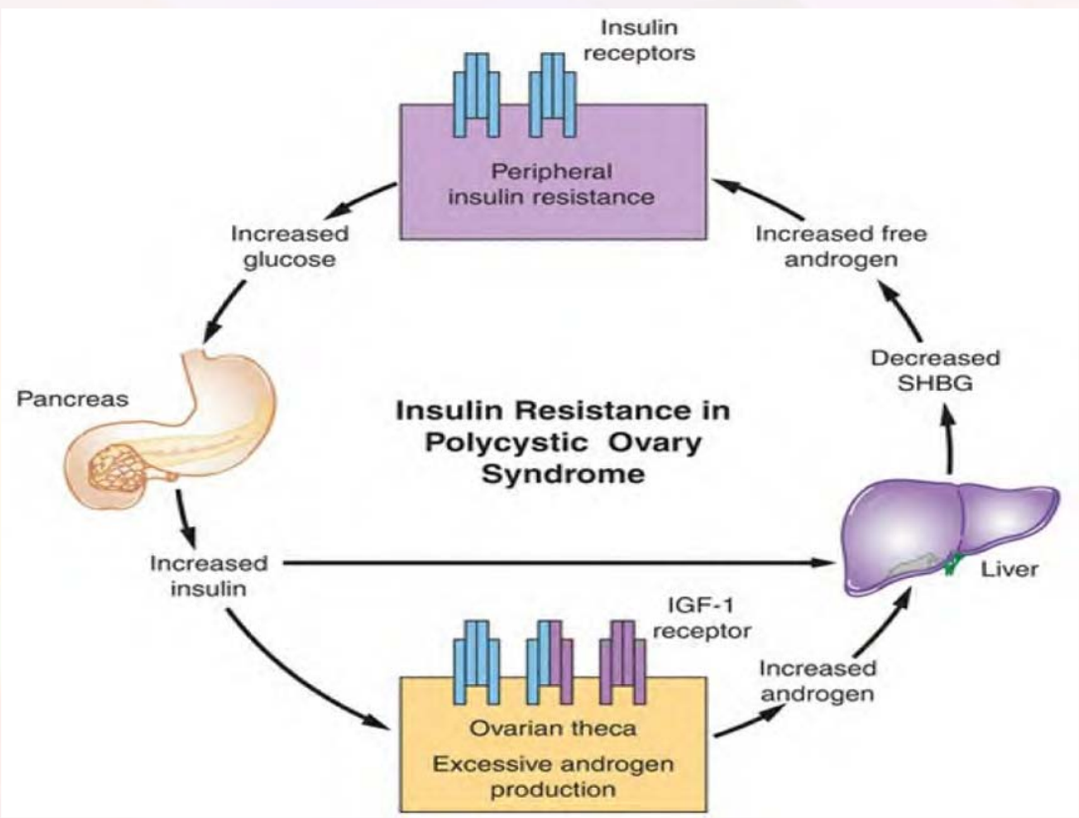

Fig 1 Insulin resistance and PCOS

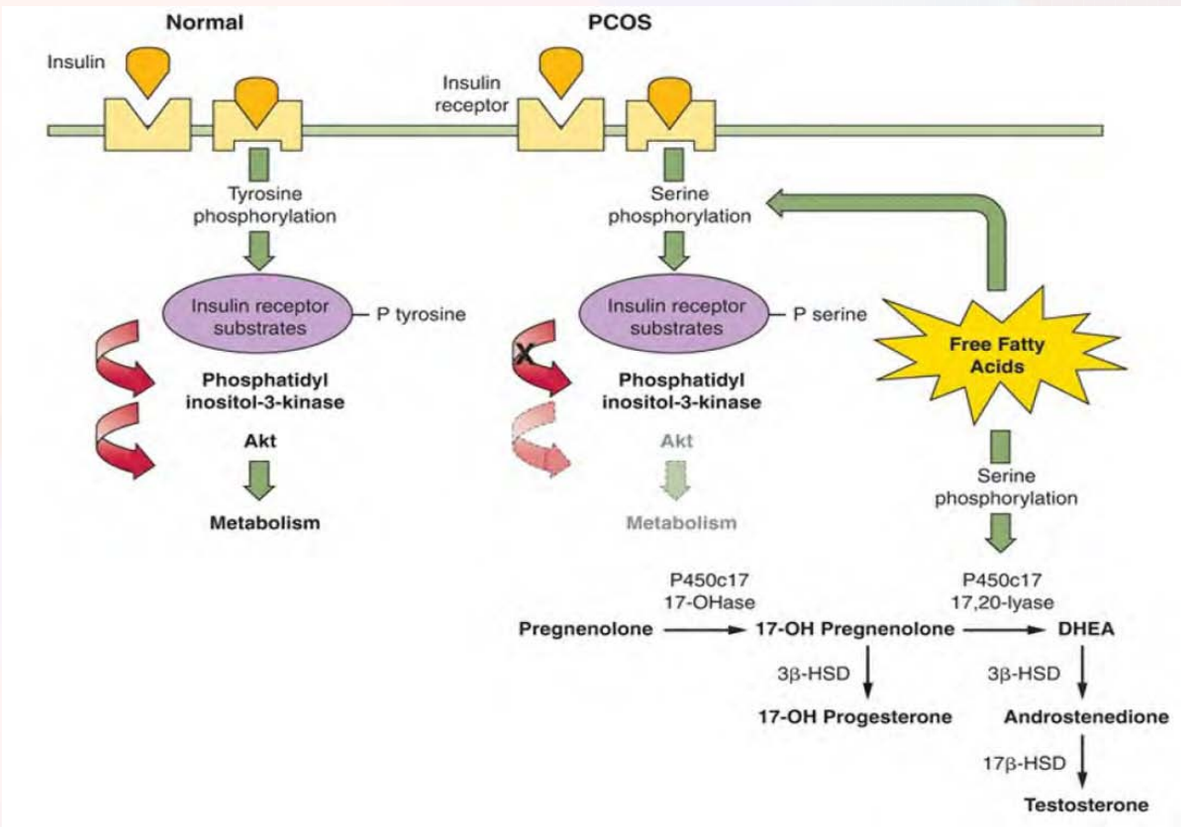

Fig 2 Insulin sensitiser actions at cellular level

Insulin sensitisers

Insulin-sensitising agents have been used to treat diabetes since several decades and there is considerable interest for their use in the treatment of women with PCOS. These include metformin, a biguanide, the thiazolidinediones (pioglitazone and rosiglitazone) and inositols.

Metformin is a biguanide which is approved for treatment of type 2 diabetes and women having insulin resistance and PCOS.[4]

It increases insulin sensitivity in the liver by:

1. reducing gluconeogenic enzyme activities (PEPCK, FBPase, glucose-6-phosphatase),
2. inhibiting hepatic uptake of lactateand alanine,
3. increasing the conversion of pyruvate to alanine, and
4. inhibiting glucose output.

5 The cellular consequence of these AMP-activated protein kinase (AMPK)-mediated effects is alterations in the AMP/ATP ratio. Metformin increases peripheral glucose uptake, decreases fatty acid oxidation and decreases glucose absorption from the gut. It may also augment hepatic fatty acid oxidation and improve hepatic insulin sensitivity.[6]

Androgen-lowering effects

In both lean and obese women with PCOS, metformin

1. decreases insulin levels and ovarian cytochrome P450c17 activity
2. increases SHBG levels, resulting in decreasedfree testosterone.[7]
3. Increases levels ofIGFBP-1 (owing to reduction ininsulin levels), with the resultant decrease in IGF-1 bioavailabilityinhibiting ovarian steroidogenesis.

Its effectiveness may be related to:

1.the dose used, particularly when metformin is used asmonotherapy, necessitating higher doses
2.the agent with which metformin is combined such as estrogen-progestin combination pills or anti-androgenic agentssuch as flutamide, spironolactone and cyproterone acetate
3.whether the patient is obese or lean, hyperinsulinemicor normoinsulinemic.

In PCOS women, it lowers the fasting insulin level, but does not appear to result in consistent significant changes in BMI or waist-to-hip ratio.Althougholigomenorrhea improves in some women with PCOS, significant numbers remain an ovulatory. The degree of improvement in ovulation frequency is the same as is achieved with weight reduction through lifestyle modification.

Metformin monotherapy

Metformin is usually prescribed in the doses ranging from 500-850 mg thrice daily. Gastrointestinal side effects are common so slow titration of the drug is recommended. Very rarely it may cause fatal lactic acidosis in patients with underlying renal failure. Before starting therapy, confirm normal renal and liver function, proper patient selection and start 500 mg once daily for 4 days followed by twice daily for 4 days, then 850-1000 mg twice daily for reducing gastrointestinal side effects and ensuring better compliance.[8]

Role in ovulation induction

Two RCTs have indicated that metformin does not increase live birth rates above those observed with CC alone in either obese or normal weight women with PCOS. CC resulted in higher ovulation, conception, pregnancy and live birth rates compared with metformin, but the combination of both drugs did not result in a significant benefit. Addition of metformin did not decrease the incidence of miscarriage, Among girls not receiving OCPs, the frequency of menses did not differ between groups;

observed menses were ovulatory 75% with metformin, 60% in the COCs group and 50% with placebo. COCs were associated with a 14% increase in total cholesterol and 40% increase in high-sensitivity CRP; these adverse metabolic effects were not observed in the other groups, with the metformin group demonstrated a 25% decrease in triglyceride levels.[12,13]

These data suggest that in obese adolescents with PCOS, OCPs and life style intervention have beneficial effects on androgen levels. COCs affect cardiovascular risk markers adversely, while metformin has beneficial effects on both lipids and glucose levels. Metformin attenuated the pro-inflammatory state resulting in reductions inIL-6, CRP levels and neutrophil counts, whereas use of COCs aggravated the pro-inflammatorystate. Metformin alone did not significantly reduce the free androgen index in obese adolescents and the combination of metformin and flutamide was as effective as COCs. Metformin was superior to COCs in increasing insulin sensitivity, decreasing dyslipidemia, an ovulation, body adiposity and the pro-inflammatory state associated with PCOS. The Thessaloniki ESHRE/ASRM PCOS Consensus Workshop Group has recommended that metformin use in PCOS should be restricted to women with glucose intolerance.[14,15]

Thiazolidenediones

These activate the peroxisome-proliferator-activated nuclear receptor (PPAR-g), leading to increased production of insulin-sensitive adipocytes and increased glucose uptake in these cells, increased secretion of adiponect in and decreased secretion of pro-inflammatory cytokines.[16]

Recent data in adult women with PCOS suggest that thiazolidinediones exert additional benefit with respect to hyperandrogenism, IR, anovulation and inflammatory mediator levels in both lean and obesePCOS. Pioglitazone and rosiglitazone ameliorate the signs and symptoms of PCOS in women who failed a previous trial of metformin. Rosiglitazone is prescribed at an initial dose of 4 mg/day upto a maximum of 8 mg/day. Pioglitazone is used in doses of 15-30 mg once a day.It is contraindicated in symptomatic heart failure, pregnancy, lactation and hepatic dysfunction. Concerns regarding potential adverse cardiovascular events in T2DM patients resulted in the recent addition of a black box warning to the package inserts, reinforcing the need for caution while prescribing.[17]

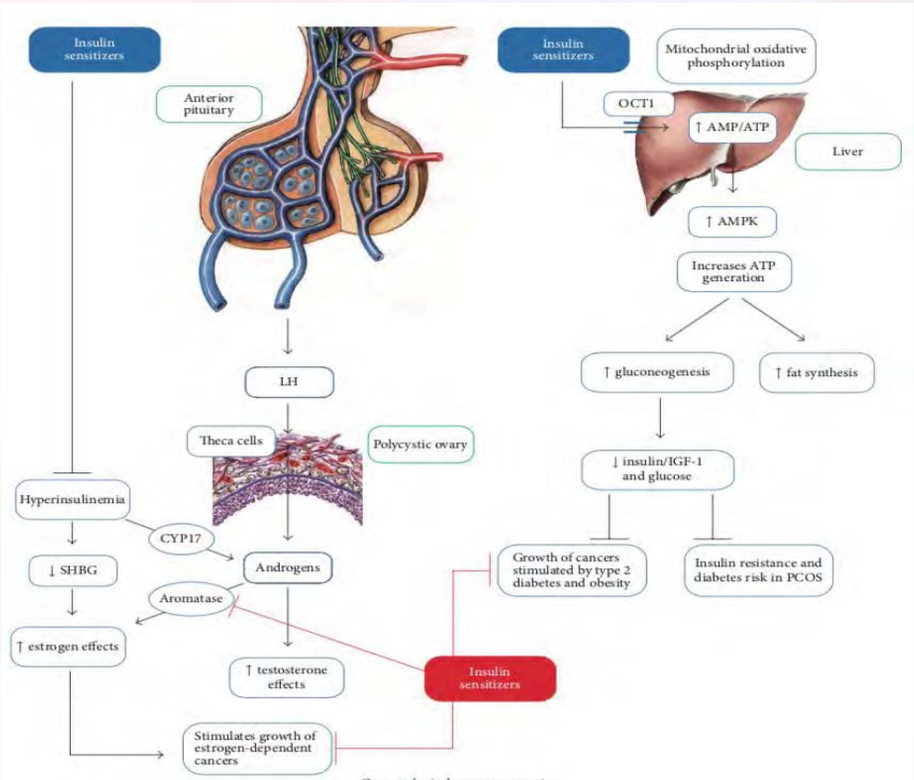

Fig 3 Metabolic effects of insulin sensitisers

Table 2 Pros and cons of insulin sensitizer therapy in PCOS

PROS	CONS
Reduces insulin resistance and addresses an important component of the pathophysiology of PCOS Useful for treating hyperglycemia in patients with PCOS-associated type 2 DM	Insulin-sensitizing effect may not persist after discontinuing medication
Metformin may cause weight reduction and is associated with improvement in lipid profile	Weight reduction is minor with metformin; TZDs may cause weight gain and peripheral lipogenesis
	Cosmetic improvements with insulin sensitizers may be less marked than with E_2-P combination pills
	Insulin sensitizers may induce ovulation with risk of unwanted pregnancy unless used with contraception
An option in patients with Factor V Leiden mutations and other risk factors for coagulopathy in whom E_2-P combination pills may be contraindicated	
Potential for use in adolescents with lean PCOS in whom lifestyle modification is likely to be ineffective	Lean PCOS responds well to conventional E_2-P combination pills in conjunction with anti-androgen medications
Excellent safety profile for metformin, with few side effects reported	Insulin sensitizers are potential teratogens Select patients may require frequent monitoring of liver and renal function TZDs have been associated with adverse cardiovascular events in adult patients
	Insufficient studies of efficacy and long term safety of insulin sensitizers in adolescents

Table 1 Pros and cons of insulin sensitisers

(Geller et al. International Journal of Pediatric Endocrinology 2011, 2011:9)

Inositols

Myo-inositol(MI) is one stereoisomer of a C6 sugar alcohol that belongs to the inositol family. It is the precursor of inositol triphosphate, acts as an intracellular second messenger and regulates a number of hormones such as TSH, FSH and insulin. Myoinositol and d-chiro-inositol (DCI), another stereoisomeric form of inositol, balance metabolic deregulations seen in insulin resistance. Myo-inositol-derived phosphoinositol-3-phosphate (PIP3) enhances glucose transport inside the cells through the stimulation of GLUT4 translocation to the cell membrane.[18,19]

Its derivative inositolphosphoglycan (MI-IPG) plays a pivotal role in down regulating the release of free fatty acids (FFA) from adipose tissues, hindering the enzyme adenylate cyclase.FFA reduce glucose disposal, causing IR and increased triglyceride synthesis. DCI upregulates pyruvate dehydrogenase leading to the production of ATP by the Krebs' cycle. MI and DCI promote glycogen synthase, inducing glucose conversion to glycogen stored inside cells. MI modulates the activation of glucose transporters and glucose utilisation and glycogen synthesis takes place under the control of DCI. Within the ovary, it regulates insulin induced androgen synthesis, whereas MI regulates glucoseuptake and FSH signalling.[20]

Current research suggests that for women with PCOS, 2 gm myoinositol combined with folic acid, taken 1-2 times daily for 3 months is effective.[21]

Meta-analysis

J Pundir et al conducted a systematic review and meta-analysis on inositol treatment in women with polycystic ovarian syndrome, published in the BJOG in 2017. Ten trials and a total of 362 women were on inositol (257 on myo-inositol; 105 on di-chiro-inositol), 179 were on placebo and 60 were on metformin. Inositol was associated with significantly improved ovulation rate (RR 2.3; 95% CI 1.1–4.7; I2=75%) and increased frequency of menstrual cycles (RR 6.8; 95% CI 2.8–16.6; I2=0%) compared with placebo. One study reported on clinical pregnancy rate with inositol compared with placebo (RR 3.3; 95% CI 0.4–27.1), and one study compared with metformin (RR 1.5; 95% CI 0.7–3.1). No studies evaluated live birth and miscarriage rates.[22]

They concluded that inositol appears to regulate menstrual cycles, improve ovulation and induce metabolic changes in polycystic ovary syndrome; however, evidence is lacking for pregnancy, miscarriage or live birth. A further, well-designed multicentric trial to address this issue to provide robust evidence of benefit is warranted.

The new ESHRE ASRM Guideline suggests that as this agent is freely available as a nutritional supplement at low to moderate cost and appears to have a limited side effect profile, it may warrant consideration for use despite limited and low quality evidence.[23]

Conclusions

Insulin resistance and consequent hyperinsulinemiaare highly prevalent and facilitate hyperandrogenaemia in PCOS.Lifestyle changes involving behavioural, dietary and exercise regimens should be considered as first linetherapy for weight reduction and improvement of insulin levels in obese adolescents with PCOS. Metformin demonstrates promising results for resumption of menstrual cyclicity and ovulation, restoration of fertility, improved insulin dynamics adipocytokine and inflammatory mediator profiles, and cardiovascular indices.

Thiazolidinediones are an alternative in patients where previous metformin therapy has failed but there are safety concerns. Myoinositol seems to be a promising novel nutritional supplement in improving metabolic derangements and insulin resistance in PCOS.

References

1. R. Azziz, K. S. Woods, R. Reyna, T. J. Key, E. S. Knochenhauer, and B. O. Yildiz, "The prevalence and features of the polycystic ovary syndrome in an unselected population," The Journal of Clinical Endocrinology & Metabolism, vol. 89, no. 6, pp. 2745–2749, 2004.
2. The Rotterdam ESHRE/ASRM-Sponsored PCOSConsensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reproduction 2004 19 41–47.
3. Ehrmann DA. Polycystic ovary syndrome. New England Journal of Medicine 2005 352 1223–1236.
4. C. N. Jayasena and S.Franks, "Themanagement of patientswith polycystic ovary syndrome," Nature Reviews Endocrinology, vol.10, no. 10, pp. 624–636, 2014.
5. V. N. Sivalingam, J. Myers, S. Nicholas, A. H. Balen, and E. J. Crosbie, "Metformin in reproductive health, pregnancy and gynaecological cancer: established and emerging indications," Human Reproduction Update, vol. 20, no. 6, pp. 853–868, 2014.
6. Ehrmann DA, Barnes RB, Rosenfield RL, et al: Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome.Diabetes Care 1999, 22(1):141-6.
7. Homburg R, Lambalk CB: Polycystic ovary syndrome in adolescence–a therapeutic conundrum. Hum Reprod 2004, 19(5):1039-42.
8. Nestler JE, Akhter N,et al.Strategies for the use of insulin sensitizing drugs to treat infertility in women with polycystic ovary syndrome.Fertil Steril.2002
9. Lord JM, Flight IH & Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. British Medical Journal 2003 327 951–957.
10. Kashyap S, Wells GA & Rosenwaks Z. Insulin-sensitizing agents as primary therapy for patients with polycystic ovary syndrome. Human Reproduction 2004 19 2474–2483.
11. Hoeger K, Davidson K, Kochman L, et al: The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. J Clin Endocrinol Metab 2008, 93(11):4299-306.
12. Ibanez L, Jaramillo AM, Ferrer A, et al: High neutrophil count in girls and women with hyperinsulinaemic hyperandrogenism: normalization with metformin and flutamide overcomes the aggravation by oral contraception. Hum Reprod 2005, 20(9):2457-62.
13. Ibanez L, de Zegher F: Ethinylestradiol-drospirenone, flutamide- metformin, or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. J Clin Endocrinol Metab 2004, 89(4):1592-7.
14. Arslanian SA, Lewy V, Danadian K, et al: Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropin with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab 2002, 87(4):1555-9.

15.Thessaloniki ESHRE/ASRM-Sponsored PCOS Concensus Workshop Group.Consensus on infertility treatment related to polycystic ovary syndrome.Fertil Steril.2008;89(3):505-22

16.Vryonidou A, Papatheodorou A, Tavridou A, et al: Association of hyperandrogenemic and metabolic phenotype with carotid intima- media thickness in young women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005, 90(5):2740-6.

17.Tarkun I, Cetinarslan B, Turemen E, et al: Effect of rosiglitazone on insulin resistance, C-reactive protein and endothelial function in non-obese young women with polycystic ovary syndrome. Eur J Endocrinol 2005, 153(1):115-21.

18.Bizzarri M, Fuso A, Dinicola S, Cucina A & Bevilacqua A. Pharmacodynamics and pharmacokinetics of inositol(s) in health and disease. Expert Opinion on Drug Metabolism and Toxicology 2016 12 1181–1196.

19.V Unfer et al. A meta-analysis of myo-inositol effect in PCOS – EndocrineConnections(2017) 6, 647–658.

20.Celentano C, Matarrelli B, Mattei PA, Pavone G, Vitacolonna E & Liberati M. Myoinositol supplementation to prevent gestational diabetes mellitus. Current Diabetes Reports 2016 16 30. (doi:10.1007/s11892-016-0726-6)

21.Costantino D, Minozzi G et al. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci. 2009 Mar-Apr;13(2):105-10.

22.J Pundir, D Psaroudakis, P Savnur, P Bhide, et al. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. BJOG 2017;125(3):299-308. doi:10.1111/1471-0528.1475

23.Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Hum Reprod. 2018;33(9):1602–18.

OHSS FREE CLINIC

Dr Atul Ganatra MD DGO FICOG
Vice President FOGSI (West Zone)
Joint Treasurer IAGE
Managing Council Member MOGS

Introduction

Ovarian hyper stimulation syndrome (OHSS) is the most serious complication of controlled ovarian hyper stimulation (COH) for assisted reproduction technologies (ART). It is characterised by a broad spectrum of signs and symptoms that includes abdominal distention and discomfort, enlarged ovaries, ascites and other complications of enhanced vascular permeability.

The syndrome can be strictly defined as the shift of serum from the intravascular space to the third space, mainly to the abdominal cavity, in the context of enlarged ovaries due to follicular stimulation. In its very severe form, OHSS is a life-threatening condition.

Pathophysiology

The pathophysiology of OHSS is not fully understood, but increased capillary permeability with the resulting loss of fluid into the third space is its main feature. In the susceptible patient, human chorionic gonadotropin (hCG) administration for the final follicular maturation and triggering of ovulation is the pivotal stimulus for OHSS, leading to overexpression of vascular endothelial growth factor (VEGF) in the ovary, release of vasoactive-angiogenic substances, increased vascular permeability, loss of fluid to the third space, and full- blown OHSS.

Two clinical forms of OHSS, both hCG related:

1. Early onset form (occurring in the first eight days after hCG administration) and
2. Late onset form (occurring nine or more days after hCG administration, related to pregnancy-induced hCG production)

Incidence	
Mild	20-33%
Moderate	3- 6%
Severe	0.1- 2%

	Clinical features	Biochemical features
Mild	▪ Abdominal distention/discomfort ▪ Mild nausea/vomiting ▪ Diarrhea ▪ Enlarged ovaries	▪ No clinically important laboratory findings
Moderate	▪ Presence of mild features plus: • Ultrasonographic evidence of ascites	▪ Elevated Hct (>41%) ▪ Elevated WBC (>15,000/microL) ▪ Hypoproteinemia
Severe	▪ Presence of mild and moderate features plus: • Clinical evidence of ascites (can be tense ascites) • Severe abdominal pain • Intractable nausea and vomiting • Rapid weight gain (>1 kg in 24 hours) • Pleural effusion • Severe dyspnea • Oliguria/anuria • Low blood/central venous pressure • Syncope • Venous thrombosis	▪ Hemoconcentration (Hct >55%) ▪ WBC >25,000/microL ▪ Serum creatinine >1.6 mg/dL ▪ Creatinine clearance <50 mL/min ▪ Hyponatremia (Na^+ <135 mEq/L) ▪ Hyperkalemia (K^+ >5 mEq/L) ▪ Elevated liver enzymes
Critical	▪ Presence of severe features plus: • Anuria/acute renal failure • Arrhythmia • Pericardial effusion • Massive hydrothorax • Thromboembolism • Arterial thrombosis • ARDS • Sepsis	▪ Worsening of biochemical findings seen with severe OHSS

OHSS: ovarian hyperstimulation syndrome; Hct: hematocrit; WBC: white blood cell; Na: sodium; K: potassium; ARDS: acute respiratory distress syndrome.

Table 1 Clinical and biochemical features of OHSS

Keys to prevention

1.Recognition of risk factors for OHSS (such as previous episode of OHSS or exuberant ovarian response to gonadotropins and polycystic ovarian syndrome).

2. Extensive clinical experience with drugs used for ovarian stimulation especially during an IVF cycle.

3. Use of individualised ovarian stimulation regimens for assisted reproduction, using the minimum dose and duration of gonadotropin therapy necessary to achieve the treatment goal.

4. Use of adjuvants like pretreatment with metformin and addition of a gonadotropin-releasing hormone (GnRH) antagonist are suggested in women with PCOS.
5. Modifying treatment when indicators for increasing OHSS risk develop: serum estradiol (E2) concentration >3500 pg/mL (12,850 pmol/L). Development of many intermediate-sized follicles (more than 20 follicles >10 mm).
6. Withholding gonadotropin therapy while continuing pituitary suppression with a GnRH agonist or antagonist until serum E2 levels fall into a range acceptable for human chorionic gonadotropin (hCG) administration (coasting) if the risk for OHSS is high.
7. Using an alternative to standarddose hCG for final oocyte maturation (lower dose hCG or gonadotropin-releasing hormone [GnRH] agonist).

Risk factors present at baseline: Before gonadotropin administration
Previous OHSS
PCOS
Potential markers:
▪ Basal serum anti-müllerian hormone >3.3 ng/mL
▪ Antral follicle count >8
Single nucleotide polymorphisms (SNPs) in genes involved in follicular growth (*BMP15*)
Risk factors related to ovarian response
Multiple follicles >20 follicles larger than 10 mm
High or rapidly rising serum estradiol concentration (>3500 pg/mL [12,850 pmol/L] in COH)
High number of oocytes retrieved
hCG given for luteal phase supplementation
Elevated serum/follicular fluid VEGF levels
Pregnancy (increase in endogenous hCG)

Table 2 Risk factors for OHSS

Gonadotropin type and dose

The current approach to ovarian stimulation emphasises an approach to dosing based upon patient variables such as age, body mass index (BMI), baseline serum anti-Müllerian hormone concentrations, antral follicle count and previous ovarian response. This approach typically uses lower doses than fixed ovarian stimulation protocols.

In contrast to dose, the type of gonadotropin preparation human menopausal gonadotropin[hMG] versus recombinant follicle-stimulating hormone [rFSH] versus urinary follicle-stimulating hormone [uFSH]) does not appear to affect the risk of OHSS.

Monitoring

It is suggested to monitor patients using both trans vaginal ultrasound (TVS) (for follicular number and size) and serum E2 concentrations. Since multiple follicle development and high E2 levels are important risk factors, early detection of either helps prevent OHSS by withholding the ovulatory dose of hCG in high-risk cycles.

Addition of GnRH agonist or antagonist

In the setting of controlled ovarian stimulation with exogenous gonadotropins for IVF, a GnRH agonist or antagonist is also administered to prevent the endogenous luteinising hormone (LH) surge. hCG is then given to induce final oocyte maturation prior to oocyte retrieval, when follicles are judged to be mature based upon size and serum E2 concentrations.

It is safer to use GnRH antagonist rather than GnRH agonist cycles in women at high risk for OHSS.The use of GnRH agonists is associated with a higher incidence of OHSS, probably due to enhanced follicular recruitment. The use of GnRH antagonists may result in lower pregnancy rates when compared with GnRH agonist therapy.

Coasting

Coasting refers to withholding gonadotropin therapy while continuing pituitary suppression with a GnRH agonist or antagonist until serum E2 levels fall into a range acceptable for hCG administration (eg, associated with a lower OHSS risk). This approach is less common now because of the availability of GnRH antagonists. The larger follicles can continue their growth and maturation when follicle stimulating hormone (FSH) is stopped; the smaller follicles have a greater FSH requirement and therefore undergo atresia.

One should start coasting when the dominant follicles are ≥16 mm and serum E2 levels are >3500 pg/mL (12,850 pmol/L). Once initiated, daily TVS and serum E2 measurements should be performed; administration of hCG should be withheld until serum E2 falls below 3500 pg/mL (12,850 pmol/L). Coasting for greater than three days (but not up to three days) has a modest adverse effect on pregnancy rates.

Withholding hCG (cycle cancellation)

Cycle cancellation before administration of exogenous hCG is an effective strategy to prevent OHSS, ie, postponing the treatment cycle until the ovaries have been rendered quiescent. However, cycle cancellation has financial and emotional implications, frustrates both patient and clinician and results in cancellation of a high percentage of cycles that would not have progressed to clinical OHSS. For patients undergoing agonist cycles at high risk for severe OHSS, this approach is still a valid and safe alternative that prevents both early and late on set OHSS forms. Consider cycle cancellation if E2 levels have not fallen by the fourth day of coasting.

Pretreatment with metformin

It is recommended to use pretreatment with metformin for women with PCOS undergoing IVF. Metformin has been extensively investigated in the management of PCOS. Its indications in the management of PCOS have diminished, but it does appear to be useful for pretreatment prior to controlled ovarian stimulation prior to IVF for reducing the risk of OHSS.

Conclusions

The prevention and management of OHSS requires considerable vigilance on the part of the clinician, using a combination of good patient selection, high index of suspicion, careful monitoring and early evidence based intervention to achieve best results and tackle this life threatening condition.

THE ONLY Sucrosomial® Iron IN INDIA

RARISET™

Sucrosomial® Iron with L-Methylfolate, L-Lysine & Vitamin B12 Capsules

POWER OF TECHNOLOGY...
TRUTH OF SCIENCE

- Hepcidin independent absorption pathway, deceives normal route of iron absorption
- Higher absorption & bioavailability of iron
- Maximum GI tolerance - better patient compliance
- Rapid Hb rise as effective as parenteral iron

Gómez-Ramírez S et al. Pharmaceuticals. 2018;11(97):1-23

Dosage:
1 Capsule Daily

In Infertility associated with PCOS

Metital

Metformin 500 mg SR + Myoinositol 600 mg Tablets

Corrects IR... normalizes ovarian function... significantly improves LIVE BIRTH RATE

NutriRight™-MOM Cookies

Healthy Snacking... Anytime... Anywhere...

India's only Nanonized progesterone

POSITO SR 200 300 400

Nanonized Progesterone 100 mg / 200 mg / 300 mg / 400 mg SR Tablets

Improved efficacy... better clinical outcome

Montana | Eris

In threatened miscarriage, recurrent pregnancy loss and spontaneous abortion

Susten SR 400 300 200

Sustained Release Natural Micronised Progesterone 400 mg/300 mg/200 mg Tablets

Empowered with EROMAT Technology

India's Most Trusted NMP... ***Made Orally Effective***

In threatened Abortion, Luteal Phase Defect, Maintenance of Pregnancy

Inj. Susten IM 200 100

Inj.Natural Micronised Progesterone I. M.

Technology has made Susten IM route less painful

For Luteal Phase Support, In Difficult-to-treat cases, High risk pregnancies

Susten Gel 8%

(Natural Micronised Progesterone Gel) with polycarbophil base

Improves Pregnancy Rate

Senora
a SUN PHARMA division

Susten Cap 400 300 200 100

Natural Micronised Progesterone 100 mg/ 200 mg/ 300 mg/ 400 mg SLDS Capsule

SLDS technology: Lipid-based delivery system facilitates Vaginal and Oral administration

AqSusten 25

Aqueous Solution of Progesterone 25mg/ml Injection

Aqua Dose. Maximize Hope.

Susten VT 200

Natural Micronised Progesterone 200 mg Vaginal Insert Tablet

Effervescent Technology for Efficient Pharmacokinetics

SPECTRA
a SUN PHARMA division

The Tested & Trusted Range to Bank On

ESTRAGEST® 2

Micronised Estradiol Hemihydrate Tablets

2 mg

Micronised Valest®

Micronised Estradiol Valerate Tablets

1 mg & 2 mg

Micronised MICROGEST® SR 200 300

Natural Micronised Progesterone Sustained Release Tablets

MICROGEST®

Natural Micronised Progesterone

Softules 100 200 **Snapules** 100 200

SMARTILON® 20

Desogestrel 0.15 mg + Ethinylestradiol 0.02 mg Tablets

SMARTILON® 30

Desogestrel 0.15 mg + Ethinylestradiol 0.03 mg Tablets

SMARTINOR® CR

Norethisterone Acetate Controlled Release Tablets (Micronised)

10 mg 15 mg

SMARTINOR®

Norethisterone Acetate Tablets (Micronised) 5 mg

SMARTICAL®

Calcium Carbonate 1250 mg equivalent to Elemental Calcium 500 mg + Vitamin D_3 250 IU + Iodine 50 mcg + Magnesium 40 mg + Zinc 7.5 mg + Manganese 2 mg + Copper 1 mg/Tablet

New

For All Round Excellence in Healthcare

Walter Bushnell

In PCOS

NORMOZ

Myo-inositol, D-Chiro-inositol, Chromium and Vitamin D_3 tablets

Right Ratio (40:1) for Quicker Action in PCOS

- Improves menstrual frequency in oligo & amenorrhoeic PCOS women[1]
- Striking improvement in ovulatory function[2]
- Improves oocyte quality in PCOS women undergoing ART[3]
- Improves metabolic profile of obese PCOS women[4]
- Chromium picolinate ensures higher ovulation rate than Metformin[5]

Reference :

1. J. Endocrinol. Invest 2011; 34:757-763
2. Eur Rev Med Pharmacol Sci 2012;16:575-581
3. Arch Gynecol Obstet 2013; 288:1405-1411
4. Eur Rev Med Pharmacol Sci 2013; 17: 537-540
5. Iranian J. Reprod Med August 2013;Vol. 11. No. 8 pp:611-618

Inca Life Sciences
A Division of
Sun Pharma Laboratories Ltd.