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Gynaecologist
Joint Secretary, The PCOS Society, India

Welcoming....

Our New Patron

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Our New Associate Members

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Dr. B. Usha
Dr. Dakshina Moorthy Janani
Dr. Hemani Saradhikey
Dr. Jigna Shah
Dr. Manju Lohiya

Dr. Paritosh Bag
Dr. Pradeep M. Musale
Dr. Sathwika Ravishankar
Dr. Shiny Surendran
Dr. Vibhuti Samartha Rao

Our New Life Members

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Dr. Anikita Sawant (Sheth)
Dr. Chanchal Kumar Saha
Dr. Manisha Nitin Davalbhakta
Dr. Veerbhadra Suresh Choudhari
Dr. Vimadalal Sonam Mrunal
Dear Friends,

Many of you must have not received our last issue of “Pandora” dated June to September, which unfortunately could not be posted to you all. But we did send it out to those whose email ids we had. We would be delighted if you send us your contact details, especially your mobile number, email id, and a correct postal address, so that we could connect with you better! You can WhatsApp your details on 9833225280.

The latest excitement in the world of PCOS has been the release of the "International PCOS Guidelines", a 200 page document with Recommendations published simultaneously in the Fertility Sterility Journal and in Human Reproduction. The PCOS Society of India was the only Indian Organization which was invited to the making of these guidelines. We will celebrate these Guidelines through a Series of 12 Webinars, one every 15 days in collaboration with Monash University, from January 2019 to June 2019. The schedule of these Webinars will be posted on the PCOS website and all those who register for it will be sent a link to log on. For all this, we need your contact details!

4 CME’s have been planned in Mumbai called “Beat-PCOS” focusing on the endocrine aspect of PCOS. The first one was held on 21st October, 2018, the details of which have been posted on page 4, of this issue and the other 3 are to follow.

This issue carries the GP Tools on PCOS created by Monash University in collaboration with ASRM and ESHRE, and is freely available online. It is a wonderful Tool to guide physicians on how to manage a PCOS patient. Please go through it, I am sure you will find it extremely useful.

We are delighted to announce a Hands-on Course in Assisted Reproduction in PCOS, called "The Art of ART in PCOS" to be held twice a year. This will be a 6 day course, conducted by excellent faculty with hands-on experience on Simulators, Microscopic and laboratory techniques. The schedules and programs for these will be announced soon!

Our Annual Conference has been planned between 23rd to 25th August, 2019 in Mumbai, please mark your calendars, we will soon be announcing the program.

We are all looking forward to exciting programs through the PCOS Society of India! I thank USV for supporting "Beat-PCOS" and Torrent and Sun Pharma for supporting this issue of Pandora.

Wishing you all a Very Happy New Year and good times ahead!

Duru Shah
Founder President
The PCOS Society of India
Dr. Reema Shah
Co-ordinator, Beat PCOS

The PCOS Society of India, in association with the Department of Endocrinology, KEM Hospital, Mumbai, conducted Beat PCOS 2018, an interactive session on the Endocrine Aspects of PCOS, on Sunday, 21st October 2018 at Hotel Ramada, Powai.

Eminent faculty from OBGY & Endocrinology spoke at the scientific program to create awareness, and highlighted the need for collaborative management of PCOS.

Dr. Anita Soni, renowned OBGY Consultant at LH Hiranandani Hospital, Powai, with special interest in PCOS and an outstanding orator, set the energy for the day with a brilliant introduction on the diagnosis & investigations for PCOS.

Dr. Anurag Lila, Associate Professor, Department of Endocrinology, KEM Hospital, Parel, gave an enlightening overview of Insulin Resistance in PCOS & rationale for Metformin Treatment.

Dr. Duru Shah, Founder & President of The PCOS Society of India, highlighted the management of Infertility in PCOS. Dr. Nalini Shah, distinguished Endocrinologist from Mumbai, simplified Hyperandrogenism & PCOS, with a Case-based approach in ruling out secondary causes of Hyperandrogenism.

The 125 delegates present at the CME actively participated and immensely benefited from the academic as well as clinical discussion that followed.

A dynamic Panel discussion by Dr. Madhuri Patil, acclaimed IVF specialist from Bengaluru, with expert panelists from OBGY & Endocrinology was a scholastic delight on a Sunday afternoon!
In summary, it would seem that AMH, as well high levels of testosterone, is implicated in the pre-natal programming of at least some of the PCOS that we see in adult life. It is another important link in this fascinating detective story. As in other pathological processes, elucidation of the etiology will give us a big lead to the ultimate prevention/treatment of the syndrome.

References
Consider ethnic variation in the presentation and manifestations of PCOS, including differences in hirsutism and acanthosis nigricans and in metabolic sequelae including obesity and insulin resistance.

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.

Ethnic variation

Consider ethnic variation in the presentation and manifestations of PCOS, including differences in hirsutism and acanthosis nigricans and in metabolic sequelae including obesity and insulin resistance.

Rotterdam diagnostic criteria requires two of:

1. Oligo – or anovulation
2. Clinical and/or biochemical hyperandrogenism (calculated bioavailable, calculated free testosterone, SHBG, FAI)
3. Polycystic ovaries on ultrasound* (and exclusion of other aetiologies such as: thyroid disease, hyperprolactinemia, FSH (if pre-mature menopause is suspected) and non-classic congenital adrenal hyperplasia)

* Vaginal ultrasound is not needed if 1 and 2 are present and not recommended for < 20yrs due to the high incidence of PCOM (Polycystic ovary morphology)

This PCOS GP Tool is based on the best available evidence and was co-designed with health professionals, and aims to assist in the delivery of evidence-based care. For more information on PCOS, see the International PCOS evidence-based guideline for the assessment and management of polycystic ovary syndrome available at:

www.monash.edu/medicine/sphpm/mchri/pcos
Clinical hyperandrogenism

**Hirsutism / Alopecia / Acne**

**Goals**

- Symptom reduction
- Hirsutism
  - Be aware of the potentially negative psychosocial impact of clinical hyperandrogenism. Unwanted excess hair growth or female pattern hair loss should be considered important in assessment and management, regardless of apparent clinical severity
  - Use standardised visual scales such as the modified Ferriman Gallwey score (mFG) with a level ≥ 4 - 6 indicating hirsutism, noting that self-treatment is common and can limit clinical assessment
  - The mFG cut-off scores for defining hirsutism are the same across ethnicities – however prevalence and degree of hirsutism severity varies by ethnicity
  - Only terminal hairs should be considered in pathological hirsutism, with terminal hairs clinically growing > 5mm in length if untreated, varying in shape and texture and generally being pigmented
- Acne
  - No universally accepted visual tool for assessment
  - Use Ludwig visual score

**Management**

- **Hirsutism - mFG scale**
  - Note that terminal hair growth has considerable ethnic variability
  - Cosmetic options: laser hair removal, depilatory creams, threading, plucking, waxing and electrolysis
  - Pharmacological therapy options (6 - 12 months to see benefit)
  - Combination therapy – if ≥ 6 months of OCP is ineffective, consider adding anti-androgen to OCP (Contraception is vital to prevent pregnancy while on anti-androgen medication)

**Reproductive**

**Irregular Periods**

**Goals**

- Regular menstrual cycles
- Reduction of risk of endometrial cancer (2 – 6 fold increased risk before menopause, however absolute risk low overall)
- Routine ultrasound screening of endometrial thickness in PCOS is not recommended

**Management**

- Consider commencing the COCP (In young women make a plan 8 years post menarche to fully assess hormone levels, will need to cease COCP for 3 months prior to assessment)
- If cycles < 4 per year - Medroxyprogesterone acetate to induce a withdrawal bleed if pt does not want to commence COCP

**Referrals**

- GP monitor

**Fertility**

**Goals**

- Family planning
- Conception if desired
- Optimise fertility

**Management**

- Encourage pt to consider conceiving prior to 35 yrs to allow time for fertility interventions, if needed
- Prevention of weight gain, lifestyle changes, weight loss of 5-10% of total body weight, if needed

**Referrals**

- Refer fertility specialist if unable to conceive after lifestyle changes at 12/12 if < 35 years or at 6/12 if > 35 years

### Metabolic features

**Cardiovascular Risk Factors**

- **Lipids**
- **Goals**
- Reduce cardiovascular risk factors

**Management**

- Lipid profile: baseline, if BMI > 25

**Referrals**

- GP to monitor

**Cardiovascular Risk Factors**

- **BP**
- **Goals**
- Target < 85/130

**Management**

- Baseline - every 12 months

**Referrals**

- GP to monitor

**Psychological**

**Emotional Wellbeing**

**Goals**

- Assess, monitor and manage depression, anxiety, body image and low self esteem

**Management**

- Assessment of anxiety and or depressive symptoms involves assessment of risk factors, symptoms and severity. Symptoms can be screened using the following stepped approach:
  - **Step 1:** Initial questions could include:
  - Over the last 2 weeks, how often have you been bothered by the following problems:
    - feeling down, depressed, or hopeless?
    - little interest or pleasure in doing things?
    - feeling nervous, anxious or on edge?
    - not being able to stop or control worrying?
  - **Step 2:** If any of the responses are positive, further screening should involve:
  - Assessment of risk factors and symptoms using age, culturally and regionally appropriate tools, such as the Patient Health Questionnaire (PHQ) or the Generalised Anxiety Disorder Scale (GAD7), and/or refer to an appropriate professional if positive to any of the screening questions.

**Referrals**

- Consider referral to a psychologist, counselor

**Lifestyle**

- Refer to Algorithm 3 and provide pt with PCOS Lifestyle and PCOS infographic.

- Lifestyle interventions are as effective in women with PCOS as in women without PCOS.

**Diet**

**Goals**

- Maintain healthy diet

**Management**

- Key messages
  - No one diet is more effective in weight reduction
  - Healthy, balanced diet
  - Reduce overall caloric intake if an unhealthy weight

*Continued on page 10*
Micronized Progesterone: Oral Versus Vaginal Route, does it matter?

Micronised Progesterone

Progesterone promotes implantation by creating suitable endometrial milieu favoring implantation, maintaining the quiescence of uterus as well as by generating pregnancy favoring immunomodulatory and anti-inflammatory effect. It is now accepted that luteal phase physiology is disrupted in in Vitro Fertilization (IVF) cycles, and that supplementation of the luteal phase with progestogens is necessary to optimize IVF cycle outcomes. The luteal insufficiency is caused by the defective functioning of the granulosa lutein cells in the pharmacologically stimulated ovaries and worsened by the loss of granulosa cells during follicular aspiration for oocyte retrieval. Progesterone for Luteal Phase support may be administered via different routes like vaginal, oral, intramuscular or rectal. This literature review assesses pros and cons of oral versus vaginal route for micronized progesterone administration.

Micronized progesterone has application as luteal phase support, early pregnancy progesterone supports and for preterm prophylaxis.

Vaginal micronized progesterone

High uterine levels of Progesterone with small systemic exposure can be attained with vaginal route for progesterone administration. Micronized progesterone, gel, capsules and tablets have all been used with equal safety and efficacy in providing luteal support.

Most clinical practice-based evidence suggest that vaginal progesterone (77% of 284, 600 IVF cycles) followed by a combination of vaginal with either IM or oral (17.3%) are the favored methods for luteal support in assisted reproductive technology (ART) cycles.

A 2001 review noted that vaginal and IM progesterone are comparable in their efficacy for luteal support and safer than hCG for luteal phase support (LPS) which is associated with increased risk for ovarian hyper stimulation syndrome. They recommended vaginal progesterone as the standard choice for luteal support.

In 2008, Kassab et al noted that micronized progesterone pessaries were the most frequently used LPS in the United Kingdom.

On the other hand, the 2015 Cochrane analysis found that the reproductive outcomes of various routes of progesterone were comparable.

Oral Natural Micronized Progesterone

Vaginal medication is not always preferred and is associated with local irritation in many women. They often prefer orally administered medication. The inconvenience associated with the use of injectable, rectal, or vaginal formulations of natural progesterone can be circumvented by using orally administered micronized progesterone. The prospective, comparative Postmenopausal Estrogens/ Progestin Intervention trial has recommended oral micronized progesterone as the first choice for opposing estrogen therapy in non hysterectomized postmenopausal women.

There has been a renewed attention about oral administration strategy since it promises compliance and convenience for the patient. The sustained release (SR) tablet formulation is an attractive option.

Pouly et al., conducted multicentric, randomized, open label, trial comparing luteal support by vaginally administered progesterone gel (8%) versus oral sustained release Natural micronized progesterone (300mg/day). Results showed that the pregnancy rates, delivery rates as well as the ratio of newborn babies per embryo transferred were comparable in both groups.

The UK based Prescription Event Monitoring Study noted that Oral progesterone was a suitable option for women with bad obstetric history due to luteal phase insufficiency as it was associated with negligible side effects and mean miscarriage rate was < 1/21.

Natural micronized progesterone support was found to be as effective as dydrogesterone in significantly reducing adverse events and increasing favorable outcomes in women with idiopathic recurrent miscarriages.

Choudhary et al and Glover et al found Oral progesterone an effective option for maintaining tocolyis and for prolonging pregnancy in women with history of recurrent preterm births.

Progesterone Assessment Survey Sheet (PASS) assessed responses from 925 Gynecologists across India found that though 58% preferred vaginal progesterone 36% preferred oral micronized progesterone for tackling Luteal Phase Defect, Luteal Phase Support for ART & preterm birth prophylaxis.

Conclusion

Natural micronized progesterone has various applications and evidence suggests that various routes of administration are equally efficacious. Currently, the vaginal route is the most commonly used and preferred. In women who are intolerant to vaginal administration or who find it unacceptable, oral micronized preparation is a feasible and effective alternative.

References

Does L-Carnitine have a role in female infertility?

Levocarnitine (L-carnitine) is a very common and familiar compound among the integrative medicine practitioners in the treatment of fertility. L-carnitine has been shown in animal models to stabilize mitochondrial membranes, increase energy delivered to organelles, and protect against cellular apoptotic death.

L-carnitine has immense functional capabilities to regulate the oxidative and metabolic status of the female reproductive system. Due to its potent antioxidant effect, and decreased side effects, researchers have now considered it for combating the various disorders of the female reproductive system.

**Mechanism of action**

**In the oocyte:**
1. Helps in the metabolism of cumulus-oocyte complex (COC) lipids by transferring fatty acids into mitochondria. LC gets converted into ALC and balances the acetyl CoA/CoA ratio, to maintain glucose metabolism and thus yields high energy production.
2. LC scavenges the ROS through its antioxidant property. It transports palmitate and other long chain fatty acids to the mitochondria to facilitate β-oxidation. It decreases the concentration of palmitate from the endoplasmic reticulum, thus eliminating the lipotoxicity and oxidative stress caused by scavenging free radicals.
3. LC minimizes cell death by apoptosis, thus promoting oocyte growth and maturation of the blastocyst.

Genazzani AD et al., in his study has shown that LC and ALC affect the hypothalamo-pituitary-gonadal axis (HPG) by regulating the serum levels of hormones like luteinizing hormone (LH), estradiol and progesterone activity. LC has reported to decrease neuronal cell death and damage associated with aging by its cholinomimetic activity thus mitigating the reproductive disorders such as PCOS, amenorrhea and endometriosis.

**Role of L-carnitine in PCOS**

Obesity, hyperandrogenemia, insulin resistance and hyperinsulinemia are the features of PCOS which is a major endocrinopathy. Samimi M et al., in his randomised double blind , placebo controlled study has shown that LC supplementation leads to LC induced increase in beta oxidation of fatty acids, thus decreasing the blood glucose levels and opposing the insulin resistance. It also leads to increase in the basal metabolic rate with significant reduction in the body weight, BMI (body mass index), waist and hip circumference.

Fencki M, in his study has shown that non-obese PCOS women have significantly decreased LC levels and increased androgen levels.

LC supplementation along with clomiphene or gonadotrophin during ovarian stimulation has shown to increase the response to ovarian stimulation, better oocyte maturation, ovulation and pregnancy rates. LC supplementation not only improved the reproductive health, but also enhanced the patients lipid profile and BMI.

**Role of carnitine in amenorrheic women**

Functional hypothalamic amenorrhea is a condition in which there is decreased estradiol production from the ovary due to decreased gonadotrophin production and indirectly due to aberration in the release of GnRh hormone.

Genazzani et al., has shown that ALC supplementation has led to increase in the LH levels by counteracting the inhibitory neuroendocrine pathways on the HPG axis. ALC acts through the opioidergic pathway and alters the protein/hormone functions by acetylation of the -OH groups in amino acids like serine, threonine or tyrosine thereby improving the functions.

**Carnitine and endometriosis**

There is dual action in cases of endometriosis due to increase in the production of both PGE1 and PGE2. PGE1 decreases the release of tumour necrosis factor(TNF), interleukins and interferon gamma, while PGE2 increases the cytokine release. Thus, role of carnitine in cases of endometriosis is still controversial.

LC has known to reduce the ROS and enhance ATP production, which contributes to the development of high quality embryo. LC supplementation in culture media has improved the human embryo quality and eventually achieved better pregnancy outcomes. LC mediated beta oxidation of fatty acids has a major role in the energy supply of oocytes and embryos. Disturbed carnitine metabolism may impair the oocyte quality and thus the reproductive outcome.

Varnagy et al., in his study reported the profiling of several acylcarnitines in serum and follicular fluids of women undergoing IVF. It was seen that IVF patients with better reproductive outcome had upregulated pathways leading to excess carnitine consumption and endogenous depletion of carnitine pool, thus suggesting that IVF patients may benefit from carnitine supplementation.

**Conclusion**

Carnitines either directly or indirectly along with other nutrients can be considered to boost the fertility and enhance the reproductive performance in humans.

**References**


**Continued on page 10**
Continued from page 7

PCOS GP TOOL

Referrals
Consider referral to dietitian

Physical Activity

Goals
Target exercise – See PCOS lifestyle infographic for age specific information.

Management
Exercise routine established

Referrals
GP to monitor
Consider referral to exercise physiologist, trainer

Weight

Goals
Prevention of excess weight gain
Target 5-10% weight loss

Management
Weigh and monitor women regularly, vital to:
- Targeting prevention
- Key message: 5-10% weight loss will greatly assist in symptom control
- Encourage simple behaviour change – prioritisation of healthy lifestyle, family support, lifestyle and exercise planning, setting of small achievable goals
- If unhealthy weight pt unable to lose weight 6/12 with lifestyle changes consider metformin (titrate dose, starting 500mgs up to 2mg)

Referrals
Consider referral via team care arrangement if appropriate:
- Dietitian for tailored dietary advice, education and behavioural change
- Exercise physiologist for tailored exercise program, motivation and support
- Group support, diet and exercise programme

For more information on PCOS, see the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: www.monash.edu/medicine/sphpm/mchr1/pcos

Continued from page 8

Micronized Progesterone: Oral Versus Vaginal Route, does it matter?


Obstructive Sleep Apnea

Goals
Use Berlin questionnaire sleepapnea.org/assets/files/pdf/berlin-questionnaire.pdf

Management
Screening should only be considered for OSA in PCOS to identify and alleviate related symptoms, such as snoring, waking unrefreshed from sleep, daytime sleepiness, and the potential for fatigue to contribute to mood disorders. Screening should not be considered with the intention of improving cardiometabolic risk, with inadequate evidence for metabolic benefits of OSA treatment in PCOS and in general populations

Referrals
Consider referral to sleep clinic

Additional GP Tools

GP tools available at: www.monash.edu/medicine/sphpm/mchr1/pcos

Algorithms
Algorithm 1 Screening, diagnostic assessment, risk assessment and life-stage

Algorithm 2 Prevalence, screening, diagnostic assessment and treatment of emotional wellbeing

Algorithm 3 Lifestyle

Algorithm 4 Pharmacological treatment for non-fertility indications

Algorithm 5 Assessment and treatment of infertility

Patient infographics
- What is PCOS and do I have it?
- Lifestyle and PCOS
- Emotional wellbeing and PCOS
- Fertility and PCOS
- PCOS treatment

Monash University.
ANNOUNCES

A Hands-on Certificate Course on

The Art of ART in PCOS

A Hands-on 6 days event

Course material will be provided

Observational Week in an IVF Centre

Dates:

Course 1 – 18th to 23rd March 2019
Course 2 – 7th to 12th Oct. 2019

Venue:

Origio India Private Limited –
A Cooper Surgical Company
C-401, Delphi, Hiranandani Business Park, Powai,
Mumbai 400 076

Register on www.pcosindia.org

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brings a series of 12 FREE Webinars based on the latest
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